STRESS ULCERATION - PATHOPHYSIOLOGY AND PHARMACOLOGIC CONTROL IN A SEPTIC CANINE MODEL

by

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SEPSIS-RELATED STRESS ULCER: PATHOPHYSIOLOGY AND CONTROL.

ABSTRACT

In order to investigate the relationship between sepsis and stress ulceration, a reproducible canine model, closely mimicking the clinical situation was developed by inducing bacterial peritonitis which led to septicemia and acute fundic erosions.

Creation of a total gastric fistula in the model enabled investigation of the relationship between sepsis-induced ulceration and changes in gastric secretion over a three-day period. Results indicate that there is increased output of acid, fucose, sodium and potassium during sepsis. With resolution of sepsis, healing of the gastric mucosa occurred and there was gradual return of all parameters to presepsis levels.

A high dose of Cimetidine was required to prevent acute ulceration because its effect depended on acid inhibition. On the other hand, 16, 16-dimethylprostaglandin E_2 prevented mucosal damage through a cytoprotective mechanism that is independent of acid inhibition.

The maximum tolerable dose of Metoclopramide used could only reduce the severity of mucosal damage.

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RESUME

Afin d'étudier la relation entre la sepsie et la formation d'ulcères de stress, un modèle canin reproductible a été réalisé; on a provoqué chez l'animal une péritonite bactérienne qui a entraîne la septicémie et des érosions fundique aigues reflétant fidèlement le tableau clinique observé chez l'homme.

La création d'une fistule gastrique chez le chien a permis d'étudier la relation entre l'ulcération provoquée par la sepsie et les modifications de la sécrétion gastrique pendant une période de trois jours. Les résultats indiquent que la production d'acide, de fucose, de sodium et de potassium est accrue au cours de la sepsie. La résolution de l'infection a été accompagnée de la guérison de la muqueuse gastrique et on a observé un retour progressif de tous les paramètres aux niveaux notés avant la sepsie.

Il a fallu administrer une forte dose de cimétidine pour prévenir l'ulcération grave puisque son effect dépendait de l'inhibition de la production d'acide. Par ailleurs, la 16,16-diméthylprostaglandine E_2 a prévenue l'atteinte de la muqueuse par son action cytoprotectrice indépendante de l'inhibition de la sécrétion d'acide.

La plus forte dose de Métoclopramide tolérée par l'animal n'a pu que diminuer la gravité de l'atteinte de la muqueuse.

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"The stomach is affected by injuries in parts of the body which have no connexion with nutrition, and more especially with parts which have the least action in the machine." John Hunter: "Lecture on the Principles of Surgery". Haswell, Barrington, and Haswell. Philadelphia 1839, Ch. V, p.44.

PREFACE

Stress ulcers continue to pose an enormous challenge to physicians and surgeons and continue to engage the attention of medical researchers. No effort has been spared in the continuing process of elucidating the pathophysiology of this condition.

In spite of the fact that stress ulceration has long been associated with septic or pyemic conditions, the relationship has not been as intensively investigated as other etiologic factors such as hemorrhage. Investigations have been hampered to a great extent by the lack of a suitable experimental model.

The successful development of a reproducible septic canine model which closely resembles the clinical situation (in our laboratory) has provided us with a very valuable tool for the investigation of some of the factors involved in the pathogenesis and control of this potentially lethal complication of severe illness.

The work reported in this thesis is embodied in four chapters. The first chapter presents highlights of the extensive literature on the subject of stress ulceration. Attention is drawn to the semantic confusion that exists in the literature about the terms used in the description of the clinical condition. A brief review of some of the experimental models that have been used in previous

investigations is presented. A detailed description of our experimental model is found in the second chapter which also contains our experimental protocol and procedures. Chapters three and four deal with the experimental results, discussion of our model and the effects of the pharmacologic agents we employed to prevent or control ulceration.

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CHAPTER 1

1.1 INTRODUCTION

Change is a hallmark of our time; and all around us, there is clear and direct evidence of the changes which mankind is going through. The swing to urban living, the revolution in our transportation systems and the rapid growth of our heavy industries have all led to congestion and pollution of our environment. Speed in our acitivities, and the use of sophisticated mechanical devices have altered the lifestyles of several individuals and have resulted in increased illness and injury.

Even though scientific public health methods have almost defeated the agony of contagion in some parts of the world, they have also brought into sharper focus and greater prominence, the increasing morbidity and mortality from stress and injury that have resulted from the changes in our lifestyle. The public has been taught to know that good health is one of the basic rights which they should demand and enjoy. The medical profession has responded, albeit sometimes inadequately, to the challenges imposed by its own tenet that requires that no patient should be denied the chance to live and recover from his ills. The hospital is, therefore, no more the place to go to die.

Modern technology and fundamental advances in the biological and medical sciences have revolutionized methods of diagnosis and treatment. The advances in life sustaining techniques of medical care that have come to the fore in the last few decades have been phenomenal and awesome. The physicians' commitment to offer every patient the chance to live has led to the evident progress made in recent years in both acute resuscitative and in the subsequent intensive care treatment offered in most hospitals these days. These potent methods for diagnosis and treatment constitute the backbone of the practice of modern medicine.

Progress is not without its own attendant ills. Many a physician has been overwhelmed by life-threatening torrential upper gastrointestinal hemorrhage in a critically ill patient who is receiving intensive care treatment and has been offered every chance to live. The dramatic, and all too often, sudden gastric bleeding, follows upon a train of complications, often seen in the critically ill patient, any one of which could very well have sounded the death knell at an earlier period of the patient's usually turbulent and chequered course.

The successful application of vigorous resuscitative and supportive measures developed over the years through clinical research and experience, ensures that certain

patients, who might otherwise have succumbed early to their primary illnesses will survive for long enough to suffer a sequential failure of several organ systems. The cascade of events ultimately comes to involve the stomach which in its turn may lead to the inevitable consequence of massive gastric bleeding. This usually spells doom to the patient and frustrates the yeoman's efforts of the attending physician and his staff.

It is the "continuing challenge" of this treacherously massive bleeding from the stomach of the critically ill patient, which, as it were, intervenes unannounced, to end the "stress and suffering" of the patient and to expose the inadequacies of the attending personnel which prompted this thesis.

1.2 PURPOSE OF STUDY

The notorious phenomenon of sudden and torrential gastric bleeding in the critically-ill patient has fascinated physicians and surgeons for several years and, for eons, medical researchers have been trying to find solutions to this problem. The successful prevention or treatment of acute peptic ulceration depends on clarification of the mechanisms which mediate the pathologic changes which take place. Unfortunately, the evidence concerned

with such mechanisms is not clear or conclusive despite long-continued intensive investigation.

The following pertinent questions have always been asked:-

a) Why is it that a patient who has no antecedent history of any gastric illness suddenly develops a bleeding condition in the stomach so severe that life is threatened despite the fact that he is benefiting from intensive care?

b) Why does the stomach react so gravely to severe illness that might be quite remote from it?

c) How can we control, if we cannot prevent, this condition which betrays the best efforts of physicians and surgeons?

These are but a few of the nagging questions which medical researchers have had to grapple with in their attempt to help the critically-ill patient. One should not be deluded into thinking that nothing concrete has been found to alleviate the plight of the critically-ill patient who has the danger of massive gastric hemorrhage hanging over his head like the sword of Damocles. The literature is quite replete with several attempts to unravel the mystery shrouding this disease phenomenon, but it looks like there are always more questions than answers; and the problem remains only partially elucidated.

One of the major problems encountered in the investigation of the pathogenesis of acute gastric ulceration has been the lack of a suitable experimental model in which the appropriate clinical situation could be simulated and reproduced under controlled conditions. Our first task, therefore, was to develop an experimental model in which the results obtained could be extrapolated as closely as possible to the human situation.

The successful development of the model encouraged us to investigate a few of the major factors that have been suggested as important in the pathogenesis of acute peptic ulceration.

Our attempt was to try to offer some answer(s) to the first and second questions posed above.

Our interest was further stimulated to try to answer the third question of control or prevention of acute ulceration by the use of some pharmacological agents in current use.

1.3 LITERATURE REVIEW

1.3.1 HISTORY

Acute gastroduodenal ulceration is not a recent discovery. It has been described extensively in the medical literature. As early as A.D. 20, Celsus (1) had observed acute ulceration in soldiers during military campaigns; but it is only within the last century that

the condition has been widely studied and discussed.

It was Morgagni (2), who in 1707, described the case of a 40 year old man who had died of "headache and ardor urinae" after three days of illness. Post mortem examination of the man's stomach revealed that "the right portion of the stomach appeared in a healthy state--- (but) the left portion of the viscus was diversified at its fundus with vivid bloody spots---some of them coated with an appearance like rusty iron, indicating a tendency to gangrene." Morgagni further observed that "even where there were no spots, and the internal coat appeared in a natural state, I could easily press out blood".

This early description of acute ulceration was further confirmed by John Hunter (3) who in his first communication to the Royal Society of England in 1772 stated that occasionally in the bodies of those who had died violent deaths, there was seen a "dissolution of the stomach". He called this condition "gastromalacia" and supposed that the process was a post mortem continuation of digestion which had started during life as a result of disease. He could however not relate it to any known disorders. In a section of his "Handbuch der pathologischen Anatomie (1841-1846) (4), Carl Rokitansky described acute softening of the stomach and esophagus in neonates with intracranial trauma and "acute affections

of the brain or its membranes". The work and reputation of Rokitansky were eclipsed by the greater fame of Virchow who in 1853 (cited by Cushing) described the same process, but attributed it to postmortem digestion due to the continued presence of free acids within the stomach.

In 1868, Carl Hoffman (5) described two cases of esophageal perforation in adults with antemortem signs of peritonitis. His second case had a gummatous interpeduncular tumor with softening of the right half of the pons and the medulla.

The neurogenic origin of gastromalacia was further emphasized in 1874 when Rudolf Arndt (6) reported the case of a 26-year old woman who had died of a sarcoma of the meninges located in the interpeduncular space. At autopsy she had hyperemic softening of the stomach with numerous ecchymoses of the fundus. In 1910, Roessle (7) recognized gastroduodenal ulceration as a complication of other diseases which reflexly irritated the vagus nerve.

Scattered through medical literature may be found other examples, but, the epochal description of 11 cases by Harvey Cushing (8) in his Balfour Lecture on Peptic Ulcers and the Interbrain, published in 1932, needs special mention. Cushing's publication was a comprehensive summary of this pathological curiosity and emphasized the close relationship between gastroduodenal ulceration and intracranial pathology. His attempt to find a

reasonable explanation for the acute perforative and hemorrhagic lesions affecting the esophagus, stomach, and duodenum which caused early fatality after operations for intracranial tumors led him to review the literature on the neurogenic aspects of ulcer pathogenesis.

In 1934, Masten and Bunts (9) recorded 6 cases of what they termed "neurogenic erosions of the stomach". In a more recent article, Strassmann (10) noted 30 cases of non-traumatic perforation of the esophagus or stomach associated with intracranial lesions observed in 1200 autopsies in New York during a 2 year period.

In 1892, the attention of Von Preuschen (11) was drawn to an infant with melena who died on the second day after birth and in whom autopsy showed subtentorial hemorrhage with extravassation into the fourth ventricle and hemorrhagic erosions of the gastric mucosa. He believed that intracranial lesions might be a common cause of melena in infants. In 1907 Shukowsky (12) reported that about 45% of instances of melena neonatorum vera, were due to ulceration in the esophagus, stomach or duodenum. This fact was supported by other authors (13, 14).

A search of the literature reveals that acute gastroduodenal ulcerations have complicated other clinical conditions. Treille (15) reported finding

multiple gastric erosions in soldiers dying from septic wounds. Cuveilhier (16) had also recognized hemorrhagic erosions as a sequel to various stress situations.

Although Curling's comprehensive report (17) concerning the occurrence of intestinal ulceration following burns directed special attention to the subject, it was Swan (18), who in 1823, reported a case with ulcers of the stomach following burns. In the same year Cummin (19) reported inflammation of the gastrointestinal tract following burns, and Dupuytren (20) also called attention to the severe congestion and ulceration of the stomach and duodenum following burns. There were other reports of duodenal ulceration following burns (21, 22). Much has been written about Curling's ulcers. Among some of the more recent series reported are those by Harkins (23) who stressed the relationship between sepsis and the development of gastroduodenal ulceration in burn patients.

Surgery itself has been known to be associated with gastrointestinal ulceration and the earliest report of a case citing the trauma of surgery as a cause of acute ulceration was communicated by Billroth (24) whose professional career spanned the pre-antiseptic era to the beginning of asepsis. He presented the case of a 42 year-old man who died of severe gastroduodenal hemorrhage four days after being operated on for a large substernal

goitre. At autopsy, there were observed four acute ulcers in the duodenum. Earlier, Rindfleisch (25) had noted a similar case after an operation for a strangulated inguinal hernia. Autopsy revealed several hemorrhagic infarcts in the stomach. Twenty-two years after Billroth's report, Von Eisensberg (26) reported a series of 8 cases in which 5 succumbed to fatal gastroduodenal bleeding which occurred after operation. Autopsy showed diffused peritonitis with about 30 fresh hemorrhagic erosions in the stomach of one of the patients. Busse (27) and Von Winiwarter (28) described cases of gastroduodenal ulceration complicating unrelated operations on the kidney, spleen, and ectopic pregnancy.

Dieulafoy (29) was the first to describe hematemesis and gastroduodenal ulceration as complications of appendectomy. He related the lesions to toxins and infections. In 1902, Nietzsche (30) reported a case of gastric hemorrhage occuring after appendectomy. The patient had been ill with peritoneal symptoms for three days before coming under observation. There was marked abdominal distention and regurgitation of coffee ground material. After the death of the patient, autopsy revealed generalized peritonitis, and the stomach showed "countless flat ulcers" of varying sizes covered with

clotted blood distributed in the fundus and along the greater curvature. Furthermore, "there were focal areas of necrosis which were interspersed between well-preserved ones". He considered the lesions to be due to sepsis.

In 1925, Silver (31) reported a fatal case in which massive upper gastrointestinal bleeding developed on the sixth day after thyroidectomy. Fatal hemorrhage was due to an acute ulcer with erosion of the superior pancreatico-duodenal artery. Penner and Bernheim (32) reviewed acute post-operative upper gastrointestinal ulcerations which followed surgery and were secondary to a wide variety of diseases. It was their impression that acute ulcer complications were due to shock, regardless of the causes.

In 1945, Herbut (33) reported five fatal cases of acute gastroduodenal ulceration following distant and unrelated operations. Two of the patients had sepsis and abscesses prior to the ulcer complications. Sepsis, as an important correlative factor in the development of acute gastroduodenal ulcer, was emphasized by Perry and Shaw (34). In their report of a series of 18 cases to illustrate this association, they wrote that "the association of ulceration of the duodenum with general septic or pyemic conditions has not, so far as we know, attracted attention".

The history of acute gastroduodenal ulceration will not be complete without reference to Hans Selye. In 1948, Selye (35) presented his celebrated concept of stress and the general adaptation syndrome. He offered evidence that gastroduodenal disease, usually in the form of superficial multiple erosions and ulcerations was a common sequel to the metabolic and pathologic responses of the organism to stress.

1.3.2 CLINICAL SETTING

Acute gastroduodenal bleeding has been noted to occur in a variety of clinical settings including:

- hospitalization for major medical illnesses (34-39)
- postoperative patients (32,33,40-45)
- burns (17,18,22,23,46-53)
- patients who have sustained major trauma (41,54-59)
- patients with central nervous system disorders (8-10,60-64)
- steroid and anti-inflammatory drug treatment (65-69)

Acute gastric ulceration may occur in patients with severe injury and almost any type of operation (32). Sepsis, hypotension, jaundice and renal and respiratory failure are the typical clinical features observed in patients who are at high risk of developing this disease (70-72).

In 1963, Levij and De La Fuente (73) correlated 665 cases of acute ulcers with co-existing disease and found that 9.5% followed recent surgery or trauma and 2.6% were in shock. Beil et al (44) reported that in 74% of 35 patients who developed postoperative gastroduodenal hemorrhage, significant infection preceded hemorrhage.

Severe medical illnesses such as chronic pulmonary disease and myocardial infarction may also be complicated by acute gastroduodenal ulceration (37,73,38,45). The high incidence is attributed to such factors as chronic hypoxia, hypercapnia and respiratory acidosis which are associated with an increased secretion of gastric juice(73).

In 1966, Andresen and Claussen (74) reported 13 cases of gastric hemorrhage associated with myocardial infarction, and Enquist and Gliedman (75) have also linked portal hypertension and cirrhosis with acute ulcerations of the stomach, esophagus, and duodenum. The mental and physical strain of chronic illness may be additional contributing factors (76).

The exact incidence of Curling's ulcers is difficult to establish since most of them do not present any clinical problems. Estimates of the incidence vary widely from 0.2% (77) to as high as 25% (50). In his review of 1938, Harkins (23) found the incidence to be highest in patients with third degree burns of the sloughing septic

type; and in a recent endoscopic evaluation, Czaja et al (78) indicated that multiple gastric erosions were present in 86% of patients with burns of mean size of 56% of the body surface area, 74% of which were evident within 72 hours after the thermal injury.

Although the duodenum was the source of massive bleeding in the cases reported by Curling (17), more recent reports by Sevitt (51) and O'Neill et al (49) indicate that multiple superficial gastric ulceration are also a common source of bleeding in patients who sustain thermal injury.

All types of intracranial lesions or operation can be complicated by the development of single or multiple ulcers which consist of deeply penetrating ulcers. These lesions may involve the full thickness of the esophagus, stomach or duodenum, and perforation is more commonly seen (8).

Some patients on steroids and anti-inflammatory drug treatment may have episodes of upper gastrointestinal bleeding. Kern et al (67) reported an incidence of 12.5% in patients with rheumatoid arthritis and who had been treated with steroids and phenylbutazone. The incidence of ulceration, however, depends on the dosage and the duration of therapy. Dubois et al (69) summarized 14 previous reports and found the incidence of steroid-

associated ulceration to range from 0-31% and to be related to dose. Smaller doses appear to be relatively safe.

The recognition that steroids possess ulcerogenic properties prompted many authors to believe that Selye's concept of stress, with increased pituitary-adrenal activity (35) might provide a common explanation for both the cause of acute ulceration and its association with a large variety of diseases (79-82). The clinical course of drug-induced acute ulceration is usually less severe than that seen in sick post-operative patients who develop acute ulcers, and withdrawal of the offending agent frequently results in healing of the mucosal lesions and cessation of bleeding (72).

Other conditions have also been reported to be associated with acute gastroduodenal ulceration. These are severe muscular exertion, fatigue, X-irradiation and shock (79).

1.3.3 ULCER

"Ulcer" is derived from the Latin word "Ulcus" which means sore. The dictionary defines ulcer as a "break in skin or mucous membrane that is characterized by a loss of surface tissue...by disintegration and necrosis of epithelial tissue..." (83).

Pathologists define an ulcer as "a local defect or excavation of the surface of an organ or tissue which is produced by the sloughing (shedding) of inflammatory necrotic tissue" (84). Ulceration is the process of forming an ulcer or becoming ulcerated.

Gastroduodenal ulcers may either be benign (simple) or malignant. In the latter, the ulcer arises because a malignant tumor (cancer) becomes ulcerated. Benign ulcers of the stomach or duodenum are either acute or chronic, but occasionally, an ulcer in an intermediate position is encountered.

Morphologically, the main feature which differentiates an acute ulcer from the chronic ulcer is the presence of fibrosis in the latter. Chronic stomach ulcers tend to occur in the antral mucosa and only rarely in the acid-secreting parietal cell areas (84). As a chronic ulcer heals, the lesions become predominantly fibrotic and the retraction of the fibrous tissue often leads to a puckered scar which changes the rugal pattern of the mucosa.

The terms erosion and ulcer are often used interchangeably (85,86) but investigators like Menguy and Walt (87) prefer to make a distinction between the two terms. Menguy (88) states that "an erosion is a mucosal defect that does not penetrate deeper than the muscularis

mucosae. A lesion beyond this layer is an ulcer". If we are to stick to our definition of acute ulcer strictly, then we should be talking about acute erosions and not ulcers. But, Skillman and Silen (72) contend that since acute erosions may progress to true ulcers, there is very little point in attempting to differentiate these terms because they are pathogenetically and clinically similar.

1.3.4 GROSS AND MICROSCOPIC CHARACTERISTICS OF ACUTE ULCERS

Acute ulcers are superficial, relatively non-inflammatory mucosal defects of the gastric or duodenal mucosa which characteristically involve only the mucosa. An important feature is that the lesions rarely extend beyond the submucosa and perforation is virtually unknown (72,85,86,88,89). In a majority of instances, the lesions are multiple and are scattered throughout the acid-secreting parietal cell area of the stomach.

The margins of acute ulcers are poorly defined because of their superficial nature, and they rarely show significant hyperemic reaction. The rugal pattern of the mucosa is not affected, and the margins and bases of the ulcers are not indurated. There may, however, be some inflammatory infiltration in the margins and bases depending upon the duration of the ulceration (32,84).

The base of an acute ulcer is usually black and hemorrhagic and there may often be a coat of fibrin (84,86). There is usually conspicuous absence of underlying scarring or thickening of blood vessel walls such as is seen in the chronic forms (84).

With the advent of fiberoptic gastroscopy, it has been possible to follow the development and resolution of acute ulcers (90). Within 24 hours of sustaining severe trauma, patients were noted to have foci of pallor and hyperemia which were located almost exclusively in the proximal body of the stomach, near the greater curvature. By 24 hours, petechiae and shallow red-based erosions appeared in the same area of the stomach. By 48 hours, the erosions were deeper, black-based and had some marginal edema. As the disease process progressed, the erosions were seen scattered throughout the entire stomach without isolated antral involvement.

Histological progression of the lesions began with focal edema and early diapedesis of red blood cells, This was followed by mucosal hemorrhage in the lamina propria and mucosal coagulation necrosis with denudation of the superficial necrotic layers of the epithelium. Dilatation of submucosal blood vessels was common (85). Scanning electron microscopy revealed discontinuation of the limiting membranes of the altered surface epithelial cells,

exposing the intracellular contents and leaving "empty" cells which resembled a honey-comb (86,90).

Acute ulcers heal by complete re-epithelialization of the mucosa as soon as the causative factors are removed (84). There is little or no scarring and consequently, it is difficult, if not impossible, to determine the site of a healed acute ulcer or erosion. This regrowth of epithelium may be quite active and it is well known that total replacement of mucosa may occur within two days after the formation of the ulcer (84). In some patients, however, acute ulcers may persist for as long as three weeks (86).

Although acute ulcers appear and disappear rapidly and are accompanied by minimal symptoms, they are fraught with potential gastrointestinal hemorrhage; massive bleeding episodes being caused by acute ulcers eroding into large submucosal vessels (50,84,86,89).

1.3.5 CLARIFICATION OF TERMS

There is an unfortunate semantic confusion in the literature concerning the descriptive terminology for acute ulcers of the upper gastrointestinal tract. The term "stress ulcer" has generally been applied whenever acute bleeding has followed some kind of stressful situation, regardless of the characteristics of the mucosal lesions (85,91).

Other terms have also been used quite often and they include:

- erosive gastritis (85,87,92,93)
- hemorrhagic gastritis (95-98)
- Curling's ulcer (49-53,96)
- Cushing's ulcer (64)

and varying combinations of these terms.

Further confusion surrounding the subject of acute ulceration derives from failure to differentiate between patients whose bleeding is related to acute exacerbation of a pre-existing chronic peptic ulcer, and patients whose bleeding episode is truly due to acute ulceration (72). Even though bleeding after stress may come from a single lesion, careful examination of the mucosa almost invariably shows multiple superficial lesions and gastroscopic examination of the mucosa of severely injured patients indicated that there were multiple gastric lesions which progress from petechiae to erosions or ulcers and then to hemorrhage.

The term "stress ulcer" came into use following Hans Selye's (35) epochal presentation of his "concept of stress" in 1948. Selye reported that "the organism responds in a stereotypical manner to a variety of widely different agents such as intoxications, trauma, nervous

strain, heat, cold, muscular fatigue, or X-irradiation". These agents, called "stressors" placed the body in a "state of general stress" and hemorrhagic erosions of the gastric mucosa were included in descriptions of the stress response.

"Stress Ulcer" has however been criticized as being too all-inclusive (70,87,94,99-101) and Walt (87) thinks "it is a bad term because sometimes there is no obvious or discernible stress, or sometimes there is no ulcer".

However, there are preponents who think that it is a satisfactory generic term because when the condition occurs, there is some form of physiologic stress (87).

For lack of a more "crisp and meaningful term" and "for euphony more than scientific accuracy", Menguy (87) will retain the term which has been widely accepted as a biological phenomenon.

It has however been recommended that the term "Stress ulcer" should be reserved for the diffuse mucosal lesion which follows on severe physical stress (e.g. accidental or operative trauma) usually associated with shock and infection (99,101). These lesions, for the most part, are restricted to the acid producing segment of the gastric mucosa (94).

Several groups of conditions have been lumped together without regard to the true nature of the lesions because many authors have failed to identify, with any precision, the type of lesions encountered after various types of stress. Ulcers occurring after trauma, sepsis or shock have been grouped together with ulcerations associated with burns, intracranial diseases and steroid or anti-inflammatory drug therapy (85). Four distinct groups of acute ulcers can be identified if the etiology and nature of the lesions are carefully considered (99).

1.3.5.1 NEUROGENIC ULCERS

Neurogenic ulcers (Cushing's Ulcers) develop in patients with intracranial processes and are very different in several respects from those which occur after shock or sepsis. They usually present as large full-thickness dissolution and perforation of poorly defined areas of esophagus, stomach and/or duodenum, with no evidence of inflammatory response (64,85,99). In a recent series of patients who sustained central nervous system injury during the Vietnam war, patients were found to have duodenal ulcers without any gastric ulcers (57). The pathogenesis of Cushing's ulcer is not clear but it is different enough from acute ulceration due to trauma

and sepsis to belong to a different category. It seems that Cushing's ulcers are related to abnormal vagal stimulation with neurogenic acid hypersecretion, stimulation of the hypothalamus with consequential anterior pituitary activity, secretion of ACTH, stimulation of the adrenal cortex and release of corticoids which impair the mucous barrier (64,101).

1.3.5.2 CURLING'S ULCER

It is difficult to establish whether or not ulcers occurring in the course of burns (Curling's Ulcers) are similar etiologically to those associated with shock and sepsis even though shock and sepsis usually accompany burns. Classical Curling's ulcers are primarily found in the depth of the rugal folds of the gastric fundus as well as in the duodenum, and they are usually deep with well-defined round margins (99). Postburn duodenal ulcers tend to be single and occur in the absence of gastric involvement, whereas gastric ulcers are multiple and diffuse (51). Curling's ulcer can therefore be placed in another group (87).

1.3.5.3 STEROID ULCERS

A third group will contain steroid-induced ulcers. The relationship of steroids to stress ulcers is poorly understood and the incidence of ulcers has been chal-

lenged because the disease for which these drugs are used may in themselves be associated with acute ulceration (85). However, it is generally accepted that long term administration of high doses of steroids will cause acute ulceration which usually involves the antral mucosa of the stomach (99).

1.3.5.4 ASPIRIN AND ALCOHOL ULCERS

It is difficult to put lesions produced by alcohol, aspirin, and perhaps many other drugs into a different category. These lesions resemble ulcers due to trauma or sepsis in that they are superficial and multiple or diffuse, and even though they may affect the fundic mucosa, they are frequently antral in location. They rarely, if ever, perforate (85). The similarity of these drug-induced lesions to stress lesions is so strong, and the clinical manifestations so similar that they will be considered together with stress ulceration associated with sepsis or trauma.

For the sake of clarity, further discussion of the subject of stress ulceration will be limited to ulceration following accidental or operative trauma usually associated with shock and infection.

Since the term "acute gastritis" has sometimes been used interchangeably with stress ulcer, a closer look at the term is called for. Gastritis is a much abused

medical term and it means different things to different people. To the layman, it is epigastric discomfort and vomiting particularly related to heavy alcohol consumption. The pathologist diagnoses gastritis by criteria such as the presence of inflammatory cells, and to the hematologist gastritis implied the total gastric atrophy characteristic of pernicious anemia. In context the term is reasonable when used by any of these individuals, but because it embraces such a variety of situations, gastritis has come to be almost meaningless as a concept of disease (102).

In relation to clinical medicine, the term gastritis is best considered as embracing two distinct and probably unrelated entities; acute gastritis which is a transient reaction of the gastric mucosa to irritants, and chronic (atrophic) gastritis, in which the mucosa is permanently altered and its normal function impaired (102).

Lucas et al (94) defined acute erosive gastritis as "multiple superficial erosions and ulcerations in the gastric mucosa which seldom extend into the submucosa", and Ivey (97) described "acute hemorrhagic gastritis" as a condition of acute diffuse superficial erosions (not extending deeper than the muscularis mucosae) or multiple petechial hemorrhages of the mucosa of the stomach, usually

confined to or predominant in the fundal region". These descriptions are similar when one looks at the pathogenesis and histology of the lesions.

Acute gastritis as the term implies, is an acute mucosal inflammatory process, usually of transient nature (84) and it usually affects the antrum. The mucosa is red with inflammatory cells on histological examination (101) and in this sense, it differs from acute ulcers caused by trauma and sepsis in which there is no significant inflammatory reaction and the lesions are limited to the fundal mucosa.

The usual cause of acute gastritis is insult by a variety of exogenous agents such as alcohol, caffeine and non-steroidal anti-inflammatory agents such as salicylates and phenylbutazone, which irritate the mucosa (84,102). Infrequently encountered, but productive of a very severe form of acute gastritis is the accidental or suicidal ingestion of such corrosive agents as acids and alkalis. Spicy foods and excessively hot or cold foods are also suspected as possible pathogenetic factors, (84,102).

Overwhelming hemorrhage can result from a large consumption of any irritant. The lesions responsible for such bleeding are erosions which are initiated by the exfoliative effect of the irritants on the gastric surface epithelial cells (102). Although we speak of hemorrhagic gastritis, the anatomical process is primarily ulcerative

and only secondarily inflammatory.

It is apparent from the above discussion that the use of the term "acute gastritis" (whether erosive or hemorrhagic) should be restricted to the effect of exogenous irritants of the gastric mucosa. However, Skillman and Silen (72) make no distinction between "acute gastritis" and "acute ulcers" because they contend that the former term simply defines the background gastric mucosal lesions upon which is superimposed acute erosions or ulcers.

1.3.6 INCIDENCE OF STRESS ULCER

Adequate estimation of the frequency of occurrence of stress ulceration presents an enormous problem. Wide variation in incidence is reported in the literature. because of difference in:

- criteria for diagnosing stress ulcer
- population at risk
- length of follow up period

Before the introduction of the fiberoptic gastroscope in the early 1960's, the diagnosis of "stress ulcer" was made only at surgery or at autopsy. In the 1950's and early 1960's, stress ulceration was held responsible for bleeding in 1-2% of cases of gastroduodenal hemorrhage. The actual incidence remained unknown, and

retrospective clinical and postmortem studies were limited because ulceration, hemorrhage, and perforation represent only the most advanced stages of this pathologic process. Acute gastroduodenal lesions that healed uneventfully were undiagnosed, whereas chronic peptic ulcers that were reactivated after stressful situations such as burns were misdiagnosed as stress ulcers (103).

To determine the actual incidence and the natural history of this acute gastroduodenal disease, early and serial endoscopic examination of the stomach and duodenum should be undertaken. With the introduction of the fiberoptic gastroscope, therefore, there appears to have been an increase in the incidence of this disease phenomenon (79,91,104,105). The fiberoptic gastroscope has helped us to realize how common this condition is, because, now, even minimal mucosal changes can be detected gastroscopically (78,87). Lucas et al (90) showed that patients subjected to shock and hemorrhage all developed gastroscopically detectable mucosal lesions, although most had no clinical signs of stress ulcers and many did not subsequently develop hemorrhage. Only 8 of 150 severely injured patients in a Surgical Intensive Care Unit had clinical signs of

stress ulcers (57). The two studies cited above suggest that stress ulceration occurs more often than it is detected clinically, and unless one uses the endoscope, the diagnosis will be missed. In a large series of patients who were subjected to vigorous diagnostic procedures including gastroscopy, approximately a third had stress ulcers (106).

Walt (87) argues that since it is very common for people who have undergone major operations to have superficial mucosal changes which rapidly revert to normal within a few days without going on to stress ulceration, it is necessary to make a distinction between such cases and stress ulceration. Menguy (87) however, contends that such changes can be considered if it is established that even such minimal changes in the gastric mucosa as edema and petechiae will be included in stress ulceration since the early mucosal changes can evolve into obvious erosions and ulcers.

Enormous variation in incidence is also reported because of differences in population at risk. A Mayo Clinic retrospective study found an incidence of post-operative stress ulceration in all their general surgical cases of about 0.3% (107), a very low in cidence. But, this was established taking into account all operations including hernia repairs and vein

strippings which would not be expected to be complicated by stress ulceration. Stress ulcers are more likely to follow cardiovascular, thoracic, neurosurgical, or abdominal operations than less extensive procedures (87).

The length of the follow up period is quite important in any meaningful estimation of the incidence of stress ulceration. Reports from a military evacuation hospital during the Vietnam war gave only a 0.4-3% rate of stress ulcers in combat injuries (56,108). Such figures are skewed because of the limited period of observation dictated by evacuation policies.

With these basic reservations in mind, we can proceed to consider some of the figures that have been quoted in the literature for the incidence rate of stress ulceration.

1.3.6.1 General

Palmer (109) reported a general incidence of 22% in 1952, and in 1964, an incidence of 26% was quoted by Katz et al (106). In series where endoscopy was not utilized, the incidence of acute gastric lesions was noted to be 2% or less (43).

1.3.6.2 Burns

Several investigators have suggested that the incidence of acute gastroduodenal disease after thermal injury, is greater than that reported (52,110). Retrospective surveys relying on clinically obvious

complications such as hemorrhage or perforation identify acute gastric disease in less than 30% of thermally injured patients (23,49,52,56).

Gastroduodenoscopy indicates that this disease is much more common in the immediate postburn period than appreciated clinically. Czaja et al (78) determined the incidence in 32 adult patients with burns using early and serial gastroduodenoscopies. Gastric erosions were present in 86% of patients with burns of 50% or more of total body surface. McAlhany et al (111) reported an incidence of 78% when they did gastroscopies in patients within 5 days after thermal injury.

1.3.6.3 Central Nervous System Lesions

More than 37% of patients with acute gastroduodenal ulceration in a large autopsy series had associated central nervous system lesions (112). In a study of autopsy cases, Dalgaard (113) reported an 18.3% incidence of acute ulceration in patients with intracranial infection. Sibily (114) found that almost all patients with head injury who were gastroscoped daily from the day of injury to about 20 days had mucosal changes consisting of edema and petechiae within 24 hours of the injury. About 40% developed erosions and 10% developed overt bleeding.

1.3.6.4 Trauma and Sepsis

In a hospital in which severe injury and sepsis were encountered frequently, stress ulcers were found in 6.2% of autopsies (38). Fletcher and Harkins (41) had found an incidence of 1-2% in a series of 4102 autopsies, and Bogardus and Gustafson (115) reported that 4.9% of 566 consecutive autopsies showed gastric or duodenal ulceration secondary to other disease processes.

During a 5 year period, 88 patients with acute gastroduodenal ulceration after trauma, surgery or severe illness were treated at Baylor University Medical Center in Dallas, Texas. During the period, 1500 patients were admitted for ulcer disease, this indicating that 6% of all patients with ulcers had acute ulcers secondary to stress (39).

In a review of 166 cases, Crawford et al (91) found 43 patients who had stress ulcers. Thirty-three (76%) of these had the diagnosis proved by autopsy or surgery. Skillman and Silen (70) reported a 5% incidence of acute multiple gastric ulcers occurring in 150 consecutive patients admitted to their Intensive Care Unit.

No hard figures are available, but some authors seem to have the impression that there has been a reduction in the incidence of stress ulceration in the last 4 or 5 years (87,116). These authors seem to think that the

reduction may be due to better care that is available to the critically ill patient who is admitted to the Intensive Care Unit. However, work done by Walt (87) and by Silen (87) seem to indicate that if one looks for mucosal changes endoscopically, one will find them in the stomach of all patients who have undergone significant surgical operations. What may be falling, then, is the incidence of overt bleeding or perforation, possibly because of better post-operative care (87).

1.3.7 CLINICAL SIGNIFICANCE OF STRESS ULCER

"Few potentially lethal complications of major trauma and surgery appear at the sickbed with as little forewarning as the clinical signs of acute gastroduodenal ulceration" (117). Superimposed upon a deranged metabolic response in a critically ill patient, massive hemorrhage or ulcer perforation represents an urgent and difficult therapeutic problem with a high mortality.

Fogelman and Garvey (39) report that 51 of 88 patients who had acute gastroduodenal ulceration died, a mortality of 58%. Death in patients was due to inadequate therapy for hemorrhage and perforation. Skillman et al (70) recorded a survival rate of only 12.5% in patients who had acute ulcers manifested by hemorrhage and other complications such as respiratory failure, renal failure, or sepsis.

It is reported (70) that in some large metropolitan hospitals, stress ulcers are the most common cause of upper gastrointestinal bleeding and mortality rates are about 30%.

Many patients with gastroscopically detectable lesions do not subsequently develop hemorrhage (or perforation). It can therefore be speculated that in the vast majority of patients, the gastric lesions observed heal rapidly unless continued shock or sepsis are present (85).

Although the mortality of stress ulceration is high when hemorrhage intervenes, the lethal course should not be accepted as inevitable. It is important that the pathologic progress of the disease be interrupted before it culminates in massive hemorrhage. The work reported in this thesis is an effort in that direction.

1.3.8 THE STOMACH

In order to appreciate fully the pathophysiology of stress ulceration, a look at the normal anatomy and physiology of the stomach is warranted.

1.3.8.1 Gastric mucosa (118-121)

The gastric mucosa is characterized by invaginations which divide the mucosal surface into a mosaic of elevated

areas varying in shape. When viewed under magnification with a lens, these areas reveal several delicate ledges and depressions, the latter known as gastric pits or foveolae. In the depth of these pits, the width and length of which vary, the glands of the stomach open.

The lining epithelium which covers the surface and extends down into the pits is composed of tall columnar cells which secrete mucus. The glands of the stomach are simple, tubular glands which open into the bottom of the pits. Three kinds of glands may be distinguished.

a) Cardiac glands - are confined to a narrow zone 0.5 to 4 cms. in width around the cardiac orifice. They are coiled and lined by mucus-producing cells.

b) Fundic glands - are frequently called gastric glands because they are the most characteristic of the stomach and occur throughout the fundus or body. They are fairly straight, simply branched tubules, with narrow lumen reaching down almost to the muscularis mucosae. They are lined by three types of cells:

   (i) the mucus neck cells which are present in the neck of the gland and differ from the cells of the surface epithelium in that their mucigen granules have slightly different staining qualities and their nuclei tend to be flattened or concave (rather than

oval) at the base of the cells. The neck cells provide a transition between the lining epithelium of the foveolae and the secreting part of the glands.

(ii) the cells of the second type, the chief or zymogen cells, extend down to the bottom of the glands and resemble the neck cells but are slightly more basophilic and have a prominent basal striation. They are thought to produce pepsinogen, the precursor of pepsin.

(iii) the cells of the third type, the parietal cells, are the most characteristic cells in the gastric glands. Their name originated from the fact that they are pushed back against the basement membrane away from the lumen to which they connect by extracellular capillaries stemming from intracellular canaliculi. They do not form a continuous layer, but are scattered all along the walls of the glands, separated by several chief cells and usually overlapped by parts of the neighboring chief cells which intervene between them and the internal surface of the gland. They are 4 or 5 times as large as chief cells, have a granular, intensely acidophilic cytoplasm, and are the source of the hydrochloric acid in the gastric juice.

c) Pyloric glands - are located in the pyloric region and spread into a transitional zone in which both gastric and pyloric glands are found and which extends diagonally and distally from the lesser to the greater curvature. These glands are lined by a single type of cell, which resembles the mucous neck cells of the fundic glands.

1.3.8.2 Origin and Composition of Gastric Juice (119,120,122,123)

The stomach is both a storage and a digestive organ. It is a digestive organ by virtue of its secretions and its mechanical activity, which mixes food and secretions.

The digestive secretion of the stomach (gastric juice) contains mainly:

- hydrochloric acid
- pepsin
- lipase
- mucus
- water and ions (Na^+ K^+ HCO_3^- Cl^- $SO_4^{=}$ $PO_4^{=}$)
- intrinsic factor

Gastric juice is the product of secretion by the surface epithelium and the various gastric glands. The composition of the juice varies depending on the individual contributions of the various secreting cells. The acidity of the juice is due to the hydrochloric acid. The phosphates and sulphates are present in such low concentrations that their possible contribution to the acidity is negligible.

It is convenient to think of gastric juice as a mixture of secretions from parietal and non-parietal cells. Hydrochloric acid is secreted by the parietal cells whilst secretions elaborated by the cells of the cardiac and pyloric glands and the mucous neck cells and chief cells of the gastric glands form the non-parietal component.

It has been estimated that the volume of gastric juice secreted by man in a 24-hour period amounts to 1200-1500 ml. The amount will vary depending upon the diet and other stimuli provoking gastric secretion.

1.3.8.3 Hydrochloric Acid

Since no procedure has yet been devised for collecting parietal secretions unmixed with non-parietal secretions, the composition of pure parietal secretion can be arrived at only indirectly by inference from the composition of the mixed juice. The evidence indicates that pure parietal secretion consists of HCl with a concentration of between 140-170 mEq/L. Over a wide range, the composition of parietal secretion remains constant, and is practically independent of the rate of secretion, nature of stimulus, or strength of the stimulus which evokes its flow. The concentration of acid, however, increases with increasing

rates of secretion up to a maximum of about 170 mEq/L (i.e. the higher the secretory rate, the greater the acidity and the lower the pH).

1.3.8.4 Mechanism of Hydrochloric Acid Secretion (119,120, 122-127,130)

The precise mechanism(s) involved in the secretion of HCl is still unknown. Various theories have been proposed concerning the manner in which the gastric mucosa forms and secretes HCl. The following facts, however, have been established, and taken together they point in a general way the processes which may be involved in the secretion of HCl.

a) There is general agreement on the fact that parietal cells are responsible for the production of HCl and for most of the water of the juice. Among the several observations which indicate the parietal cell origin of HCl is the direct correlation between the number of parietal cells and the acidity and total chloride content of gastric juice.

b) The secretion of HCl involves expenditure of energy. One estimate is that the secretion of 170 mEq/L acid requires the expenditure of 1532 cal/L of juice secreted. This energy is derived from oxidative processes in the mucosal cells, probably oxidation of substances such as glucose, lactate, pyruvate, fructose

and acetoacetate. The oxidative processes generate high energy phosphate bonds (ATP). The involvement of ATP is supported by the fact that dinitrophenol, which makes high energy phosphate bonds unavailable for work, inhibits acid secretion. ATPase has been found in large quantities in the gastric mucosa.

c) For every H ion produced, a HCO_3 ion is released into the interstitial fluid and ultimately into the blood by an unknown process. This requires carbon dioxide (CO_2) which may be derived from the matabolism of the parietal cell itself or from the blood. The need for CO_2 arises from the fact that whatever the reacting system may be, removal of H ion results in accumulation of an excess of hydroxyl (OH) ions. If these were not neutralized, the resulting alkalinity would soon destroy the secreting cells. The discharge of HCO_3 ions into the blood explains the so-called post-prandial alkaline tide seen in the urine.

d) Parietal cells have a high concentration of carbonic anhydrase (128) which participates in the mechanism of acid secretion. Its apparent role is the replenishment of the H ion in the parietal cell through its action in catalyzing the hydration of CO_2 to produce carbonic acid (H_2CO_3) that is utilized in neutralizing OH ion

produced during secretion. The secretion of HCl is is inhibited by acetazolamide (Diamox) which is an inhibitor of carbonic anhydrase (129).

A postulated mechanism for secretion of HCl is depicted in Fig 1. Carbon dioxide, either formed during metabolism in the cell or entering the cell from the blood, combines with water under the influence of carbonic anhydrase to form carbonic acid. This in turn dissociates into HCO_3 ion and H ion. By some yet unknown active transport process, the H ion is transported through the wall of the canaliculus of the parietal cell and into the lumen. The HCO_3 ion, in turn, diffuses backward into the blood. Chloride ion, is actively transported from the blood into the canaliculi, though the basic process for this, too, is unknown. In some way that is not understood, the secretion of Cl ions is coupled with the secretion of H ion so that the two kinds of ions are secreted in equal quantities. Finally, water passes into the canaliculi by passive diffusion.

1.3.8.5 Pepsin and other Enzymes

Pepsin is the principal proteolytic enzyme in the gastric juice. It is stored in its cell of origin (chief cell) as an inactive precursor or zymogen (pepsinogen). The enzyme becomes active only in acid medium (activation is optimal at pH 2). At a pH 5 the action of pepsin is

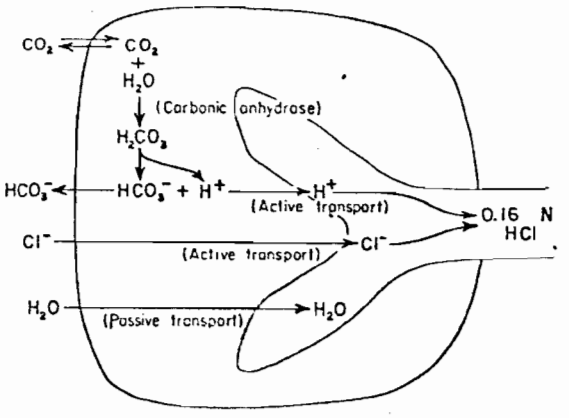

Fig. 1 Postulated mechanism for the secretion of hydrochloric acid (from Guyton A.C. (122))

almost abolished. Pepsin digests protein by attacking those peptide linkages in which the amino groups are attached to aromatic amino acids. The products of protein digestion by pepsin consist mainly of proteoses and peptones and relatively few amino acids and polypeptides. Pepsin is constantly present in acid gastric juice and is probably secreted continuously. During inter-digestive periods, pepsin is stored in the chief cells. The major stimulus for pepsin secretion is vagal impulses.

Small quantities of other enzymes are also secreted in the gastric juice, including gastric lipase, gastric amylase, cathepsin, gastricsin and rennin.

1.3.8.6 Mucus

Mucus that is present in the gastric juice may originate from three sources:

a) the cardiac gland cells
b) the surface epithelial cells
c) the neck cells of gastric and pyloric glands

The latter two groups of cells secrete the largest amounts of mucus. The process or processes of synthesis, secretion, and hydration of gastric mucus remain to be elucidated.

Gastric mucus occurs in two forms: visible and soluble mucus. Visible mucus is the portion of the total mucus that is insoluble in HCl, that forms shreds and clumps when acidified, that consists of a complex gel of mucinous substances and enzymes, and that is secreted by the surface epithelial cells. It is thick, and viscous and forms a transparent coating over the surface of the gastric mucosa. Visible mucus may be separated from the gastric juice by filtration or centrifugation. Soluble or dissolved mucus is that portion of gastric mucus which becomes liquid when acidification of gastric mucus occurs. It contains several substances known as mucins. Mucin is a glycoprotein and its carbohydrate moiety includes galactose, glucosamine, galactosamine, fucose, sialic acid, and mannose. Mucin is produced by the mucous neck cells.

The secretion of visible mucus is stimulated by vagal stimulation and by any irritation of the gastric mucosa.

1.3.9 REGULATION OF GASTRIC SECRETION

Gastric secretion is regulated by both neural and hormonal mechanisms. Neural regulation is effected through the parasympathetic fibers of the vagus nerves as well as

through local myenteric plexus reflexes. Sympathetic pathways regulate gastric secretion indirectly through their control over vasomotor mechanisms and blood flow to the mucosa. Hormonal regulation takes place by means of gastrin which is released from the gastric antrum and it stimulates gastric secretion. Certain hormones (secretin and cholecystokinin) released from the mucosa of the duodenum inhibit gastric secretion.

Gastric secretion occurs in three separate phases which greatly overlap each other. These phases are:

- cephalic phase
- gastric phase
- intestinal phase

1.3.9.1 Cephalic Phase

The cephalic phase results from the sight, smell, thought, or taste of food, and the greater the appetite, the more intense is the stimulation. Neurogenic signals causing the cephalic phase of secretion can originate in the cerebral cortex or in the appetite centers of the amygdala or hypothalamus. They are transmitted through the dorsal motor nuclei of the vagi to the stomach. The cephalic phase of secretion is therefore abolished by bilateral section of the vagus nerves.

Vagal signals to the gastric glands cause secretion of vast quantities of both pepsin and acid. Also, vagal signals to the pyloric glands, the cardiac glands, and the mucous neck cells of the gastric glands cause some increase in secretion of mucus as well. Another effect of vagal stimulation is to cause the antral mucosa to secrete the hormone gastrin. This phase of secretion accounts for about a tenth of the gastric secretion which normally occurs during eating.

1.3.9.2 Gastric Phase

The introduction of food into the stomach excites the gastrin mechanism, which in turn causes secretion of gastric juice that continues throughout the period that the food remains in the stomach. The presence of food in the stomach also causes:

a) local reflexes in the myenteric plexus of the stomach
b) vasovagal reflexes that pass all the way to the brain stem and back to the stomach

Both of these reflexes cause parasympathetic stimulation of the gastric glands and add to the secretion caused by the gastric mechanism.

In addition to the chemical substances in food, such as meat extracts and products of protein digestion, which excite gastric secretion when present in the antrum, alcohol and mechanical stimulation of the pyloric protein are also highly effective stimuli.

Gastrin is released from the pyloric mucosa by local mechanical and chemical stimuli acting through a cholinergic nervous mechanism that comprises the myenteric plexus and its local and central connections. Neither gastrin alone, nor vagal stimulation alone, can cause maximal stimulation of the gastric glands to secrete HCl. Abundant secretion is obtainable only when neural and hormonal stimuli act simultaneously.

The gastric phase of secretion accounts for more than two-thirds of the total gastric secretion associated with eating a meal and therefore, accounts for most of the total daily gastric secretion. Hormonally produced juice from the intact innervated stomach, unlike cephalic phase or vagal juice, is high in acid and low in pepsin and mucin. It is never pepsin-free and, in fact, the pepsin rises with the acidity but it is always low.

1.3.9.3 Intestinal Phase

The presence of certain food substances in the upper small intestine also stimulates the stomach to secrete small amount of gastric juice. The following substances have been observed to excite gastric secretion when placed in the upper small intestine: water, meat extract, and other products of protein digestion, alcohol etc. The secretory

activity of the intestinal phase is much less than that of the cephalic and gastric phases.

Some other hormones released from the mucosa of the duodenum play minor roles in causing secretion of gastric juice. For instance, under certain conditions, secretin and cholecystokinin can cause increased secretion of pepsin by the gastric gland in much the same way that gastrin acts on gastric glands. However, under other conditions, both hormones have significant inhibitory effect rather than excitatory effects on gastric secretion.

Though chyme stimulates small amount of gastric secretion during the intestinal phase of secretion, it usually inhibits secretion in two ways which involve neural and hormonal mechanisms.

a) Appropriate duodenal stimulation activates a feedback mechanism, the enterogastric reflex, transmitted through the myenteric plexus, the sympathetic nerves and the vagus nerves, that cause a decrease in gastric secretion as well as in motility. This inhibitory reflex mechanism is elicited by excessive activity, fat digesta, distension and hyper- or hypo-osmotic solutions of various sorts (sugar, peptones etc.).

b) The presence of acid, fat, protein breakdown products, and hyper- or hypo-osmotic fluids in the small intestine cause the release of several intestinal hormones. Two

of these have been identified as secretin and cholecystokinin (CCK). Secretin depresses gastric motility and acid secretion but it stimulates pepsin secretion. CCK depresses motility, pepsin and acid secretion.

The duodenum, therefore, acts as a regulator of gastric emptying as well as of gastric secretion.

1.3.9.4 Secretion During the Interdigestive Period

Gastric secretion elaborated during the interdigestive period has often been termed "basal secretion", "interdigestive secretion" or "nocturnal secretion". The interdigestive secretion is defined by Lim (131) as "the juice secreted by the stomach in the absence of all intentional and avoidable stimulation".

In both man and dog, the interdigestive secretion of HCl apparently occurs in an intermittent or periodic fashion. The causes of such secretion are not known but the fact that this phase of secretion in fasting patients is inhibited following complete surgical vagotomy suggests a neural pathway. A subcutaneous autotransplanted gastric pouch in the dog, devoid of all extrinsic nerve during a fast will secrete acid intermittently. This indicates that the stimuli for secretion might also be hormonal in nature.

1.3.10 THE PYLORUS

The pylorus, situated at the gastroduodenal junction, is an important part of the mechanism by which gastric emptying is regulated and by which duodenogastric reflux is prevented. The pylorus can be identified as an area of thickened circular muscle. Its gross appearance suggests that it might function as a sphincter; and the recent observation (132) that the pylorus has inhibitory innervation is consistent with sphincteric function.

Sphincters such as the lower esophageal and anal sphincters are demonstrable by manometry as zones of tonically elevated pressure, but whether the pylorus can reliably be defined in this manner is debatable. Studies designed to measure pyloric sphincteric activity (using different techniques) have yielded conflicting results.

Cannon (133) concluded from radiological observations on cats that the junctional zone functioned as a sphincter and was closed except when a peristaltic antral contraction approached. It has been demonstrated in the dog (134,135) that there is a zone of increased pressure at the gastroduodenal junction. Recent manometric studies on the human pylorus have demonstrated a high pressure zone at the gastroduodenal junction which exhibited relaxation with antral persistalis and increased with intraduodenal perfusion of hydrochloric acid (136,137).

The results of some earlier workers (138-140) had implied that the gastroduodenal region did not act as a sphincter because there was no sustained pressure elevation in the zone. They had concluded that the zone was usually open. This has been confirmed by more recent work by Kaye and associates (141) who showed that in contrast with the lower esophageal sphincter, the human pylorus is open for most of the time in fasting, healthy individuals. This conclusion is in agreement with endoscopic findings.

Kaye and his group (141) observed that the mechanism which prevents duodenogastric reflux and controls gastric emptying depends upon the integrated function of antrum, pylorus, and duodenum. They conclude, however, that this "...function is not dependent upon tonic closure of the pylorus". During antral motility, when a peristaltic wave reaches the pylorus, it closes. Thus, "the purpose of the pylorus is to prevent reflux into the stomach during duodenal cap systole (142)".

1.3.11 THE GASTRIC MUCOSAL BARRIER

In 1954, Hollander (143) postulated a two-component, self regenerating mucosal barrier to explain the protective action of mucus. The first component is a layer of viscous

mucus which covers the inner wall of the stomach; the second component is the layer of tall columnar cells immediately beneath this sheet of mucus, together with the lower columnar and cuboidal cells which line the crypts of the gastric glands.

It has been suggested that gastric mucus plays little more than a minor protective role against mechanical injury because H ions and many injurious agents such as aspirin, bile salts and alcohol traverse the mucous layer (85). Whether mucus is anything more than a lubricant remains unresolved. Its protective function has been attributed to its specialized characteristics: its adhesiveness, cohesiveness, adsorptive power and slight acid neutralizing capacity. The mucus sheet is removed continuously, but slowly. The layer however, is replenished with considerable speed under normal circumstances. If some disruptive agent induces a rate of removal so great that the rate of secretion is unable to keep pace with it, the mucous layer will be broken through and the underlying cellular layer comes into action as a second line of defense.

The cellular component of the barrier seems to be more important (85,144). The precise anatomic nature of the barrier, however, remains unknown. In 1967,

Davenport (145) suggested that the tight junction between cells represents the anatomic element of the barrier and that agents which disrupt the barrier do so by disrupting the tight junctions and allow H ions to enter via that route. It has however been shown that even severe damage of the surface mucus cells of mice with aspirin leaves the intercellular junctions intact (146). Work done by Silen and his group (144) have demonstrated that mucosal injury of surface cells of amphibian mucosa occurs with bile salts but the tight junctions and desmosomes remain undisturbed.

Since an anatomical description of the barrier has been difficult, Silen (144) has proposed that "the barrier is a dynamic phenomenon and not a specific anatomic gate, a dynamic phenomenon influenced by many factors, among them the secretory status, acid-base balance, and blood supply of the mucosa".

A large number of agents which disrupt the barrier are fat-soluble. It has therefore been inferred that the lipoprotein plasma membrane of the epithelial cells plays an important role in the integrity of the barrier (144).

1.3.11.1 Properties of the Barrier

Compared to the rest of the alimentary tract, the gastric mucosa is relatively impermeable to a solution

of pH less than 1 even though there is a H ion gradient of more than a million to one between the gastric lumen and the plasma (85).

When he instilled acid into the stomach of a cat, Teorell (147) noticed a gradual disappearance of H ions in the gastric lumen. He showed that there was only a negligible production of CO_2 in the lumen, therefore, the disappearance of luminal acid could not be due to neutralization by secreted HCO_3 ions. He proposed that there was continuous diffusion of acid from the lumen to the mucosa and he called the process "back diffusion". He also showed that "back diffusion" was linearly related to the intraluminal concentration of H ion (i.e. as the concentration of H ion within the lumen increases, the back diffusion of H ion increases). This has been confirmed by Silen and colleagues (144). It appears, therefore, that back diffusion is a true passive diffusion process dependent on the concentration gradient of H ions(144).

Reitemeier et al (148) found that sodium passes slowly, if at all, from the gastric lumen through the gastric mucosa of man. The barrier to the movement of sodium is abolished by instillation of several chemicals such as aspirin, alcohol, bile salts, urea and detergents (145,149-151). These "barrier breakers" reduce the ability

of the mucosa to contain H ions within the lumen and allow increased amounts of Na ions to enter the lumen from the interstitial tissue. Originally Teorell (147) proposed a direct exchange of H ions for Na ions but Altamirano (152) and Berkowitz and Janowitz (153) were unable to demonstrate a specific exchange mechanism for these two ions.

Davenport (154) stated that "Defense against acid is a function of the gastric mucosal barrier. The barrier may be defined as that property of the gastric mucosa which impeded diffusion of acid from the lumen into the mucosa and impedes diffusion of Na ion from the mucosal interstitial space into the lumen".

Severe injury to the mucosa can occur at a pH at which there is no back diffusion of H ion (144). For example, bile salts can cause mucosal damage at a pH of about 6. Excessive disappearance of luminal H ion can, therefore, no longer be considered a hallmark of gastric mucosal injury (144).

Increased luminal accumulation of Na ion has also been used as an indicator of the integrity of the barrier (59) but no consistent relationship has been established between the appearance of luminal Na ions and other parameters used to assess the barrier (155). The work of

Moody and Aldrete (155) shows that endotoxemia is associated with a large increase in the appearance of luminal Na without a significant disappearance of luminal H ions.

Using the transmucosal potential difference (PD) of the stomach as an indication of mucosal integrity, Geall et al. (157) found that aspirin, alcohol and bile salts cause a profound decrease in PD. The question has therefore been asked whether the maintenance of a normal PD across the mucosal membrane is a good measure of the intactness of the mucosal barrier. This is what Silen (144) has to say: "The PD represents the resultant of such a complex electromotive forces across both the surface and oxyntic cells (parietal cells) which can be influenced by so many and diverse factors, that it is tenuous on physiologic grounds to assume that a reduction in PD is equivalent to injury of the mucous membrane or the barrier. For example, it is well known that the onset of active secretion is associated with a definite reduction in PD, a circumstance which can hardly be regarded as an example of mucosal injury. Similarly, recent suggestions that agents such as H2 receptor antagonists (which increase the PD) 'tighten' the barrier are hardly tenable since the inhibition of active transport can by itself cause an increase in the PD".

1.3.12 PATHOPHYSIOLOGY OF GASTRIC MUCOSAL DAMAGE

The gastric mucosal barrier has been the subject of considerable investigation since its existence was postulated by Teorell (147). The nature of the normal barrier and the sequence of events that follows injury, are however, still poorly understood. While back-diffusion does occur under normal conditions (158), it increases significantly in the presence of agents that break the barrier and may result in mucosal damage (85,159). Normally, there is a direct linear relationship between intraluminal concentration of H ion and the amount of back diffusion, and this is maintained even when the mucosa is damaged. If sufficient H ion accumulates to overwhelm intracellular buffer systems, the cellular metabolic machinery might begin to fail, acid hydrolysis of intracellular protein might occur, and given a sufficiently severe or prolonged insult, cell lysis and death might eventuate (160). At the same time that there is increased disappearance of luminal H ions, there is increased luminal appearance of Na ion and protein with a concomitant fall in electrical potential difference (PD) and a reduction in mucosal resistance (161).

Back-diffusion of H ion enhances the development of stress ulcer. As H ion re-enters the gastric mucosa, it releases histamine and other vasoactive amines (150,162).

Histamine is released from mucosal mast cells (163) and there is direct evidence that during mucosal damage, histamine appears in the gastric mucosal interstitial fluid (164,165). Histamine also appears in the gastric venous blood and in the contents of stomachs from control animals (165). The released histamine and other vasoactive amines further augment capillary dilatation, edema and ischemia, abetting the development of erosions and ulcers (165,169).

The discovery of two types of histamine receptor by Black et al (170) has led to the suggestion that the vascular responses to histamine are mediated by both H-1 and H-2 receptors (171).

The mechanisms responsible for damage to the gastric mucosal barrier are at present poorly understood. Fiocca et al (172) and Moody and Davis (173) have shown that topical or intravenous histamine may increase the ionic permeability of the gastric mucosal barrier. Histamine released from gastric mucosa may affect mucosal blood vessels and change their permeability (174). This effect may be responsible for the increased ionic flux that occurs during mucosal damage. Histamine released results in more H ion secretion by parietal cells with a consequent increase in back-diffusion (150).

Large quantities of pepsin are released by most agents which cause disruption of the gastric mucosal barrier. (175-178)

Increased back-diffusion of H ion also causes an increase in local parasympathetic stimulation, with subsequent increases in acid secretion and the tone of the gastric musculature (150). The latter phenomenon may accentuate venous congestion, aggravate mucosal ischemia, and initiate bleeding (150). Superficial erosions and even discrete ulcerations occur, especially in the fundus and body of the stomach. This establishes a vicious cycle which enhances and perpetuates mucosal injury.

Electron micrographs reveal a constant pattern of cellular damage: clumped nuclear chromatin, swollen mitochondria, decreased cytoplasmic and nuclear density, cytoplasmic vacuolation, dilatation of the perinuclear spaces, and cellular swelling (160). Although these changes are most prominent in the surface epithelial cells, other cell types of the gastric glands may be similarly affected, given a sufficient degree of injury.

1.3.13 PATHOGENESIS OF STRESS ULCER

The pathogenesis of stress ulcer is a controversial subject; it is controversial partly because its causes are numerous; its etiology only poorly understood. The

accummulated evidence suggest a complex, multifactorial pathogenesis. Acute ulcers can result from:

a) pituitary-adrenal activity

b) hypothalamic-parasympathetic activity

c) changes in gastric mucosa

For the purpose of this presentation, the etiology of stress ulcer will be discussed under the above headings. Although the ulcers have different geneses, the common factor in all is stress.

1.3.13.1 Pituitary-Adrenal Activity

It has been postulated that stress-stimulated posterior hypothalmus might be the trigger for a sequence of events which culminate in the development of acute ulcers (190). The stress-stimulated posterior hypothalamus acts on the posterior pituitary gland, which in turn stimulates the release of epinephrine from the adrenal medulla. Epinephrine activates the production of corticotropin by the anterior pituitary, stimulating the adrenal cortex into releasing cortisone, which increases the gastric secretion of acid and pepsin.

Gray et al.(191) and Drye et al.(192) found that acute physical stress results in greater gastric acid production. Zubiran et al.(193) showed increased acid production in dogs given cortisone; this led them to

believe that cortisone has a direct stimulating effect on the gastric parietal cells. Davis and Zeller (194) found that steroid-induced ulcers in rheumatoid arthritis patients healed when cortisone treatment was stopped.

Adrenal steroids can cause stress ulceration because at high levels, these steroids sensitize the stomach to noxious influences and at the same time stimulate increased secretion of gastric acid (195).

Dragstedt and associates (196) expressed different opinions. They did not find increased HCl production in dogs given ACTH, cortisone and epinephrine. They commented that "if ulcerations are due to adrenocorticoid hormones released by injury, the effect is brought about by some mechanism other than simply hypersecretion of gastric juice".

1.3.13.2 Hypothalamic-Parasympathetic Activity

Acute gastric ulcerations have been noted following central nervous system infection, injury, or tumor by Cushing (8) and many other workers.

The first relationship was made between disturbances in the hypothalamic region and the formation of acute ulcers. Subsequently, it was noted that electrical stimulation of the anterior hypothalamus of monkeys caused prompt hypersecretion of gastric acid and this effect could

be abolished by vagotomy (197). Posterior hypothalamic stimulation was abolished by adrenalectomy.

Davis et al.(198) frequently encountered upper gastrointestinal hemorrhage and ulceration following neurosurgical procedures. However, there appeared to be no correlation between the histologic character of the central nervous system lesion and the occurrence of lesion in the gastrointestinal tract. They concluded that the central nervous system pathology was not a requisite for the gastrointestinal complications since they were encountered following such procedures as laminectomy and trigeminal neurectomy. In a group of 15 cats, they were unable to induce gastrointestinal tract pathology following discrete anterior and posterior hypothalamic destructive lesions. This led them to suggest that the gastrointestinal tract ulcerations and hemorrhages represent an extreme pathophysiologic response to the physical stress of surgery, wherever its location.

1.3.13.3 Mucosal Changes

Changes in the gastric mucosa are measured physiologically in terms of the gastric mucosal barrier to the movement of H and Na ions (159). The role of the gastric mucosal barrier in the pathogenesis of stress ulceration is however unclear.

Silen (144) asserts that "...the gastric mucosa will not ulcerate unless H ion is present in the mucosal solution (and that) the gastric mucosal barrier protects the mucosa against ulceration".

1.3.13.3.1 Role of H ion

It is generally accepted that H ions are a requisite for the genesis of stress ulceration and all experimental models for the disease require a low intraluminal pH.

Skillman et al (71) observed an increase in back-diffusion of H ions through rabbit gastric mucosa following a period of hypovolemic shock. They also reported the results of ionic flux measurement in critically ill patients. In 12 of 26 patients in an Intensive Care Unit, there was greater than normal back-diffusion with disruption of the gastric mucosal barrier.

The above findings are in marked contrast with those of Gerety and Guth (199) who were unable to demonstrate increased back-diffusion of H ion in rats subjected to restraint despite development of ulcers. Moody and Aldrete (155) also reported ulceration in shocked dogs in the absence of back-diffusion. It appears therefore, that back-diffusion may not be a prerequisite for ulceration.

Silen (144) explains that even though the absolute amount of luminal H ion which back diffuses to the mucosa may not be important for the development of stress ulcers, a critical concentration of H ion on the luminal surface is a requirement for ulcerogenesis. Mersereau and Hinchey (200) demonstrated that ulceration does not occur below a H ion of 25 mEq/L in the lumen during hemorrhagic shock. In an experiment with rabbits in which mucosal blood flow was diminished by luminal distention, back-diffusion of H ion was demonstrated and ulceration occured only in the presence of luminal acid (201).
Hydrochloric acid plays a key role in the genesis of stress ulcer and its presence within the gastric lumen appears to be mandatory for stress ulceration to occur (144). In healthy patients, only small amounts of H ion diffuse from the lumen into the blood, and almost all the secreted H ion can be aspirated (150). In patients with stress ulcer, however, the damaged mucosa is no longer an effective barrier to back diffusion of H ion, and less of H ion from the lumen to the blood may occur at an increased rate (71).

Studies in man have been done completely under uncontrolled conditions at varying times after the initial insult. Hypersecretion of acid has not been a consistent finding (71,103). Lucas and his co-workers (90) have

however claimed that hypersecretion is pathogenetically important and they have shown this in seriously ill patients.

1.3.13.3.2 Mucosal Microcirculation

The etiology of stress ulceration is intimately linked to changes in the mucosal microcirculation (202). It was Virchow (203) who first proposed the vascular embolic theory of stress ulceration. The theory has since been supported by Friesen's (46) observation that hemoconcentration with stasis, and low blood flow in Curling's ulcer patients, precede infarction and ulceration. He concluded that "the mucosa, lacking an adequate supply of oxygen, is increasingly susceptible to the erosive action of gastric acid-peptic secretions which are not necessarily increased in degree".

Although multiple factors have been proposed in the etiology of stress ulcers, a common factor assumed for most hypotheses has been gastric mucosa ischemia secondary to a decreased blood flow either throughout the stomach or limited to the proximal stomach (71,94,99,185,204,205). This assumption was proved experimentally by Skillman et al. (71) and Harjola and Sivula (205) who obtained significant decrease in blood flow to the proximal stomach in rabbits

subjected to hypotension induced by hemorrhage. Skillman et al. (71) observed marked back-diffusion of H ions into the gastric mucosa. This reached a maximum three hours after hemorrhage. There was also increased net flux of Na ions into the gastric lumen and the rabbits developed superficial fundic erosions. They attributed the stress ulceration to arteriovenous shunting of blood away from the mucosa. In a similar study in dogs, Sales et al. (206) obtained a decrease in gastric blood flow to all portions of the stomach.

Early endoscopic studies performed on injured patients who were in hypovolemic shock have also shown hypoperfusion of the proximal stomach. This was evidenced by irregular areas of pallor at the same sites that later contained superficial erosions (94).

In a study on dogs with hypovolemic shock, Ritchie and Fischer (207) noticed increased H ion back-diffusion during the shock period. Even though the absolute H ion back-diffusion may not be significantly altered in many species by ischemia (156), "the ability to remove a normally harmless amount of H ion is clearly impaired" (144).

The role of hypotension and gastric ischemia in the disruption of the gastric mucosal barrier have recently been questioned by work done by Davenport and Barr (208). Using Heidenhain pouch preparations in conscious dogs,

these authors produced mucosal ischemia with vasopressin, norepinephrine and hemorrhage. They could however not show a break in the barrier when they instilled acid test solutions into the pouches. It is not known whether mucosal ischemia caused by vasoconstriction differed quantitatively from that induced by trauma or hypotension.

The effects of hemorrhagic shock on the gastric mucosal barrier in the intact stomach of subhuman primates has been studied by Ritchie (209). He measured the ionic fluxes of H and Na ions and the electrical PD and observed no change in PD, no significant increase in H ion back-diffusion, and no outpouring of Na ions into the lumen either during the three-hour hypotensive period or for the $2\frac{1}{2}$ hours following re-infusion of shed blood. The study suggested that in an animal phylogenetically close to man, there was no disruption of the barrier during or following hemorrhagic shock.

Whether diminution of mucosal blood flow can be the sole cause of disruption of the gastric mucosal barrier remains a debatable issue. Moody and Aldrete (156) showed that mucosal ulceration occured in association with ischemia, but only in the presence of acid. Hamza and DenBesten (210) working with dogs subjected to hemorrhage, found ulceration only in those animals in which the mucosa was exposed to

bile. Similarly, Guilbert et al.(204) found ulceration in dogs after hemorrhage only when the pylorus was allowed to remain patent, but not when the pylorus was occluded. This suggested that reflux of duodenal contents had an injurious effect in addition to that of ischemia.

1.3.13.3.3 Bile Reflux

Beaumont (211) first drew attention to the relation between bile in the stomach and disease when he wrote in a case report in 1833 that "bile is seldom found in the stomach except under peculiar circumstances. It is never found in the gastric cavity in a state of health, and it is only in certain morbid conditions that it is found there".

In 1914 Smith (212) illustrated in cats and dogs that when gastric mucosa was exposed to bile alone, there was no damage, but in the presence of acid, bile caused precipitation of surface mucus and necrotic areas appeared in the gastric epithelium. In 1951, Grant and associates (213) demonstrated that bile in contact with gastric mucosa caused severe cytolysis of surface cells. They also showed that it was bile salts that caused the cellular destruction.

The physiologic and morphologic consequence of topical application of bile salts to the gastric mucosa, particularly

to the acid-peptic secreting area, have been studied extensively both in vitro and in vivo. Topical bile acids increase the physical permeability of the gastric mucosa in both humans and experimental animals (214,216). The magnitude of the mucosal damage was found to be a significant linear function of the concentration of bile salts applied (217).

Active transport processes in the gastric mucosa have been found to be inhibited by topical application of bile acids (218). The precise locus of action of bile acids in this regard is unknown (160).

Although Smith (212) indicated that bile plus acid was more toxic on the gastric epithelium than bile alone, the relationship between bile and hydrochloric acid in the pathogenesis of acute gastric erosions has only recently been investigated. In explants of antrum placed within lucite chambers, Himal and colleagues (219) demonstrated that bile alone did not cause erosions. Bile plus hydrochloric acid, however, caused increased net H and Na ion flux and led to the development of acute erosions.

Even though acute gastric erosions occur secondary to bile or duodenal reflux in animals, these erosions do not occur in normotensive animals (220). Decreased blood flow in the gastric mucosa appears to be an important factor in the mechanism of erosion (204,210).

Duodenogastric reflux of bile into the stomach underlines the importance of the pyloric sphincter. Reflux of bile and pancreatic juice into the stomach, associated with adynamic ileus, will produce a detrimental effect.

1.3.13.3.4 Mucosal Energy

In 1974, Menguy and co-workers (221-224) proposed that stress ulceration complicating hemorrhagic shock results from a severe deficit of gastric mucosal energy. They reported the following experimental evidence to support their hypothesis:

a) The appearance of gastric mucosal erosion in shocked rats is associated with a reduction in ATP levels in the gastric mucosa.

b) The breakdown of high-energy phosphate during hemorrhagic shock in rabbits is significantly more rapid in regions of the gastric mucosa characteristically involved by stress ulceration (i.e. fundus and body) than in antral mucosa, which is usually spared. This provides a possible explanation as to why stress ulcers may be more common in the fundic region (70,90). The amount of acid in the mucosa in relation to the state of mucosal energy production may therefore be a critical determinant

of whether or not ulceration will occur.

c) Fasting increased both the rate of breakdown of high-energy phosphate in the mucosa and the severity of ulceration.

They reasoned that if the hypothesis was correct, an agent known to augment the severity of stress ulceration would be expected to have an adverse effect on gastric mucosal metabolism. They have subsequently showed that the introduction of taurocholic acid into the stomachs of rabbits subjected to hemorrhagic shock increases the severity of the shock-induced gastric mucosal energy depletion (225), a finding that is in agreement with the energy deficit hypothesis of stress ulceration that they have proposed. They found that taurocholic acid uncouples oxidative phosphorylation in gastric mucosal mitochondria and inhibits gastric mucosal ATPase; an effect which can reduce the efficiency with which mitochondria synthesize ATP and explains the greater mucosal energy deficit when shock is accompanied by the presence of added bile salt in the stomach.

The foregoing discussion underlines the fact that it is impossible to explain the pathogenesis of stress ulcer formation with a single factor. Gastric mucosal ischemia, intraluminal acidity and H ion back-diffusion, the ability

of the gastric mucosa to tolerate the H ion load, bile reflux into the stomach and reduction of the gastric mucosal cellular content of ATP are probably all important determinants of the development of stress ulcers in the critically ill patient. The pathogenesis of stress ulcer is therefore multifactorial.

1.3.14 ROLE OF SEPSIS

Sepsis, ranging from urinary tract infection to peritonitis, has been associated with stress ulceration. Adams (179) was the first to document this association. The relationship was further emphasized by Billroth (24) in Curling's ulcer patients. In 1893, Perry and Shaw (34) compiled a series of 21 cases of acute systemic and localized infection associated with acute gastroduodenal ulcers. Harkins (23) in a review of 24 cases of Curling's ulcers pointed to the presence of sepsis in all patients. More recent work by Fogelman and Garvey (39) and O'Neill et al. (49) have confirmed this association.

In a report of 35 cases of post operative gastro-intestinal hemorrhage, Beil et al. (44) found that infection played a significant role in 26 (74%). Moncrief et al. (50) noted sepsis in 74 of 103 cases of Curling's ulcers. Sepsis increases both the frequency of stress ulceration

(117) and associated mortality rates (100,119). The progression of mucosal damage is closely related to the duration of sepsis. Ulceration becomes worse as sepsis is prolonged and there is dramatic improvement when infection and septicemia are eradicated (180).

Among patients developing stress ulcer in association with sepsis, the offending organisms are usually gram negative bacteria, and the single most common species isolated is E. Coli. Some infections may be caused by various members of the Enterobacter-Klebsiella group. Coagulase-positive staphylococci are usually cultured in the majority of gram positive infections (181).

The association between sepsis and acute gastric ulceration has been investigated in experimental animals. Lebert (182) noted gastric ulceration in a dog after intravenous injection of pus. Later, Rosenow (183) produced gastroduodenal ulceration in 60% of animals who had received intravenous injection of streptococci. In 1945, Hartmann (184) studied acute ulceration in penicillin-treated experimental burns in dogs. He reported a 77.7% incidence of ulceration in control dogs while ulceration developed in only 23% of the animals treated with penicillin.

Even though there is enough clinical and experimental evidence to prove that sepsis abets acute gastroduodenal

ulceration, it is still unclear whether sepsis is just a coexistent phenomenon or an etiologic factor. It has been difficult to explain the exact nature of the association.

The development of stress ulcers in septic patients has been generally attributed to mucosal ischemia as a result of decreased blood flow. Endotoxic shock has been used to induce gastric erosions. Richardson et al.(185) demonstrated that acute gastric erosions developed in pigs made septic by endotoxin administration were associated with a decrease in gastric mucosal flow to the body and fundus of the stomach. Endotoxin tends to produce a hypodynamic state with decreased blood flow and increased resistance. The observations of Richardson and his colleagues cannot be extrapolated to septic man because sepsis in man characteristically produces a hyperdynamic state with increased cardiac output and decreased peripheral resistance (186,187).

The mechanism of lesion formation caused by sepsis in acute gastric ulceration may be favored by ischemia of the gastric mucosa, as it is with acute ulcers of other origins (180). Early endoscopic examination in septic patients have often shown a pale ischemic and marbled mucosa in association with acute erosions, and

this supports the ischemia hypothesis. Other factors which appear to be important in the pathogenesis of sepsis related stress ulceration are the reaction to stress, fever, bacterial toxins and gastric secretory response to stress. Fever has been shown to produce a reduction in acid output (188). While studying gastric secretory responses to stress in dogs, Howe et al. (189) noted an increase in acid output after inadvertent wound infection. Their subsequent studies indicate that a clean surgical wound is without effect on gastric secretion, but a deliberately infected wound results in a significant rise in acid output.

The causal relationship between shock, operative and accidental trauma, and sepsis remains to be resolved. Sepsis added to a traumatic episode is associated with a much more florid type of acute gastric erosion.

1.3.15 EXPERIMENTAL MODELS OF STRESS ULCER

The study of the pathogenesis of stress ulcer has been hampered by the lack of a suitable experimental model. Several animal models have been described and used in the investigation of acute gastric ulcers. The following is a brief review of only a few of the more commonly used models.

1.3.15.1 Restraint Models

The restraint model was introduced by Rossi and associates (226) and it involved immobilizing the rat for a period of 24-48 hours. Brodie and Hanson (227) confirmed the efficacy of restraint as a technique for producing experimental stress ulcers in the mouse, and guinea pig, but not in the rabbit and monkey. The efficiency of this technique is increased by adjuvant stresses imposed on the animal such as starvation, changes in ambient temperature and the use of drugs.

The immobilization technique applied vary with investigators and include wrapping the animal in plaster of Paris bandages (228), taping the animal to a board (229), folding the animal in a wire screen (227) or placing the animal in a small cage or perforated metal tube (230). All these procedures have the same purpose: that of restricting the animals' movements; and the tighter the restriction, the severer the stress and the higher the incidence of gastric ulceration.

The restraint model is a rapid and inexpensive method for the study of some of the fundamental factors which influence the genesis of stress ulcers. No surgical intervention is required. Its main disadvantage, however, is that immobilization as a cause of ulcers in rats does not mimic the clinical situation in man where there is no restraint on the patient.

1.3.15.2 Neurogenic Models

Experiments have shown that acute gastric ulcers can be produced by lesions of the hypothalamus and brain stem. Electrical stimulation of the hypothalamus is known to affect gastric acid secretion (197). Gastric hemorrhage and erosions in rabbits (231) and in cats (232) have been caused by stimulating the lateral hypothalamus and the ventromedial nucleus of the hypothalamus.

Other studies reported in the literature (104) appear to confirm that gastric erosions and bleeding can be induced by lesions in either the anterior or posterior hypothalamus. The mechanisms involved, however, are still not clear. The parasympathetics appear to be involved in the causation of lesions of anterior hypothalamic origin (104).

1.3.15.3 Burn Models

It has been shown that a 40% burn in the rat will produce gastric ulcers similar to other forms of stress (233). This has a close analogy to gastric damage or Curling's ulcer produced in human burn victims.

Hartmann (184) produced third degree burns over 50-65% of the body surface of rats while the animals were under morphine and ether anesthesia. In 1950,

Friesen made a study of Curling's ulcers in which he used the dog as a model (46).

For reproducibility sake, a standard method of experimental burns in the animal must be found. In most experiments, burns are inflicted on the anesthetized animal by immersion in water at 100°C. The body surface area and period of exposure is standardized for the experiment. Immersion has been found to be a satisfactory method of producing burns in that a) accurate standardization is possible, b) the tissue is not broken at the time of the burn, and, c) no added factor of pressure on the tissue is present (46).

Since most cases of Curling's ulcer were associated with sepsis, the latter was considered as an important pre-requisite for ulcerogenesis (96,184). However, since ulcers can occur within 24 hours after scalding (233) and since germ-free animals have been found just as susceptible to burn ulcers as ordinary animals (234), it can be concluded that infection is not a pre-requisite for ulceration.

1.3.15.4 Hemorrhagic Shock Models

Shock and hypotension have been closely associated with acute upper gastrointestinal ulceration and hemorrhage in patients suffering extensive trauma or undergoing

operation (32,33,40-45,54-58), experimental hypovolemia markedly enhances ulcer formation in the restraint model (235).

Even though hemorrhage alone can cause acute ulceration in the stomach (200), the incidence of ulcer is increased when the gastric mucosa is bathed in acid solutions (71) or solutions of bile salts (210).

Sublethal hemorrhagic shock has been used to induce stress ulcers in rats (200), rabbits (71,205), dogs (210) and piglets (99).

The evolution of ulcers has been consistently described as starting with uniform blanching of the glandular mucosa immediately after induction of hemorrhage. With stabilization of the blood pressure at a hypotensive level, some color returned, leaving patchy areas of blanching which subsequently became hemorrhagic and ulcerated (104). Most of the lesions occured in the fundus (99).

1.3.15.5 Gastric Chambers

Ex vivo gastric chamber preparations have been used to study acute gastric erosions. Mersereau and Hinchey (200) used the technique to investigate the effects of different H ion concentrations on the production of acute

gastric mucosal lesions in normotensive and hypotensive rats and Himal et al. (236) have studied the effect of aspirin on ionic movement in explants of canine stomachs.

The technique is simple and inexpensive and allows continuous observation and timing of the sequence of events in the evolution of mucosal lesions. It is possible to control the concentration of agents in contact with the mucosa.

1.3.15.6 Sepsis Models

The sepsis models have a long history. As early as 1857, Lebert (182) produced experimental acute gastric ulcers by injecting pus into animals. In 1916, Rosenow (183) induced gastric and duodenal ulcers by intravenous injection of streptococci and more recently Douglas et al (181) were able to increase the incidence of perforated gastroduodenal ulcers in histamine-stimulated guinea pigs by injecting them with gram-positive staphylococci.

E. coli endotoxin has been found to increase ulcerogenesis in the restrained rat (237) and in piglets (185). Endotoxin causes selective regional gastric ischemia as a result of a redistribution of gastric blood flow.

We have developed a reproducible septic canine model in our laboratory (238) and it is this model which has been used in the investigations reported in this thesis.

CHAPTER 2

MATERIALS AND METHODS

Twenty-five male mongrel dogs weighing between 20 and 25 kg. were used in the experiments. The experimental protocol consisted in:

1. Construction of total gastric fistulae
2. Gastric secretory studies
3. Serum gastrin assay
4. Gastroscopic examination
5. Induction of peritonitis
6. Blood culture and rectal temperature studies
7. Post mortem studies

The dogs were divided into six groups as follows:

Group 1 - No drug treatment (5 dogs)

2 - Treatment with intramuscular Cimetidine 6 mg/kg QID (4 dogs)

3 - Treatment with intramuscular Cimetidine 12 mg/kg QID (4 dogs)

4 - Treatment with 16,16-dimethyl PGE_2 0.2 mg/kg QID(i.m.) (4 dogs)

5 - Treatment with 16,16-dimethyl PGE_2 0.4 mg/kg QID(i.m.) (4 dogs)

6 - Treatment with metoclopramide 1.5 mg/kg QID (i.m.) (4 dogs)

Cimetidine (Tagamet) was a gift from Smith, Kline and French, Canada Ltd., Montreal, Quebec.

16,16-dimethyl PGE_2 ($DMPGE_2$) was a gift from the Upjohns Company (Kalamazoo, Mich.).

Metoclopramide (Maxeran) was obtained from Nordic Pharmaceutical Co. (Laval, Quebec).

2.1. Construction of Gastric Fistulae

Gastric fistulae were constructed in all dogs used in the experiments.

The dogs were starved of food, but not water, for 24 hours before the operation. All operative procedures were performed under sterile conditions and under Nembutal (Pentobarbital sodium inj. USP/Abbott Laboratories Ltd., Montreal, Quebec, 6 mg/kg) anaesthesia with endotracheal intubation.

A midline supraumbilical incision (about 10 cm. long) was made into the peritoneal cavity and the stomach was brought out through the incision. After identifying the pylorus, a 2-3 cm. transverse incision was made into the most dependent part of the stomach close to the greater curvature.

A modified Thomas cannula was then inserted, through the incision, into the stomach. The cannula was brought out to the exterior through a separate left paramedian incision (about 3 cm. long). The abdominal incisions were closed in layers. The dogs were allowed to recover over a period of three weeks.

2.2. Gastric Secretory Studies

The dogs were trained to stand quietly in Pavlov's

slings (Fig. 2). For each study, the cannula was opened and the stomach was thoroughly irrigated with tap water and allowed to drain freely until the return was free of debris. After the drainage, three 15-min. collections of gastric juice were made and designated "basal gastric juice". At the end of the basal collection, 100 ml. of meat extract (three Oxo bouillon cubes dissolved in water and brought up to pH 7.0 by addition of 1.0 M $NaHCO_3$) was instilled into the stomach via the cannula. The meat extract was kept in the stomach for 15 min. after which the stomach was drained and these were designated "food stimulated gastric juice". After this, 6 ug/kg Peptavlon (Pentagastrin Inj. B.P. Ayerst, Montreal, Quebec) was administered intramuscularly and four 15 min. gastric juice collections, called "pentagastrin stimulated gastric juice" were made.

For each gastric secretory study, there were a total of eleven 15 min. gastric juice collections. Each collection was centrifuged at 2500 r.p.m. for 15 min. after its volume and pH has been recorded. Sediments were discarded and supernatants were saved for biochemical analyses.

Two control studies were done on different days for each dog. When drug treatment was instituted, two additional control studies were done with the drug. Secretory studies were done on three consecutive days after induction of peritonitis. Drug treatment was always started

Fig. 2. Dog with total gastric fistula in Pavlov's sling during an actual experiment.

24 hours before each secretory study, and also, 24 hours before induction of peritonitis and through the period of sepsis.

2.3 Biochemical Analysis of Gastric Juice

The supernatant of each 15 min. gastric juice was analyzed as outlined below.

a) H ion concentration was determined by titrating an aliquot of the sample with 0.1 M NaOH to pH 7.0.

b) Na and K ions were determined in the basal juice using an Instrumentation Laboratory (Lexington, Mass.) flame photometer.

c) Protein concentration in the basal juice was determined using the technique of Lowry et. al. (239).

d) Sialic acid level in the basal juice was found by the fluorometric technique developed for unbound sialic acids by Murayama et al (240).

e) Fucose determination was done by the spectrophotometric micromethod described by Dische and Shettles (241).

2.4 Gastrin Assay

Serum gastrin radioimmunoassays were done in the Group 1 dogs. Venous blood was obtained at the end of each 15 min. period during the gastric secretory studies. The assay was done using the Gastrin Immutope Kit (E.R. Squibb and Sons, Inc., Princeton, N.J.).

2.5 Gastroscopy

Gastroscopic examination of the stomach was carried out

under Pentothal (Sodium thiopental Inj. U.S.P. Abbott Laboratories Ltd., Montreal, Quebec 12-15 mg/kg) anesthesia and with endotracheal intubation. An Olympus fiberoptic gastroscope was used. Gastroscopy was done prior to induction of peritonitis to exclude any pre-existing mucosal damage. Gastroscopic examination was repeated on each of the three days following induction of peritonitis. The state of the gastric mucosa on each day was recorded.

2.6 Induction of Peritonitis

Dogs were fasted, water being allowed freely, for 24 hours prior to the induction of peritonitis. Under Pentothal anesthesia and with an endotracheal tube in place, a small infraumbilical midline incision (about 2 cms. long) was made into the peritoneal cavity. Through the incision, a mixture of bacteria and bile was instilled into the peritoneal cavity. The composition of the inoculum of 18-hour broth culture was as follows:

- Bacteroides fragilis (0.4 mg/kg)
- Pseudomonas aeroginosa (0.04 ml/kg)
- Klebsiella pneumoniae (0.04 ml/kg)
- Streptococcus faecalis (0.04 ml/kg)

Bacteria were prepared in a concentration of 10^9 colony forming units per ml. and were obtained from the Department of Microbiology, McGill University. Canine gallbladder bile (0.4 ml/kg) was added to the inoculum as adjuvant.

In a preliminary experiment, 0.4 ml/kg Normal Saline (0.9% NaCl solution) was instilled into the peritoneal cavity of six dogs instead of the bacteria-bile mixture).

2.7 Rectal Temperature and Blood Culture Studies

Rectal temperature was recorded and blood was taken for culture before induction of peritonitis. These were repeated four hours after peritonitis and on each of the three days following the induction of peritonitis.

2.8 Post-Mortem Studies

The dogs were sacrificed on Day 3, after the secretory studies. Wound swabs were taken for culture and the abdominal cavity was examined for abscesses, adhesions, or fluid accumulation. Omental tissue was also obtained for culture. The stomach was excised and examined for gross mucosal changes and erosions. Pieces of gastric mucosal tissue were taken, fixed, and stained with Hematoxylin and Eosin for histological examination.

2.9 Statistical Analysis

Results were analyzed using the Olivetti Programma 101 Electronic Desk Computer and facilities at the McGill University Computing Center. Statistical significance was determined by the Student's t test for paired values and correlation between various parameters was determined by computing Pearson's Coefficient of Correlation (r).

CHAPTER 3

RESULTS

3.1 GENERAL CONDITION OF THE DOGS

Four hours after induction of peritonitis, all the dogs exhibited varying degrees of some of the clinical features of severe peritonitis. Rectal temperatures were significantly elevated to $41.5 \pm 0.4^{\circ}C$ compared with presepsis levels of $38.4 \pm 0.7^{\circ}C$ (Fig 3). The increased temperature was accompanied by moderate to vigorous generalized shivering in all dogs. Heart and respiratory rates rose from presepsis rates of 85 ± 9 beats/min and 18 ± 5/min to 142 ± 11 beats/min and 29 ± 7/min respectively. Some degree of abdominal guarding was exhibited in most of the dogs and a few of them vomited. In a preliminary study, it was found that blood pressure dropped from a presepsis level of about 190/150mmHg to about 120/95mmHg four to five hours after the induction of peritonitis.

The dogs appeared weak, apathetic and inactive on day 1. By the second and third days after induction of peritonitis, the temperatures were approaching presepsis values and the heart and respiratory rates were almost normal. The dogs were alert and more active.

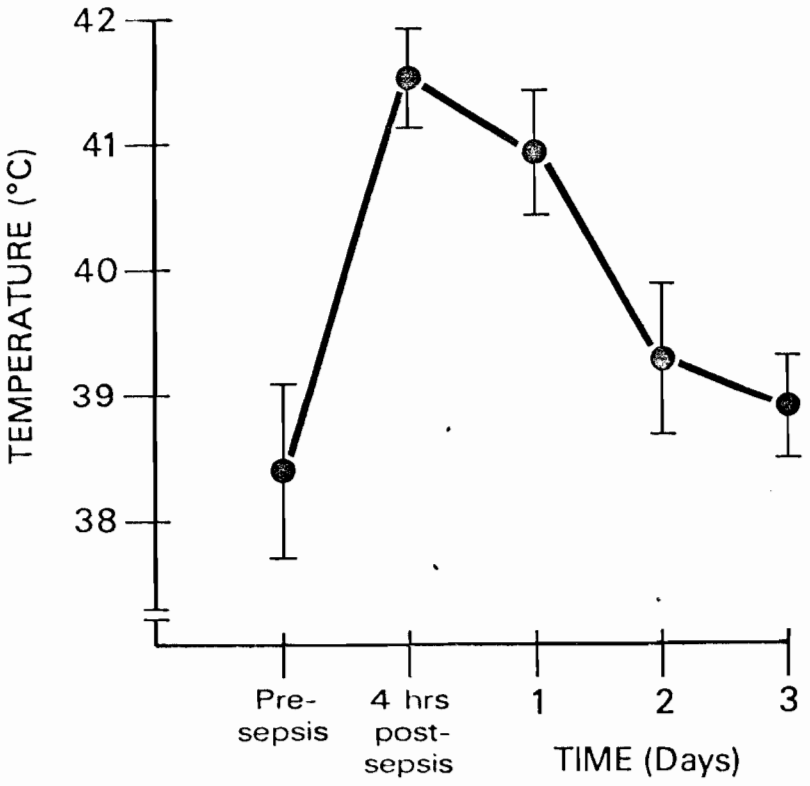

Fig. 3. Temperature pattern in septic dogs.(n=25)

3.2 RESIDUAL GASTRIC JUICE DURING SEPSIS

Residual gastric juice was collected everyday before acid secretory studies. With the exception of the dogs treated with metoclopramide, the residual gastric juice was 150 - 475 ml in volume and was heavily bile-stained in all dogs on Day 1. The residual juice on Day 2 was 60 - 230 ml and the juice was only moderately bile-stained. By Day 3 the volume had dropped to 25 - 160 ml and there was only light bile staining.

Metoclopramide-treated dogs had 20 - 35 ml of residual gastric juice which was only moderately bile-stained. On Days 2 and 3 the residual juice was 0 - 10 ml in volume and only lightly bile-stained.

3.3 BACTERIOLOGIC EXAMINATION

Blood culture results are shown in Fig 4. Four hours after induction of peritonitis, 21 of the 25 dogs had Pseudomonas in the blood. Bacteroides was cultured in 9 dogs and in 6 dogs Strep. fecalis was found. Klebsiella appeared in the blood of only one dog four hours after induction of peritonitis. On Day 1, 19 dogs had positive blood cultures for Pseudomonas, Bacteroides and Strep. fecalis, whilst 5 dogs grew Klebsiella. Septicemia persisted in only about half the total number of dogs on

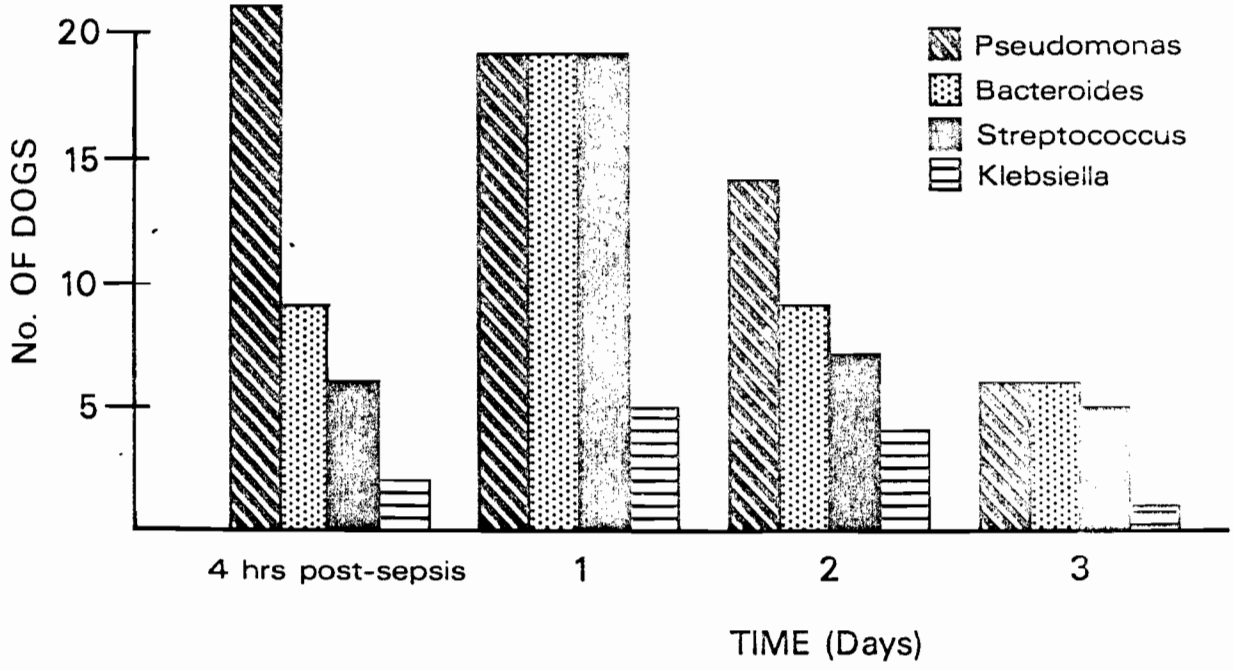

Fig. 4. Blood culture results in septic dogs.(n=25)

Day 2, and by Day 3, only about a quarter of the dogs had positive blood cultures.

Wound and omental cultures were positive for all the four different bacteria instilled into the peritoneal cavity.

3.4 PATHOLOGIC FINDINGS

Fig 5 is a typical picture of the fundic mucosa as seen at endoscopy (of dogs which developed acute gastric erosions). There are multiple erosions which are confined exclusively to the fundus of the stomach. The lesions, which may be round or linear, are frequently less than 3mm in diameter. They are soft, non-indurated, and superficial and sometimes may have black or hemorrhagic bases. Other stages of mucosal damage such as mucosal hemorrhages or petechiae are often present.

Fig 6 is a microscopic demonstration of marked mucosal and submucosal necrosis with extensive vascular engorgement and edema in the lumina propria. There is little or no evidence of inflammation.

The antral and cardiac mucosae are normal in appearance throughout the period of sepsis.

Fig. 5. Gastroscopic evidence of acute erosions

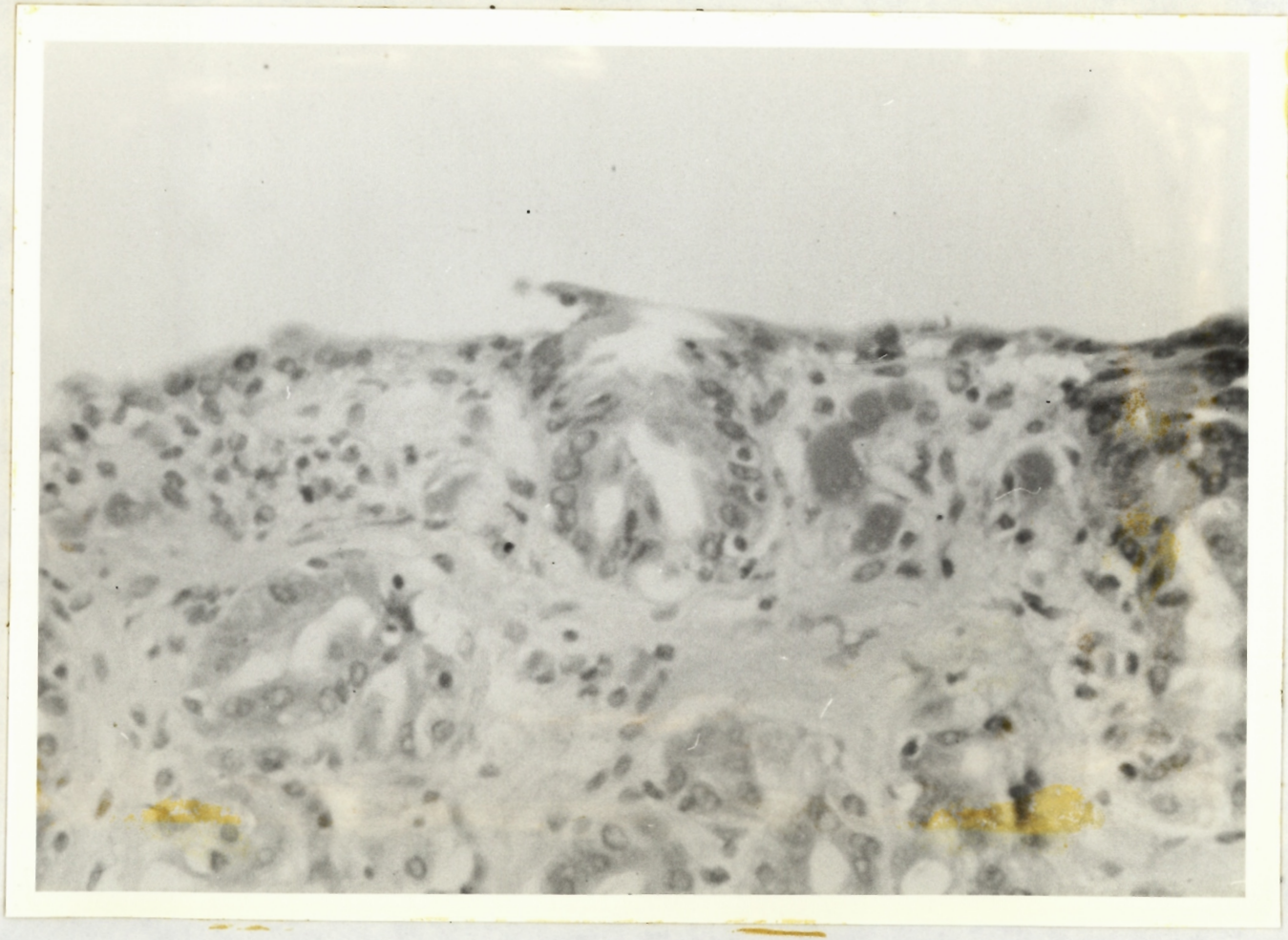

Fig. 6. Microscopic evidence of acute erosions. Epithelial lining is completely sloughed off and there is no evidence of tissue inflammatory reaction.

3.5 GROUP 1 DOGS (NO DRUG TREATMENT)

Results of gastroscopic examination and autopsy findings are recorded in Table 1. All dogs had normal undamaged gastric mucosa before the induction of peritonitis. On Day 1, all the five dogs had actively bleeding gastric erosions as well as patchy areas of erythema localized to the fundus. On Day 2, three dogs had bleeding erosions and two had non-bleeding erosions. At autopsy on Day 3, three dogs had non-bleeding erosions and two had only mild mucosal petechiae.

Acid secretory results are depicted in Table 2. B.A.O.* was calculated by multiplying the acid output in the last two 15-min periods by two. F.A.O.* was also calculated by multiplying the highest two consecutive 15-min acid outputs by two and P.A.O.* was calculated in a similar way by multiplying the two highest acid outputs for consecutive 15-min periods by two. (*BAO, FAO and PAO were calculated in the same manner for all the other groups of dogs).

Compared with control values, BAO, FAO and PAO were significantly elevated ($p < 0.01$) on the first two days of sepsis. Acid secretion returned to control values on Day 3.

Basal and food-stimulated serum gastrin levels did not show any significant change from control levels during the period of sepsis.

Table 1. Gastroscopy and Autopsy Results in Untreated Septic Dogs.

	Gastroscpy		Autopsy
Dog No.	Day 1	Day 2	Day 3
608	+++	+++	++
609	+++	+++	++
610	+++	++	+
611	+++	++	+
620	+++	+++	++

\+ = mucosal petechiae
++ = multiple non-bleeding erosions
+++ = multiple bleeding erosions

Table 2. Acid, Sodium and Potassium Levels in Gastric Secretion of Untreated Septic Dogs. (n=5)

	BAO†	FAO†	PAO†	Na ions††	K ions††
Control (Pre-sepsis)	2.0±0.4	3.6±1.1	21.9±6.2	74.4±13.0	12.9±3.0
Septic Day 1	3.8±1.1*	10.6±2.6*	33.3±6.8*	99.5±15.8*	16.4±2.2*
Septic Day 2	3.8±0.7*	7.3±1.3*	28.6±8.2*	92.5±14.4*	15.3±2.2*
Septic Day 3	2.2±0.6	2.6±0.6	26.4±4.8	79.2±10.6	12.9±1.6

± = S.E.M. † = mEq H^+/hr. †† = mEq/L *=$p<0.01$ (compared with control)

Table 3. Protein, Fucose and Sialic Acid Levels in the Gastric Secretion of Untreated Dogs. (n=5).

	Protein†	Fucose††	Sialic Acid††
Control (Pre-sepsis)	7.6±0.6	3.7±0.0	5.3±0.9
Septic Day 1	4.8±0.0*	6.1±0.2*	8.3±0.7*
Septic Day 2	6.5±0.3*	5.3±0.1*	8.0±0.5*
Septic Day 3	7.9±0.5	3.9±0.0	6.3±0.7

± = S.E.M. † = mg/ml †† = µg/mg protein *=$p<0.05$ (compared with control)

Table 2 also shows that there was a statistically significant influx of Na and K ions into the gastric lumen on septic Days 1 and 2, compared with the control levels. The gastric lumenal contents of Na and K ions, however, returned to normal values by Day 3.

The results of protein, fucose and sialic acid analyses of the gastric secretion are depicted in Table 3. Fucose and Sialic acid values are reported here as µg/mg of protein. The results show that gastric juice protein dropped significantly ($p < 0.01$) on the first day of sepsis, but by Day 3, it had risen to presepsis levels. Fucose and Sialic acid levels, on the other hand, were significantly raised ($p < 0.05$) on Day 1 and 2 and returned to within normal range by Day 3.

It was not possible to determine the correlation between mucosal damage and the parameters measured because of the uniformity of the gastric mucosal bleeding that occured in all the dogs. On Day 2, however, the gastric mucosae were at different stages in the evolution of stress ulcer. There was positive correlation between mucosal damage and BAO ($r=0.87$); FAO ($r=0.83$); PAO ($r=0.91$); Na ($r=0.78$); K ($r=0.72$); fucose ($r=0.55$) and Sialic acid ($r=0.57$). There was a strong negative correlation between mucosal damage and the gastric juice protein ($r=0.82$).

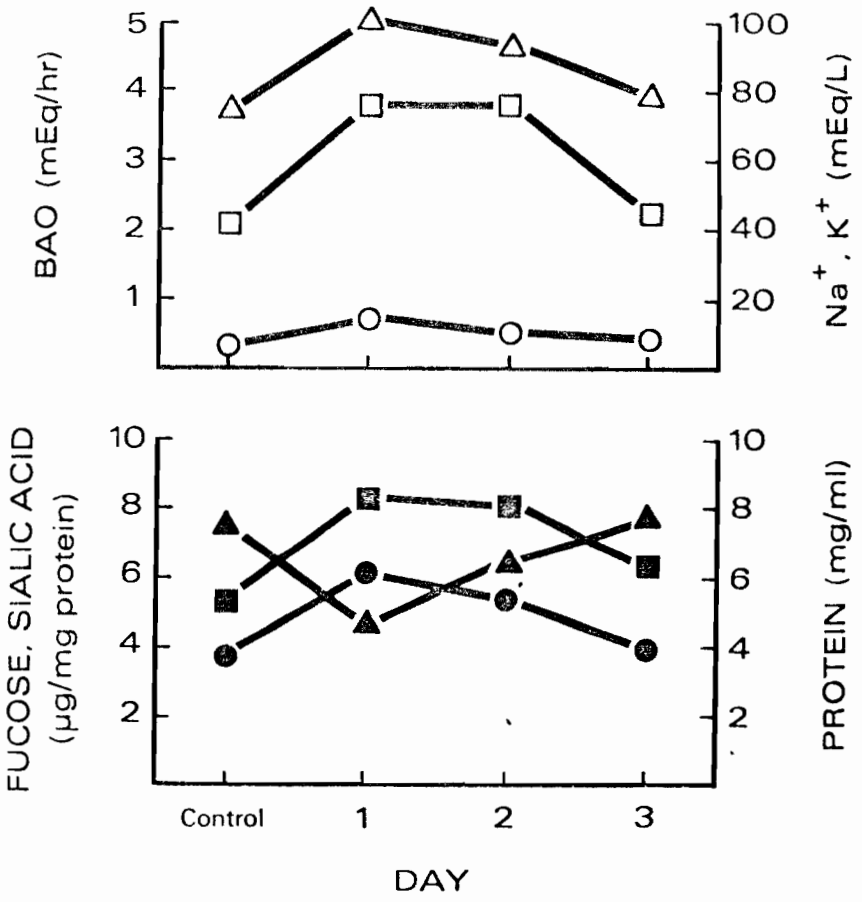

Fig. 7. Composite graph of all parameters in untreated spetic dogs.(n=5)

Legend

□ BAO △ Na^+ ○ K^+

■ Sialic Acid ▲ Protein ● Fucose

Fig 7 is a composite graph of all the parameters. It shows that apart from protein, all other parameters are increased on Day 1 when the gastric erosions are worst. By Day 3, the gastric mucosa and the various other parameters return to normal levels.

3.6 GROUPS 2 & 3 DOGS (TREATED WITH TWO DOSES OF CIMETIDINE)

Gastroscopy and autopsy findings in the two groups of dogs are shown in Table 4. All the four dogs receiving the lower dose of Cimetidine (6mg/kg QID) had multiple bleeding erosions on Day 1. On Day 2 only one dog still had actively bleeding erosions; the rest showed non-bleeding erosions. At autopsy, two dogs had non-bleeding erosions and one dog exhibited only a few patchy areas of erythema. The gastric mucosa of one dog was completely normal.

In the group receiving the higher dose of Cimetidine (12mg/kg QID) all four dogs had normal gastric mucosa throughout the three days of sepsis.

Results of acid secretory studies in the two groups of dogs treated with Cimetidine are illustrated in Table 5. Even though 6mg/kg QID of Cimetidine significantly reduced ($p < 0.01$) acid secretion during the drug control period, there was a statistically significant elevation ($p < 0.05$) in all phases of gastric acid secretion on

Table 4. Gastroscopy and Autopsy Results in Cimetidine-Treated Septic Dogs

	Gastroscopy		Autopsy
Dog. No.	Day 1	Day 2	Day 3
Cimetidine 6 mg/kg QID (n=4)			
612	+++	+++	++
613	+++	++	++
614	+++	++	+
615	+++	++	+
Cimetidine 12 mg/kg QID (n=4)			
622	-	-	-
623	-	-	-
624	-	-	-
627	-	-	-

\- = normal gastric mucosa
\+ = mucosal petechiae
++ = multiple non-bleeding erosions
+++ = multiple bleeding erosions

Table 5. Acid Output in Cimetidine-Treated Septic Dogs

	Cimetidine 6 mg/kg QID(n=4)			Cimetidine 12 mg/kg QID(n=4)		
	BAO†	FAO†	PAO†	BAO†	FAO†	PAO†
Control (no drug)	1.3±0.2	4.9±1.3	27.3±8.7	1.0±0.0	1.4±0.1	24.7±7.3
Drug Control (pre-sepsis)	0.4±0.0*	1.4±0.2*	14.0±0.4*	0.0±0.0	0.0±0.0	3.1±0.5*
Septic Day 1	0.0±0.0**	1.8±0.3	17.2±1.6**	0.0±0.0	0.0±0.0	4.7±0.6**
Septic Day 2	0.7±0.0	1.5±0.2	14.9±1.7	0.0±0.0	0.0±0.0	4.5±0.6
Septic Day 3	0.4±0.0	1.4±0.1	14.5±0.7	0.0±0.0	0.0±0.0	3.8±0.6

± = S.E.M.

† = mEq H^+/hr.

* = $p < 0.01$ (compared with control)

** = $p < 0.05$ (compared with drug control)

Table 6. Sodium and Potassium Levels in the Gastric Juice of Cimetidine-Treated Septic Dogs

	Cimetidine 6mg/kg QID (n=4)		Cimetidine 12 mg/kg QID (n=4)	
	Na ions†	K ions†	Na ions†	K ions†
Control (no drug)	70.9±3.7	14.8±3.1	78.5±11.1	10.1±4.0
Drug Control (pre-sepsis)	72.1±7.1	15.0±3.4	79.3±7.3	10.1±3.8
Septic Day 1	104.3±7.1*	19.5±3.1*	78.7±2.2	10.4±1.8
Septic Day 2	92.0±4.0*	17.9±3.0*	72.7±10.0	8.1±2.6
Septic Day 3	79.0±10.8	14.9±3.2	78.4±14.2	10.5±4.7

± = S.E.M.

† = mEq/L

* = $p < 0.05$ (compared with drug control)

Table 7. Protein, Fucose, and Sialic Acid Levels in the Gastric Secretion of Cimetidine-Treated Dogs.

	Cimetidine 6 mg/kg QID(n=4)			Cimetidine 12 mg/kg QID (n=4)		
	Protein†	Fucose††	Sialic Acid††	Protein†	Fucose††	Sialic Acid††
Control (no drug)	6.2±0.5	3.7±0.0	5.1±0.4	5.3±0.4	3.6±0.2	5.1±0.6
Drug Control (pre-sepsis)	7.1±0.4	4.1±0.2	6.2±0.3	4.6±0.1	6.0±0.5**	10.6±1.2**
Septic Day 1	3.9±0.4	6.3±0.5*	7.7±0.4*	5.9±0.4	6.4±0.6	11.3±1.7
Septic Day 2	5.1±0.3	5.9±0.4*	7.3±0.4*	6.7±0.6	6.1±0.3	10.4±0.4
Septic Day 3	6.5±0.4	4.2±0.4	6.7±0.3	6.4±0.5	6.3±0.3	11.7±1.4

± = S.E.M.

† = mg/ml

†† = μg/mg protein

* = $p < 0.05$ (compared with drug control)

**= $p < 0.05$ (compared with control)

septic Day 1, compared with the drug control levels. On Day 2 there was still significant elevation ($p < 0.05$) of BAO; FAO and PAO were not significantly altered. Acid secretion was back to drug control levels by Day 3.

On the other hand, dogs that received 12mg/kg QID of Cimetidine showed complete anacidity in BAO and FAO during the period of drug control and sepsis. PAO was significantly reduced ($p < 0.01$) by the high dose of Cimetidine and the slight rise during the period of sepsis was only significant on Day 1 ($p < 0.05$).

Sodium and potassium results are shown in Table 6. The two doses of Cimetidine did not affect the levels of Na and K ions in the gastric juice during the drug control studies. With Cimetidine 6mg/kg QID however, there was significant elevation ($p < 0.05$) in the levels of both ions during the first two days of sepsis compared with the drug control values. In the dogs that were treated with Cimetidine 12mg/kg QID, however, Na and K levels remained at the presepsis levels.

Table 7 depicts protein, fucose and Sialic acid levels obtained during treatment with the two different doses of Cimetidine. Cimetidine did not have any significant effect on protein levels in the gastric juice during the drug control period. Fucose and Sialic acid levels were elevated slightly ($p < 0.05$) during control studies

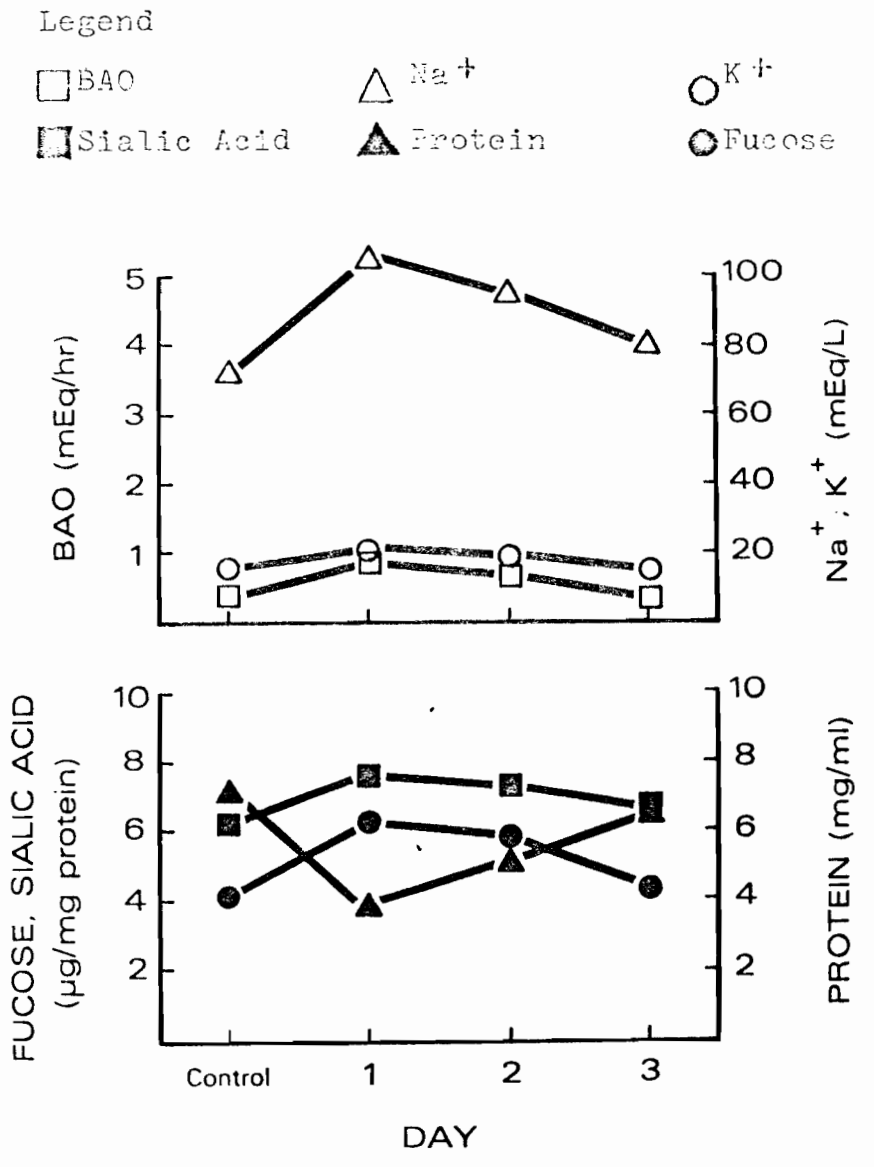

Fig. 8. Composite graph of all parameters in septic dog treated with Cimetidine 6mg/kg QID.

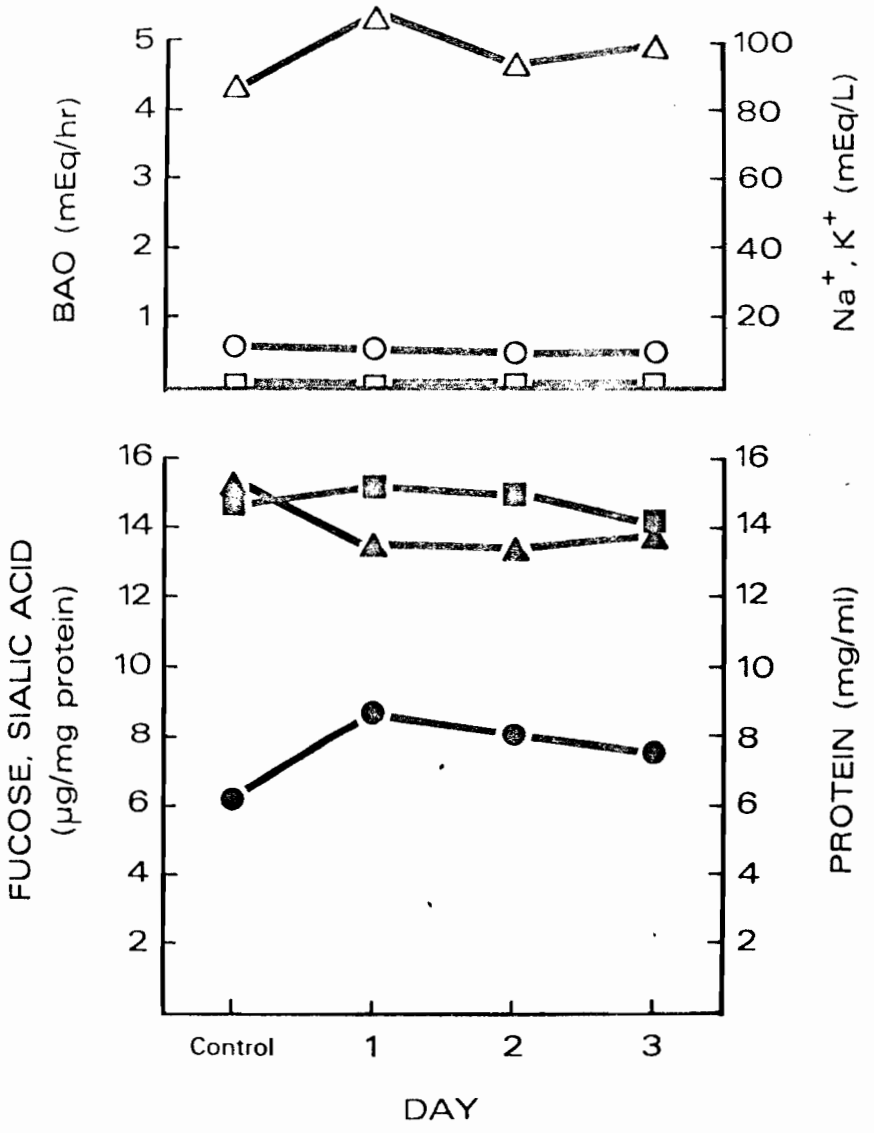

Fig. 9. Composite graph of all parameters in septic dogs treated with Cimetidine 12mg/kg QID.

Legend

□ BAO △ Na^+ ○ K^+

Sialic Acid ▲ Protein ● Fucose

with Cimetidine 12mg/kg QID, (but not 6mg/kg QID). During the first two days of sepsis, however, slight but significant elevation ($p < 0.05$) was obtained in the dogs that were treated with Cimetidine 6mg/kg QID, whereas there was no change in the levels of fucose and Sialic acid in the higher dose group.

Composite graphs are shown in Figs. 8 and 9.

3.7 GROUPS 4 & 5 (TREATED WITH $DMPGE_2$)

Gastroscopy and autopsy results are shown in Table 8. There were no gastric erosions in any of the dogs treated with $DMPGE_2$.

Results of acid secretory studies are shown in Table 9. $DMPGE_2$(0.2 µg/kg QID)did not have any significant effect on all phases of gastric secretion during the drug control studies. There was however significant elevation ($p < 0.05$) in acid secretion on Day 1 and 2. $DMPGE_2$(0.4µg/kg QID),on the other hand, abolished all phases of acid secretion during the drug control period. BAO and FAO were completely inhibited on all three post-sepsis days and PAO was significantly reduced ($p < 0.01$) during the septic period.

Table 10 illustrates results of Na and K ion determination in the gastric juice. There was no statistically significant change in the levels of Na and K ions during the drug control and septic periods.

Table 8. Gastroscopy and Autopsy Results in $DMPGE_2$-Treated Septic Dogs

	Gastroscopy		Autopsy
	Day 1	Day 2	Day 3
$DMPGE_2$ - 0.4 mg/kg QID			
634	-	-	-
635	-	-	-
636	-	-	-
637	-	-	-
$DMPGE_2$ - 0.2 mg/kg QID			
640	-	-	-
641	-	-	-
642	-	-	-
643	-	-	-

- = normal gastric mucosa

Table 9. Acid Output in $DMPGE_2$-Treated Septic Dogs

	$DMPGE_2$ 0.2 µg/kg QID (n=4)			$DMPGE_2$ 0.4 µg/kg QID(n=4)		
	BAO†	FAO†	PAO†	BAO†	FAO†	PAO†
Control (no drug)	2.2±0.4	3.2±0.6	14.9±2.8	1.3±0.2	1.5±0.2	12.0±1.6
Drug Control (pre-sepsis)	2.0±0.4	3.1±0.5	14.6±2.8	0.0±0.0	0.0±0.0	0.0±0.0
Septic Day 1	2.5±0.4*	4.2±0.5*	29.2±3.4*	0.0±0.0	0.0±0.0	1.0±0.2
Septic Day 2	2.4±0.5*	3.9±0.3*	21.0±4.6*	0.0±0.0	0.0±0.0	0.7±0.3
Septic Day 3	2.1±0.5	3.0±0.6	15.3±3.8	0.0±0.0	0.0±0.0	0.6±0.2

± = S.E.M.

† = mEq H^+/hr.

* = $p < 0.05$ (compared with drug control)

Table 10. Sodium and Potassium Levels in the Gastric Juice of $DMPGE_2$-Treated Septic Dogs

	$DMPGE_2$ 0.2 μg/kg QID(n=4)		$DMPGE_2$ 0.4 μg/kg QID (n=4)	
	Na ions†	K ions†	Na ions†	K ions†
Control (no drug)	72.9±7.5	12.6±2.1	85.9±16.3	12.0±1.0
Drug Control (pre-sepsis)	74.4±9.9	12.2±3.1	85.9±17.7	11.9±1.4
Septic Day 1	75.8±10.7	12.5±0.5	106.3±5.4	11.8±0.9
Septic Day 2	76.3±13.2	12.4±1.4	91.9±8.9	11.3±1.7
Septic Day 3	70.5±13.0	11.5±1.3	96.5±6.3	11.8±0.4

± = S.E.M. † = mEq/L

Table 11. Protein, Fucose and Sialic Acid Levels in the Gastric Secretion of $DMPGE_2$-Treated Septic Dogs.

	$DMPGE_2$ 0.2 μg/kg QID (n=4)			$DMPGE_2$ 0.4 μg/kg QID (n=4)		
	Protein†	Fucose††	Sialic Acid††	Protein†	Fucose††	Sialic Acid††
Control (no drug)	6.8±1.0	3.3±0.3	6.1±1.0	6.1±0.3	3.7±0.3	5.7±0.8
Drug Control (pre-sepsis)	8.6±1.2	3.8±0.5	10.2±1.1	7.6±1.0*	6.2±0.3*	14.6±1.5*
Septic Day 1	7.3±0.8	5.0±0.8	10.8±1.0	6.7±1.0	8.7±0.4	15.2±1.6
Septic Day 2	7.8±0.7	3.4±0.5	10.4±1.1	6.6±1.0	8.0±0.4	14.9±1.5
Septic Day 3	7.4±0.5	2.9±0.5	10.3±1.4	6.8±0.8	7.6±0.4	14.1±1.6

± = S.E.M.

† = mg/ml

†† = μg/mg protein

* = $p < 0.05$ (compared with control)

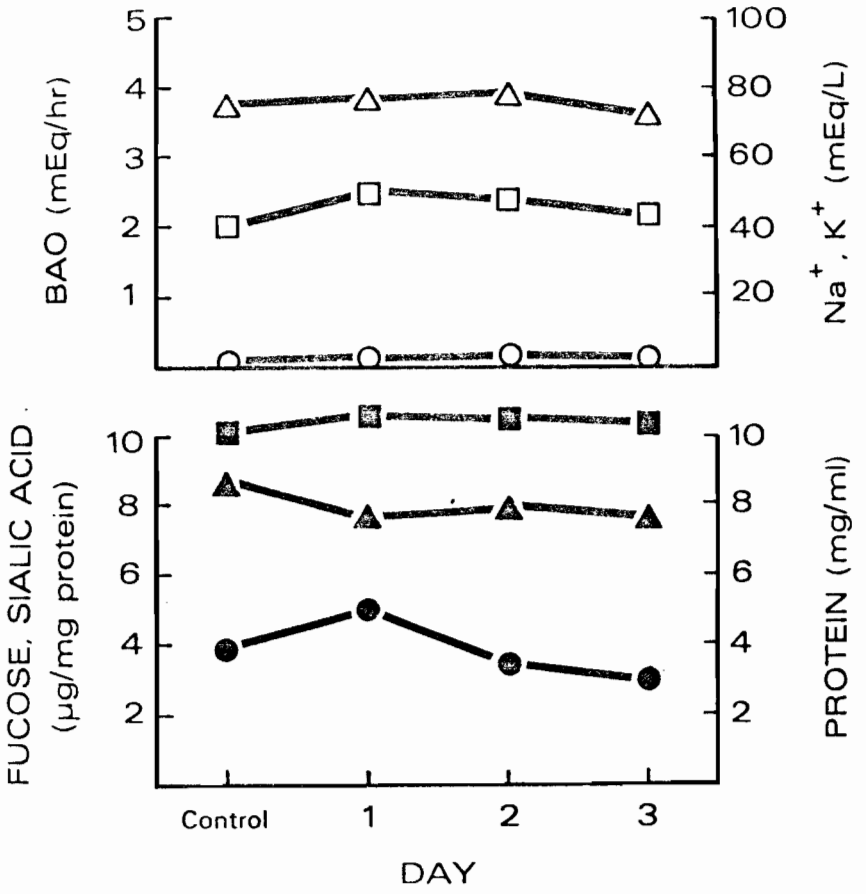

Fig. 10 Composite graph of all parameters in septic dogs treated with $DMPGE_2$ 0.2mg/kg QID.

Legend

□ BAO △ Na^+ ○ K^+

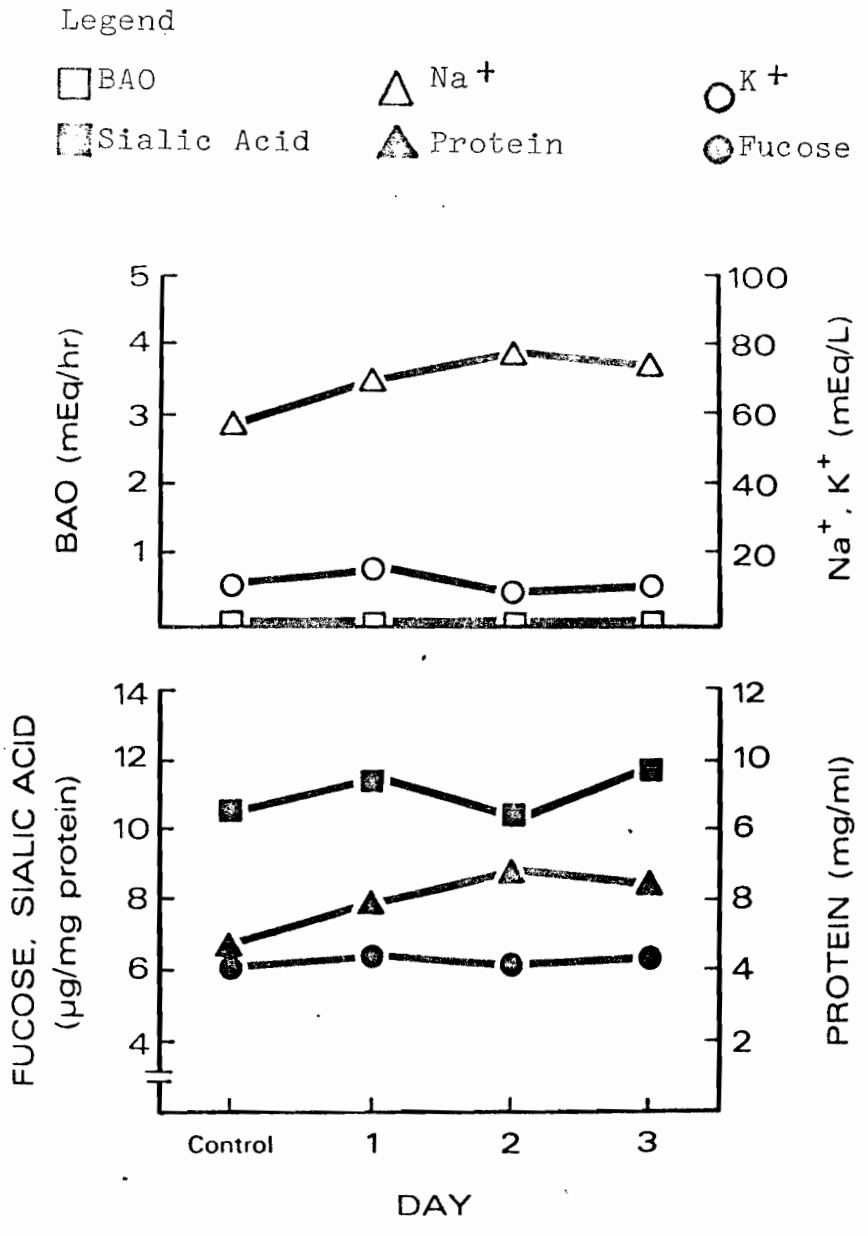

Fig. 11. Composite graph of all parameters in septic

Protein, fucose and Sialic acid results are depicted in Table 11. The lower dose of $DMPGE_2$ did not have any significant effect on protein, fucose and Sialic acid levels in the gastric juice. $DMPGE_2$ (0.4µg/kg QID), on the other hand, significantly increased ($p<0.05$) the presepsis values of protein, fucose and Sialic acid. The values during sepsis, however, were not significantly altered when compared with the presepsis levels.

Composite graphs are shown in Figs 10 and 11.

3.8 GROUP 6 DOGS (TREATED WITH METOCLOPRAMIDE)

Table 12 shows the results of gastroscopic and autopsy findings. On Day 1, one dog had bleeding erosions and another had non-bleeding eriosions. Two dogs exhibited only mucosal petechiae. On Day 2, those dogs that had petechiae showed complete recovery and the mucosae were normal. The other two dogs had non-bleeding erosions and mucosal petechiae respectively. On Day 3, the two dogs had only mild mucosal petechiae.

Metoclopramide did not have any effect on acid secretion (Table 13). There was significant elevation ($p < 0.05$) in all phases of acid secretion on Days 1 and 2. By Day 3, acid secretion was approaching normal presepsis levels.

Table 12. Gastroscopy and Autopsy Results in Metoclopramide-Treated Septic Dogs.

	Gastroscopy		Autopsy
Dog No.	Day 1	Day 2	Day 3
628	++	+	+
630	+++	++	+
632	+	-	-
633	+	-	-

- = normal gastric mucosa
+ = mucosal petechiae
++ = non-bleeding erosions
+++ = bleeding erosions

Table 13. Acid, Sodium and Potassium Levels in Gastric Secretion of Metoclopramide-Treated Septic Dogs

	BAO†	FAO†	PAO†	Na ions††	K ions††
Control (no drug)	1.0±0.0	2.3±0.2	10.5±0.8	86.0±17.8	11.3±0.8
Drug Control (pre-sepsis)	1.1±0.1	2.0±0.3	10.9±1.5	82.0±8.2	11.4±1.1
Septic Day 1	1.9±0.2*	4.2±0.4*	18.2±1.0*	106.0±17.6*	18.9±2.8*
Septic Day 2	1.4±0.2*	3.1±0.1*	14.2±1.5*	103.3±13.8*	17.6±2.5*
Septic Day 3	1.2±0.1	2.1±0.5	10.4±1.0	79.6±7.9	12.9±1.6

± = S.E.M. † = mEq H^+/hr. †† = mEq/L
* = $p < 0.05$ (compared with drug control)

Table 14. Protein, Fucose and Sialic Acid Levels in the Gastric Secretion of Metoclopramide-Treated Septic Dogs.

	Protein†	Fucose††	Sialic Acid††
Control (no drug)	6.8±0.7	3.5±0.3	5.5±0.6
Drug Control (pre-sepsis)	7.5±0.3	3.7±0.2	5.9±0.6
Septic Day 1	8.1±0.6	6.2±0.5*	7.5±0.7*
Septic Day 2	7.6±0.5	5.3±0.6*	7.4±0.9*
Septic Day 3	6.8±0.5	4.1±0.6	6.1±0.6

± = S.E.M. † = mg/ml †† = µg/mg protein
* = $p < 0.01$ (compared with drug control)

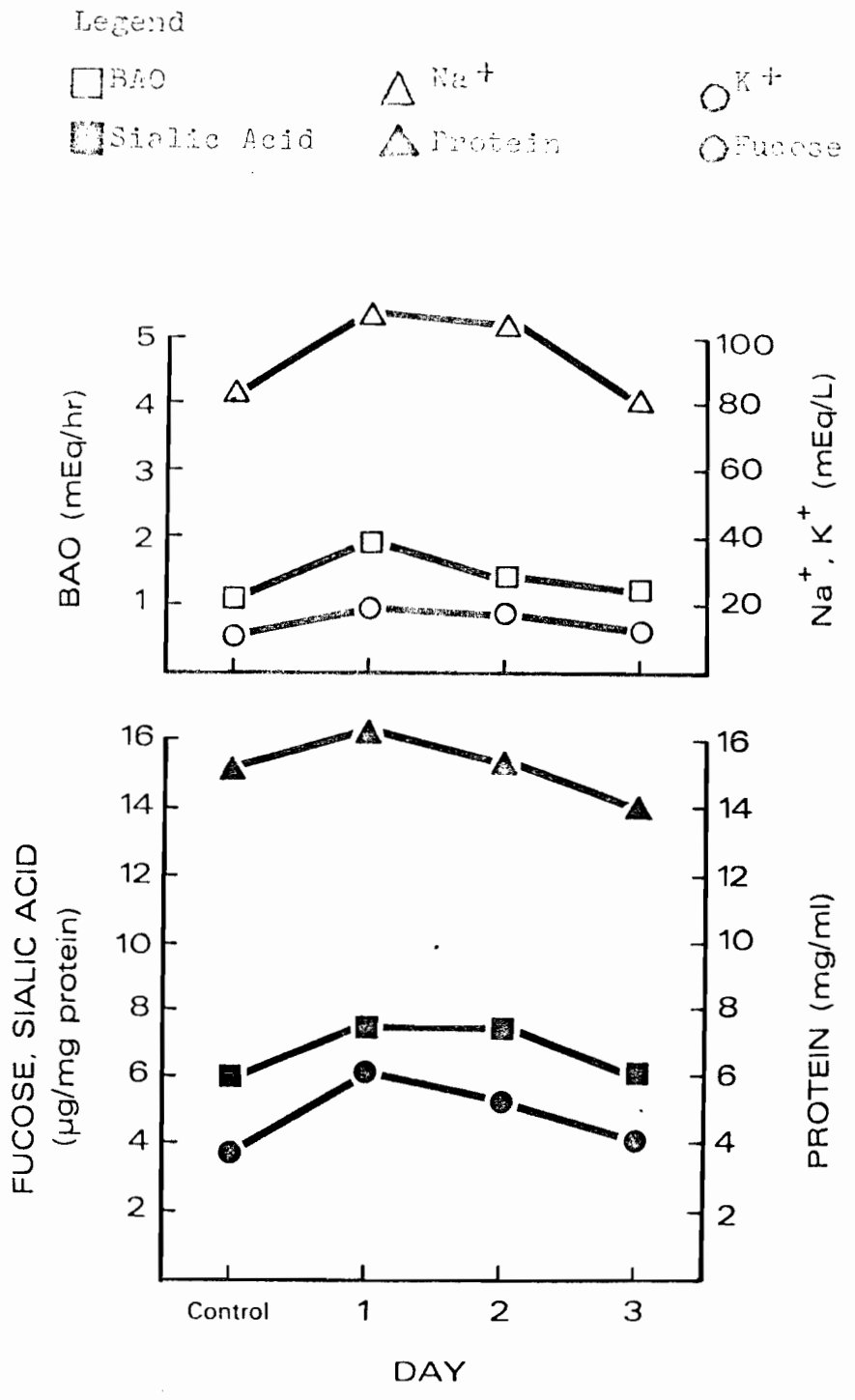

Fig. 12. Composite graph of all parameters in septic dogs treated with metoclopramide.

Na and K ion levels are also shown in Table 13. The levels of these ions were not significantly altered by metoclopramide in the presepsis control study. During the first two days of peritonitis, the levels of Na and K in the gastric juice were significantly increased ($p < 0.01$).

Results for protein, fucose and Sialic acid, depicted in Table 14, reveal that metoclopramide per se, did not have any effects on these parameters. However, on Days 1 and 2, the levels of fucose and Sialic acid were significantly elevated ($p < 0.01$). By Day 3, these parameters were returning to their presepsis levels.

A composite graph is shown in Fig 12.

CHAPTER 4

4. DISCUSSION

4.1 Septic Canine Model

The question has often been asked: "What is the best experimental model for stress ulcer?" There have been several suggestions, but it has not been easy to arrive at a reliably reproducible animal model that closely mimics the clinical situation. A reliable model would be helpful in exploring the poorly defined etiology, pathophysiologic changes and therapy of stress ulcer in man.

The restrained rat model (226) develops acute gastric ulcers similar to the human situation but the rat has a rumenal stomach which is not physiologically comparable to man's glandular stomach (242). There is an additional disadvantage with the use of this model in that the use of immobilization does not mimic the clinical condition in man where there is no restraint on the patient.

Silen (144) has suggested the dog or the pig as the best experimental animal models suitalbe for stress ulcer research. The pig has been used extensively for studies of gastric physiology (243) because the porcine stomach is similar to the human stomach (244) with the same geographic areas as are classically described for man (118). The pig is an omnivore, as man, and therefore its digestive tract with its contents, juices, and enzymes may reasonably be expected to resemble that of man. The pig, however, has

the propensity for spontaneous ulceration (245).

Even though the dog is a carnivore, its gastric anatomy and physiology come quite close to the human's, and unlike the pig, there is no known tendency for spontaneous ulceration. Like the pig, a lot of our knowledge about gastric physiology, and most of what we apply in treating gastric disease came from canine experimentation (87).

Walt (87) has suggested the use of the subhuman primates in order to reduce species differences. Indeed, the subhuman primates may give us the best animal model since they come closest to man, but is the expense involved worthwhile? Acutally, the best model for stress ulcer will be the human patient, but working with the animal gives better control over the factors being studied. In the patient, there may be so many extraneous factors that may not be adequately controlled, and hence the results may be difficult to interpret.

During the last two decades, the association between sepsis and stress ulceration has been mainly investigated by inducing endotoxic shock through systemic administration of E. coli endotoxin. However, due to the numerous patho-physiologic differences between human septic shock and experimental endotoxic shock, the latter has frequently been criticized as being an inaccurate reproduction of the clinical situation. E. Coli endotoxemia leads to hypodynamic

circulation in which there is decreased cardiac output and increased peripheral resistance due to peripheral vasoconstriction (246, 247). In man, septic shock is associated with a hyperdynamic circulation in which there is elevated cardiac index, high central venous pressure, and decreased peripheral vascular resistance (248-250). Metabolic acidosis, profound oliguria and transient portal hypertension are characteristic of early canine endotoxic shock, whereas respiratory alkalosis, portal normotension or hypotension and a variable amount of oliguria are found in early human septic shock (251).

The need for an experimental model of septic shock which closely approximates the clinical condition has prompted several investigations in the last decade. Hemreck and Thal (252) injected fecal material into the hind limbs of dogs and observed a hyperdynamic circulatory response. Recently, peritonitis has been used in the design of animal models of sepsis and septic shock (253,254). Three main approaches have been adopted for the induction of peritonitis (254). These are:

a) Surgical operation to simulate the sequence of events occurring in the clinical situation.

b) Administration of fecal material into the peritoneal cavity.

c) Intraperitoneal administration of pure bacterial cultures.

The surgical techniques consist of devascularization of a segment of intestine which is allowed to slough, thus mimicking strangulation of severe transmural infection. The main disadvantage is that the situation is entirely uncontrolled. A certain mortality and morbidity will be due to the anesthesia and trauma of the operation. The severity of the peritonitis depends upon the rate of development and upon the bacterial contents of the intestine at the time of rupture.

The administration of feces also has the disadvantage of an uncontrolled situation in which both the dosage and the species and strain of bacteria are impossible to quantify. It is, therefore, difficult to reproduce exactly the experimental situation of another worker, or even one's own earlier results.

The use of pure bacterial cultures, like the types in our experiments, seems more attractive. It allows precise control over the dosage and strains of bacteria and it is completely reproducible.

We have been able to develop a reproducible model based on bacterial peritonitis giving rise to septicemia, septic shock, and acute gastric ulceration. We have used four different bacteria that are found in the fecal flora of man. Bacteroides fragilis, an anaerobic organism, accounts for 90% of the normal flora (255). Bacteroides has been

found to be an important contributory factor in the high mortality associated with colonic perforation (254). Streptococcus fecalis, Pseudomonas aeroginosa, and Klebsiella pneumoniae are also commonly found in blood cultures of septic patients (256) and they have been used in the induction of experimental peritonitis (253).

The mixture of organisms mimics many forms of clinical peritonitis and duplicates most aspects of septic shock in man discussed earlier. Hemodynamic studies performed in septic models similar to ours reveal a hemodynamic state akin to that found in cases of peritonitis and septic shock in man (186, 248, 252). In addition to the systemic hemodynamic changes, the respiratory system reacts, as seen in man, with an increase in the mean pulmonary artery pressure and the pulmonary vascular resistance with reduction of arterial oxygen tension.

This model for inducing experimental bacterial peritonitis does not eliminate the variations in intrinsic host resistance noted among different experimental animals (253) but it uses a standardized inoculum based on body weight for which the exact bacterial composition is known.

By constructing total gastric fistulae in our dogs, we have been able to study several aspects of gastric secretory function during stress ulceration. The use of conscious dogs has allowed us to follow the evolution of stress ulceration over a period of four days thus eliminating

some of the pitfalls of acute preparations and the effect of anesthesia.

Our model can be used for the investigation of other factors involved in the pathophysiology of stress ulceration such as gastric blood flow, gastroduodenal motility, and potential difference changes across the gastric mucosa. The use of this model would facilitate comparison of data from workers in this field.

4.2 Acid Secretion in Septic Erosion

Our experimental data have demonstrated that in a reproducible canine model in which bacterial peritonitis led to septicemia and acute gastric erosions, all the three phases of gastric acid secretion (i.e. vagal, parietal and antral) were significantly elevated during the period of sepsis. As the sepsis was controlled by the animal, all phases of acid secretion returned to normal values, and there was healing of the gastric erosions.

In febrile conditions, derangement of gastric function is frequently present. It may be either in the form of motor disturbance or manifested as secretory anomaly. For instance, nausea or vomiting frequently marks the onset of many acute infections. Anorexia as a rule persists throughout the course of such illness. These phenomena point to an impairment of the tone and motility of the stomach and have been attributed to the action of toxins on the gastric musculature. They usually disappear after the disease

process subsides.

There is evidence in the literature suggesting that there is lowered gastric activity in human subjects in the presence of many infectious diseases (257, 258). This contention has been supported by experiments with gastric pouches in dogs (259,260). On the other hand, many authors (261,262) have presented clinical observations which suggest that there is a rise in human gastric acidity in the presence of infection.

Howe and associates (189), while studying gastric secretory response of dogs following various surgical processes, noted marked increase in acidity in those dogs whose wounds had become inadvertently infected. After the sepsis had subsided, gastric acidity returned to normal. The increased acid output following sepsis has been confirmed in our experiments in which all phases of gastric acid secretion were significantly elevated during the first two days after induction of peritonitis despite concurrent temperature elevation.

The role of gastric acid secretion in the etiology of stress ulcer is debated, but it is generally conceded that the "presence of acid within the gastric lumen is mandatory for the experimental production of stress ulcer". Acid must be present if erosion, ulceration and hemorrhage are to occur (72). In all experimental models, acid is the

prerequisite to mucosal injury (71, 149, 156, 201). Skillman et al. (71) and Moody and Aldrete (156) have demonstrated that adequate H ion concentrations are necessary for ulcerogenesis. Exposure of the gastric mucosa to hydrochloric acid in the presence of hemorrhagic or endotoxic shock and for bile acid will result in the development of acute gastric erosions (71, 210), but erosions do not occur if vigorous antacid treatment is instituted (263-265). In clinical studies, acid is important in the initiation and potentiation of bleeding acute gastric erosions in severely ill patients (265).

Values of acidity in patients and animals stressed by operative or accidental trauma, burns, and sepsis have been reported to be elevated (265, 267), low (57-59, 97) and normal (49, 268). Robbins, Idjadi, Stahl and Essiet (267) studied 32 patients with major trauma, 13 patients with sepsis and 6 patients who had suffered burns of more than 30% of the body surface. There was a significant increase in the titratable acid in all patients in the various categories and the acid values were very elevated in those patients who developed bleeding. Stremple (269) studied 36 civilian patients who were admitted to hospital because of multiple trauma. Twelve-hour acid output was determined. In the more severely injured, acid output continued to increase markedly in the first 72 hours after injury. Patients with

less severe trauma had relatively normal mean acid output throughout this period.

The differences reported may be partially explained on increased gastric mucosal permeability that occurs in severely ill patients. It has been pointed out that because an abnormally permeable gastric mucosal barrier may be the salient gastric mucosal abnormality precipitated by stress, the inability to measure gastric hyperacidity in stressed patients may be due to an abnormally high degree of back diffusion of H ion through an abnormally permeable gastric mucosal membrane (71, 72). In other words, H ion may be secreted in higher concentrations but may not be measured because it is escaping through the barrier.

The apparent discrepancy may also be explained on the fact that acid secretory studies have been carried out under completely uncontrolled conditions and at varying times after the initial insult. Gastric acidity may depend on the time after the injury, being low in the first few post-injury hours or days, and increasing if the insult persists (94).

Another major problem has been the different techniques used in studying acid secretion. These have consisted of one hour basal secretion, 12-hour overnight secretion, 90-150 minute total titratable acid and non-augmented 2-hour fasting gastric analysis. In none of the acid

studies have the vagal, antral and parietal phases of gastric secretion been specifically analyzed.

Silen and Skillman (85) suggest that hypersecretion of acid may not be important for ulcerogenesis because "even a small amount of acid appears to be capable of producing stress ulcers in the presence of ischemia". Eastwood (270) has also found that the presence of small amounts of acid was sufficient to produce bile-salts-induced acute gastric injury.

It is not clear at this time what the mechanism responsible for the increased acid output in sepsis is. Since all phases of gastric secretion were significantly elevated, we assayed serum gastrin in the dogs. There was no elevation in gastrin levels. Rosenthal, Czaja and Pruitt (271) measured serum gastrin levels and gastric acidity in 31 patients with burns. Although the gastrin levels were not elevated, acid output increased to above normal values. In 1970, Felming, Bowen and Thompson (cited by Stremple in discussion of paper by Stremple et al.(58)) prospectively measured serum gastrin levels in 37 wounded soldiers in Vietnam but found no significant difference between those who developed bleeding stress ulcers and those who did not. The causes of the increased acid output may therefore not be attributable to gastrin stimulation.

Histamine has been suspected as being involved in stress

ulcer. Singh et al (167) found increased blood histamine concentrations in guinea pigs in which experimental stress ulcers developed. In 1968, Levine and Senay (272) found that in association with stress there was significant increase in gastric histidine decarboxylase activity, and the degree of increase correlated positively with the incidence and severity of gastric lesions. They also found that Brocresine, an inhibitor of histamine biosynthesis, afforded the gastric mucosa protection from the ulcerogenic effects of stress.

The etiologic significance of histamine in stress ulcer remains conjectural. During stress, histamine is liberated from mucosal stores and histamine capacity is increased (120, 150, 154, 273). As a result, histamine reaches a high concentration in mucosal interstitial fluid and exerts its characteristic actions upon the mucosa. Secretion of acid is stimulated and even though acid diffuses rapidly into the mucosa, the amount of acid in luminal contents may actually be increasing as the result of copious secretion (273).

It is interesting to note, in this respect, that our studies and studies done elsewhere on the effect of Cimetidine, a histamine H 2 receptor antagonist, attenuates and even prevents experimental stress ulceration.

Even though it is difficult to underline any neural

or neurohumoral mechanisms which might be involved in increasing the acid output in sepsis, it is equally difficult to exclude completely any such mechanism. The role of the vagus might not be significant because if it was involved, one would expect elevation in serum gastrin level since vagal stimulation causes gastrin release from the antrum. Also, vagotomy alone in patients bleeding from acute erosions, does not give satisfactory results and it is associated with a high rate of rebleeding.

Selye (35) asserted that "gastrointestinal changes, especially erosions, are not the result of ACTH and corticoid discharge and indeed are aggravated by hypophysectomy or adrenalectomy". In 1972, Stremple et al(58). did not find any elevation in urinary excretion of adrenocorticosteroid metabolites in trauma patients whether they did or did not develop stress ulcers. They consequently disagreed with the postulate that increased endogenous corticosteroids are involved in stress ulceration.

4.3 Role of Cimetidine in the Evolution of Stress Ulcer

Bleeding stress ulcers are a difficult problem to manage since they often occur in critically ill patients who are debilitated and may have overwhelming sepsis. The prevention, control and therapy of this disease phenomenon remains an unresolved problem. In some patients,

hemorrhage is massive and continues, in spite of gastric lavage with iced saline and replacement of blood. Surgical intervention is usually necessary in such cases. The operation of choice to control bleeding and prevent recurrence is still controversial. Analysis of the literature (162) reveals that subtotal gastrectomy alone was associated with a high incidence of rebleeding (52%) and mortality is about 30%. The addition of vagotomy significantly reduced the recurrence of bleeding and the mortality. Control of rebleeding was greater with vagotomy and partial gastrectomy (15%) than with vagotomy and pyloroplasty (29%). Menguy and associates (274) have advocated total gastrectomy for severe stess bleeding. Although this will stop the bleeding and offer complete protection against rebleeding, it is associated with high morbidity and mortality and cannot be recommended as a routine primary procedure. Any kind of surgery adds further stress to the critically ill patient. The need for prevention of stress ulceration is therefore obvious.

Experiemtnal evidence shows that raising the gastric pH with antacid or anticholinergic drugs reduces the incidence of stress ulceration and hemorrhage (227, 275), emphasizing the important pathogenetic role of gastric acidity.

Because of evidence (276) that the H-2 receptor

antagonists cause a strong inhibition of gastric acid secretion, it was logical to assess the effectiveness of one of these compounds, Cimetidine (Tagamet, Smith, Klein and French, Canada Ltd.) in preventing stress ulceration.

The H-2 receptor antagonists, a family of drugs whose main property is to inhibit gastric acid secretion, were developed by Black and associates (276) in 1972. These drugs are similar to histamine in that they are imidazole derivatives, but they differ from histamine in that their side chains are longer (Figure 13). The early compounds were partial agonists at low doses and antagonists of histamine only at high doses, when they reduced acid secretion (277). In order to separate the agonist and antagonist activities, the guanidine group was substituted with non-basic groups and the result was a thiourea derivative which had no agonist properties, but was active as an antagonist. The first such substance was burimamide which was used to characterize histamine H-2 receptors pharmacologically (276). The compound, however, lacked adequate activity when taken orally for exploration of its clinical potential (278). In an attempt to achieve a further increase in antagonist potency, metiamide was obtained by altering the basicity and tautomeric properties of the rings in burimamide (279). Metiamide was shown to be highly effective clinically reducing hypersecretion of gastric acid. However, the occurrence of a reversible

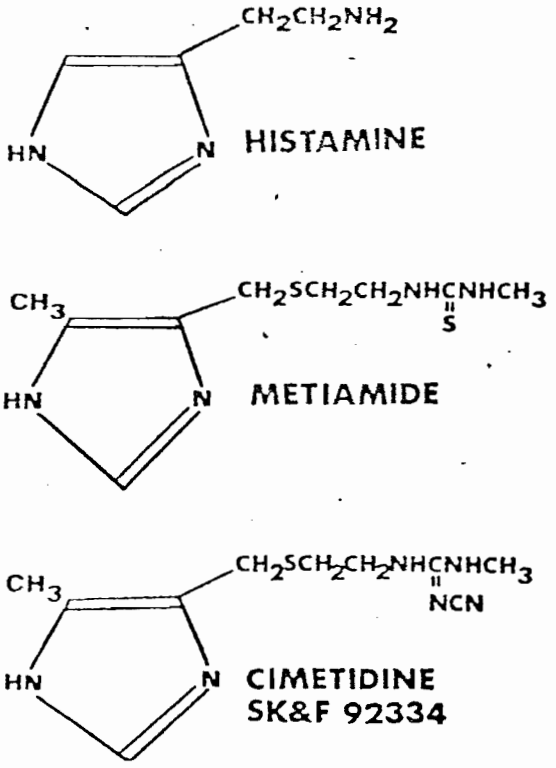

Fig. 13 Chemical structures of histamine,

agranulocytosis in a small number of patients limited the use of metiamide (280). Agranulocytosis was suspected to be related to the thiourea group in metiamide so it was replaced with a cyanoimino group. This gave birth to Cimetidine.

The effect of cimetidine on acid secretion has been investigated quite extensively. After oral or parenteral administration, cimetidine has been found to produce a dose-related reduction of the volume and concentration of basal gastric acid secretion as well as acid secretion stimulated by gastrin, food, caffeine, histamine, insulin, gastric distention and cholinergic agonists (281, 282, 283).

Cimetidine, in contrast with metiamide has been found to have almost no known toxicity. In human and experimental animals, cimetidine is rapidly absorbed from the gastrointestinal tract and it is excreted unchanged in the urine (284).

This broad antagonism raises the question of a critical physiologic, perhaps intermediary role of histamine in the stimulation of gastric acid secretion by all stimuli. The obvious application of the antisecretory effect is to the treatment or prevention of acid-peptic diseases of the upper gastrointestinal tract. Cimetidine has been found to be effective in the control of duodenal ulcers. Binder and associates (285) conducted a double blind multicenter trial of cimetidine in both inpatients and outpatients with

duodenal ulcer disease. There was a significant relief of ulcer symptoms in all patients treated.

Since acid plays an important role in the pathophysiology of stress ulcer, inhibition of acid secretion must be important in the control or prevention of these lesions. There are several studies in the literature that have addressed themselves to this problem. MacDonald and asscoiates (286) treated a group of patients with stress-induced upper gastrointestinal bleeding. They found that metiamide successfully stopped the bleeding in most patients. Cimetidine (300 mg QID) given simultaneously with aspirin (650-975 mg QID) to arthritic patients protected the gastric mucosa from injury and significantly reduced fecal blood (287).

In 50 patients with fulminant hepatic failure, MacDougall, Bailey and Williams (288) demonstrated that cimetidine or metiamide therapy significantly reduced stress bleeding. They showed that only one of 26 patients given cimetidine bled, compared with 13 of 24 controls who were given placebo.

In a preliminary experimental study from this laboratory (238), it was demonstrated that cimetidine might have an important role to play in preventing the development of sepsis-induced gastric erosions. In the present study, prophylactic cimetidine (6 mg/kg QID) decreased basal acid output over 30%, food-stimulated acid output by 63% and pentagastrin-stimulated acid output by about 37% on the first day after induction of peritonitis. Endoscopy

demonstrated acute fundic erosions with bleeding in three dogs and non-bleeding erosions in two dogs. When prophylactic cimetidine (12 mg/kg QID) was given basal acid output was decreased by 70%, food-stimulated acid output was abolished completely, and pentagastrin-stimulated acid output decreased by about 35%. On gastroscopic examination, and at autopsy, there were no erosions in the stomach.

The precise mechanism by which cimetidine prevents acute erosions in the stomach is not settled yet. Since cimetidine had been demonstrated as a strong inhibitor of gastric secretion and since the presence of acid is very important in the pathogenesis of stress ulcer, it was easily postulated that the antiulcer effect might be related to the suppression of gastric secretion (289). The effect of cimetidine on gastric acid secretion has been attributed to its antagonistic action at H-2 receptors which when extrapolated reflects its inhibition of the action of endogenous histamine. This in effect concedes that histamine is the final common mediator for acid secretion, a hypothesis that still remains controversial.

Some recent studies have suggested that cimetidine protects the gastric mucosa from stress ulceration by some other mechanisms apart from inhibition of acid secretion. In 1975, Dai et al.(290) observed that metiamide did not further reduce the already inhibited secretion in the stressed

rat, but did significantly reduce lesion formation. They suggested that the antiulcer effect of metiamide was not related to the effect on gastric secretion. This observation was confirmed by Bugajski et al (291) who also reported that metiamide, at a dose range that did not reduce acid (0.2 - 1.2 mg/kg), produced marked inhibition of cold-restraint stress ulcers in rats.

Using parenteral aspirin plus topical acid in a rat model, Kauffman and Grossman (292) found that cimetidine protected against antral ulceration. In a more recent study by Guth and coworkers (293) in which acute gastric lesions were produced by intragastric instillation of aspirin plus HCl in the pylorus-ligated rat, acid was given exogenously so as to negate any protective antisecretory effect of cimetidine. In spite of the presence of topical aspirin plus HCl, cimetidine decreased lesion formation, indicating that cimetidine can protect against lesion formation by a mechanism other than inhibition of acid secretion. They have suggested cytoprotection by cimetidine whilst cautioning that "the importance of antisecretory effect in protecting against lesion formation should not be denied".

On the other hand, Carmichael et al (294) using a rat aspirin plus HCl model, reported no significant reduction in lesion score by cimetidine. Our study reveals that

gastric erosions were only prevented by the higher dose of cimetidine (12 mg/kg QID) which reduced basal acid output by 70%. The lower dose of 6 mg/kg QID reduced basal acid output by only 30% and did not prevent acute gastric ulceration. If cimetidine prevents acute stress ulceration via a cytoprotective mechanism, we would expect protection in our 6 mg/kg QID dogs, but this was not the case. Our study thus demonstrates that cimetidine prevents gastric erosions in the septic dog model only when significant acid reduction occurs.

Since seriously ill patients, especially those with sepsis, are at great risk to develop stress bleeding, prophylactic cimetidine treatment would be warranted in this group. A controlled clinical trial would answer the question as to whether prophylactic cimetidine is necessary in critically ill patients.

4.4 Role of Prostaglandins in Stress Ulceration

Prostaglandin E_2 (PGE_2), one of a group of 20-carbon unsaturated fatty acids (Fig. 14) has several known actions that may modify the course of acute stress ulcerations (295,296). Even though previous reports have demonstrated that the PGs protect the gastric mucosa against the damaging effects of a variety of ulcerogens (295-299), their effect on the evolution of sepsis-induced acute gastric erosions has not been investigated.

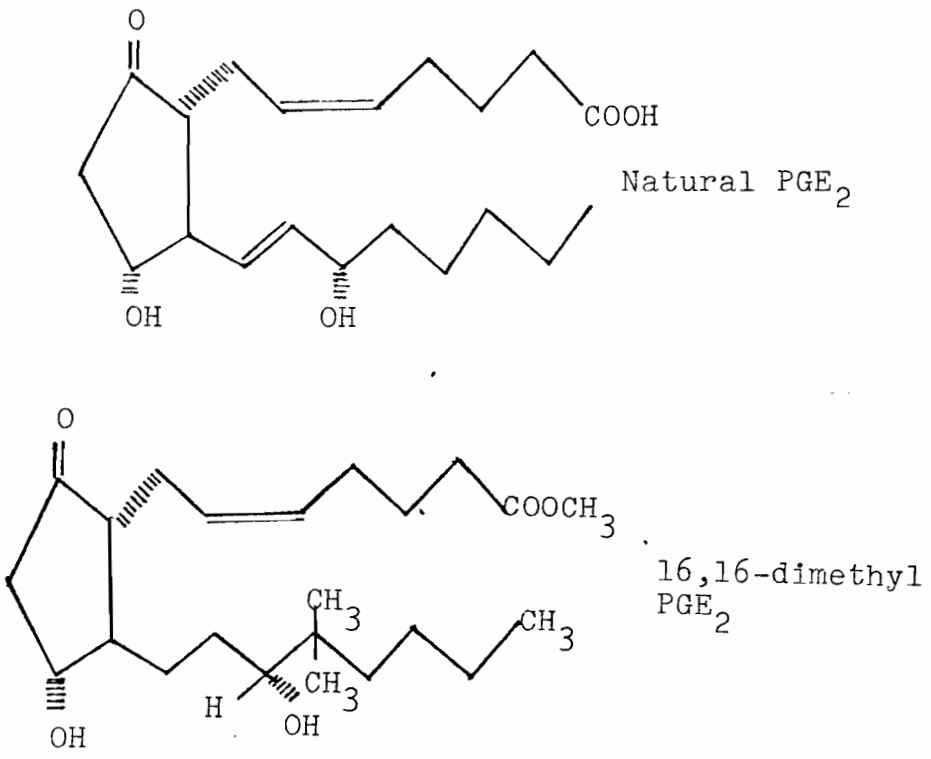

Fig. 14. Chemical structures of natural prostaglandin E_2 and 16, 16-dimethylprostaglandin E_2.

Prostaglandins and PG-forming enzymes have been found in all gastrointestinal tissues studied so far. Little is known about the distribution within the gut wall, but in the human stomach, most of the PGE_2 occurs in the mucosa (300). More specific localization within the different layers of the gut wall and within cells remains to be determined. The mechanisms of PG storage in the gut is uncertain. It is not known whether the PGs exist free in the cell or not. Release of PGs is increased by vagal stimulation (301) and it has been shown that radioactively labelled PG absorbed from the lumen of the rat intestine is mostly metabolized in the gut wall (302).

Prostaglandins have been found to influence three major functions of the gastrointestinal tract.

a) Motor activity: A clear role for PGs in gut motility has not yet been established. In vivo, it has been shown that whether contraction or relaxation takes place depends on species and on segment of the gastrointestinal tract studied.

b) Intestinal ion transport: PGs enhance net secretion of water and electrolyte from the jejunum (303). This explains the development of diarrhea after administration of certain PGs.

c) Gastric secretion: Certain natural PGs, particularly of the E and A type, have been found to inhibit gastric secretion in several species, regardless of the gastric

stimulant (295, 304-309). Inhibition is dose-related, becomes evident within 15 minutes, reaches a maximum after 30 minutes and returns to pretreatment levels within 60-90 minutes. The short half-life coupled with the inactivity of the natural PGs on oral administration led to the development of PG analogs which could be administered orally and which would have a longer duration of action.

Some of the PG analogs that have been synthesized and tested for their antisecretory properties are 15-methyl PGE_2 and 16,16-dimethyl PGE_2 ($DMPGE_2$) (310-311). $DMPGE_2$ is found to be 50-100 times more potent than PGE_2 in inhibiting gastric secretion (311) and exerts a longer acting effect of over two hours when given either orally or parenterally. The unique properties of 15-methyl PGE_2 may be due, in part, to the fact that the methyl radical protects the OH^- at the C 15 from being degraded by 15-hydroxydehydrogenase into 15-ketoprostaglandin which is usually of diminished biological activity.

We have demonstrated in our septic dog model that $DMPGE_2$ (0.4 µg/kg QID) completely abolished basal acid output and food-stimulated acid output and significantly ($p < 0.01$) decreased pentagastrin-stimulated acid output on the three septic dogs. Acute fundic erosions were also totally prevented. The results further show that even though $DMPGE_2$ (0.2 µg/kg QID) did not significantly

decrease acid output during the first two days of sepsis, gastroscopy did not demonstrate any fundic erosions. This study shows that $DMPGE_2$ protects the gastric mucosa against sepsis-induced erosions at a dose that does not significantly affect gastric acid output.

This finding is in agreement with the conclusions of several other workers who have also found that various PGs and their synthetic analogs produce striking inhibition of gastric mucosal ulceration in many animal models (296, 297, 312) without inhibiting acid secretion. This anti-ulcer effect has been termed "cytoprotection"(304). Recently, Kauffman and Grossman (292) and Carmichael et al. (294) have shown that treatment with methyl analogs of PGE_2 reduced the severity of antral ulceration caused by parenteral aspirin and gastric perfusion with hydrochloric acid. Using a constant exogenous acid load delivered to the mucosa allowed separation of effects related to inhibition of acid secretion from other mechanisms. In another study, Tepperman et al. (313) established that $DMPGE_2$ effectively protected canine gastric mucosa against the damaging effects of alcohol. They found this protection to be independent of inhibition of acid secretion because there was protection both in the presence and absence of hydrochloric acid.

Although the cytoprotective effect of PGs appears to

be well confirmed at this time, the mechanism of protection afforded by these agents is not established. Among the possibilities that have been considered are:

a) Cytoprotection may be related to the potent anti-secretory properties of PGs. Available evidence (292,294,296, 312,313) militate against such a mechanism. Firstly, PGs which lack antisecretory activity still possess cytoprotective properties (296,314). Secondly, several PGs have been found to prevent the development of multiple ulcerations of the small intestine produced in rats by non-steroidal anti-inflammatory compounds (296). Furthermore, it has been demonstrated that effective doses for cyto-protection are often much lower than the median effective doses (ED_{50}) for antisecretion (296,315).

b) Attempts have been made to relate the concentrations of PGs in gastric juice to gastrointestinal ulcers. Hinsdale et al (316) measured E prostaglandins in plasma and gastric juice of normal subjects and in patients with duodenal ulcers. Gastric juice and plasma levels of PGEs were significantly higher in normal volunteers than in ulcer patients, during basal state. The authors suggested that "the relative deficiency of PGEs in the ulcer group may indicate a role for PGs in the patho-physiology of gastric hypersecretion. If PG deficiency is the cause of gastrointestinal ulcers in man, then it should be possible to correct this by administering

the deficient PG. Cheung's group (299, 317) have disputed this hypothesis. In a similar study, they found that patients with acid peptic disease have slightly higher PGE output and concentrations than normal subjects during basal and stimulated acid secretion.

c) Aspirin is known to inhibit PG synthetase (318), the enzyme system responsible for endogenous PG production; therefore, the cytoprotective action of $DMPGE_2$ against aspirin-induced injury may be explained on the basis of replenishing gastric mucosal PG. However, $DMPGE_2$ has also been shown to protect against gross mucosal ulceration induced by Ethanol (296, 313, 321), bile (319), and serotonin (320) in the rat. Because these agents have not been shown to inhibit the PG synthetase system, mechanisms other than alterations in PG synthesis must be involved in cytoprotection.

d) PGs may act as trophic hormones for the gastrointestinal mucosa and they may be necessary to maintain the morphological integrity of the mucosa (321). There is however, substantial evidence to indicate that PGs do not behave as circulating hormones but they act at the site of production (299, 322).

e) It has recently been shown by Soll (323) that PGE_2 inhibits cAMP in the isolated parietal cell. Mangla and coworkers (324) have also demonstrated stimulation of

adenylate cyclase activity in rat gastric mucosa bathed with aspirin. It is possible that drugs which influence cAMP production in the gastric mucosa may have significant effects on mucosal resistance to injury. The protective effect of PGs may involve this mechanism. Whether the PGs promote the formation of cAMP which would be cytoprotective is unresolved.

f) The ability of the PGs to stimulate alkaline secretion may contribute to their cytoprotective action in the stomach. It has been suggested that HCO_3 ions secreted by surface epithelial cells of the stomach may protect the gastric mucosa from injury by intraluminal acid. This protective role is reported to be inhibited by a variety of ulcerogens such as aspirin and indomethacin (325-327). Recently, Garner and Heylings (314) demonstrated that $DMPGE_2$ and $PGF_{2\alpha}$ stimulate gastric HCO_3 ion secretion and they suggested that this may contribute to some of the cytoprotective actions of the PGs in vivo.

The mucosal cytoprotection afforded by the PGs offers a very good hope in the search for a safe and effective protection against damage to the mucosal lining of the upper gastrointestinal tract caused by the ingestion of noxious agents or the stress of severe illness and injury. The cytoprotective effect of PGs makes these agents very attractive since mucosal protection can be achieved without

compromising acid secretion.

4.5 Role of Metoclopramide in Septic Erosion

The role of metoclopramide in the evolution of stress ulcers in our septic model has been examined. Metoclopramide (1.5 mg/kg QID), while attenuating the severity of acute gastric erosions in the dogs was unable to prevent the development of the erosions. Only one out of the four dogs in the group had actively bleeding gastric erosions. The other three dogs had less severe injuries varying from simple mucosal petechiae to non-bleeding erosions.

Whereas metoclopramide did not have any significant effect on the secretion of gastric acid, there was a remarkable reduction in the amount of duodenal content that is regurgitated into the stomach during the period of peritonitis. As discussed in 1.3.13.3.3, duodenogastric reflux of bile into the stomach is a very important pathophysiologic factor in the etiology of stress ulcers and the competence of the pylorus is important in the prevention of retrograde flow of duodenal contents in health (141).

It has been shown that in the presence of gastritis and gastric ulceration, the pylorus is incompetent and allows reflux of duodenal contents into the stomach (136). A similar situation occurs in peritonitis. We have found that during the period of peritonitis large quantities of bile-stained duodenal contents are refluxed into the

stomach; an indication of a possible compromise of the pyloric mechanism caused by paralytic ileus.

Paralytic (adynamic) ileus is the most common complication of diffuse peritonitis and massive trauma (328, 329). The gastrointestinal wall becomes congested and edematous, and neuromuscular mechanisms responsible for peristalsis are thrown out of function. In the early stages of peritonitis, the extrinsic sympathetic nerves of the gastrointestinal tract are likely to be irritated by congestion and edema of the mesentery in which they run, and gastrointestinal inhibition may occur (329). Suppression of the neuromuscular mechanisms responsible for gastroduodenal peristalsis has very serious consequences. Since the pyloric sphincteric action depends on the development of antral peristalsis, atony of the antrum leaves the pylorus incompetent and there is regurgitation of bile from the duodenum into the stomach (160). The presence of bile in the stomach coupled with the increased gastric acidity demonstrated in these studies set the stage for the development of severe acute gastric erosions in the fundus of the stomach.

We postulated that perhaps if we could stimulate the pylorus to maintain its competence during the period of peritonitis, we would eliminate retrograde flow of duodenal content into the stomach and hence delete the bile factor. To achieve this goal, we used Metoclopramide (Maxeran).

Metoclopramide was first synthesized in 1961 following a decade of development originating from the synthesis of procainamide, a drug with local anesthetic and therapeutically useful antiarrhythmic properties (Figure 15). It is a potent antiemetic drug (330) which has also been found to have a stimulatory action on the gastrointestinal motor activity (331,332). Extensive studies in man and in a variety of experimental animals (137, 331, 333-336) have established that metoclopramide after oral or parenteral administration, rapidly affects the motility of the gastrointestinal tract. Its effects include improved resting tone of the esophageal sphincter, improved tone and peristalsis of the stomach with accelerated gastric emptying, enhanced pyloric acitivty, distention of the duodenal bulb and increased peristalsis of the duodenum with accelerated transit through the duodenum and jejunum. It has comparatively little overall effect on colonic motor activity in vivo.

Many studies have shown that metoclopramide increases both esophageal motility and lower esophageal sphincter pressure in normal subjects and in patients with gastroesophageal reflux (337, 338). Metoclopramide increases resting sphincter pressure without affecting relaxation; the rise in pressure is proportional to the dose of the drug and the basal pressure (338).

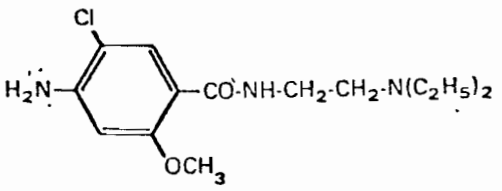

Fig. 15. Chemical structure of metoclopramide. Procainamide lacks the 5-chloro and 2-methoxy aryl substitutes.

The effect of metoclopramide on gastric contractions in man is, in general, more pronounced in the antrum where it induces vigorous and large antral contractions and tends to produce coordination of the antral and duodenal wave complexes (339-341). This effect is also observed in both conscious and anesthetized dogs (336, 341). In vitro experiments with isolated preparation from the guinea pig or rat stomach show that metoclopramide produces two to three-fold increase in the amplitude of antral contraction (342).

Manometric and radiologic studies showed that metoclopramide stimulated pressure in the stomach and small intestine. The resultant vigorous antral contractions enhanced gastric emptying and small bowel transit. Gastric emptying is accelerated particularly in subjects with abnormally high gastric emptying times (336). The enhanced duodenal contractions occur during the terminal antral contraction. This is the most favorable pattern for gastric emptying and also prevents reflux of duodenal contents into the stomach. Pyloric sphincter pressure, like that of the lower esophageal sphincter, is increased by metoclopramide (137).

Metoclopramide produces changes in gastric activity in the absence of any significant alteration in gastric secretion. Extensive investigations in man and in a variety

of experimental animals have shown that the drug has no significant effect on gastric acid secretion or serum levels of gastrin (333, 337). In the esophageal and pylorus-ligated rat preparation, metoclopramide had no effect on volume or acidity of gastric secretion at a dose which accelerated gastric emptying (336).

The precise mechanism of action of metoclopramide in the gastrointestinal tract is uncertain. It stimulates gastrointestinal motility in in vitro experiments (339, 343) and its action is inhibited by atropine but not hexamethonium (a ganglion blocker) (343). The mechanism of action may therefore not be dependent on the integrity of the vagus nerve or on other ganglionated extrinsic nerve pathways (336). It has been suggested that the possible locus of action of metoclopramide may be at intramural cholinergic neurons which are responsible for modifying gastric motility but not acid secretion, either by a direct stimulation or removal of inhibitory circuits or pathways (335, 336).

From the results of our studies and those of Jacoby and Brodie(336), it would appear that metoclopramide would be useful in conditions associated with gastrointestinal hypomotility and stasis; conditions which in our septic model give rise to duodenogastric reflux of bile into the stomach with subsequent development of acute gastric erosions. We were not successful in completely abolishing

mucosal injury with the dose of 1.5 mg/kg QID of metoclopramide. A higher dose might have been more successful but in a preliminary study, 2.0 mg/kg QID had some side effects including severe vomiting.

Our results demonstrate that metoclopramide may only attenuate the severity of stress ulceration. Complete prevention may require higher, and perhaps intolerable, doses of the drug.

4.6 The Gastric "Mucous Barrier" in Sepsis

Our results show that in the untreated septic dogs, there is a significant increase in the levels of free fucose and sialic acids in the basal gastric juice obtained on septic Day 1. The increase is less (but still significant) on Day 2, and by Day 3, they had returned to near-normal values. Protein content, however, dropped significantly on Day 1 but started rising to normal values on Days 2 and 3.

Normally, the level of fucose is about 4-5 times higher than that of sialic acids in the soluble mucin of gastric juice (344). Fucose is found mainly in the stomach, but sialic acid is found in large quantities in the saliva and in the duodenum (345). Since we could not prevent our dogs from swallowing saliva and since we could not abolish regurgitation of duodenal content into the stomach, it is quite likely that the large amount of sialic acid that

we found in the soluble mucin had come from these other sources.

The drop in protein level is difficult to explain. It could be that most of the protein was shed into the residual gastric juice which was discarded at the beginning of the gastric secretory studies. The subsequent return of protein to normal levels may be explained by the fact that healing of the gastric mucosa occurs rapidly if the initial insult is removed or reduced in severity. Statistically, there was no correlation between the protein level and the levels of fucose and sialic acid.

Drug control studies with Cimetidine (6 mg/kg QID), $DMPGE_2$ (0.2 µg/kg QID), and Metoclopramide (1.5 mg/kg QID) did not have any significant effect on the levels of protein, fucose and sialic acids. Subsequently, there was increase in the levels of fucose and sialic acid in septic dogs which were treated with these durgs at the doses indicated above. On the other hand, Cimetidine (12 mg/kg QID) and $DMPGE_2$ (0.4 µg/kg QID) completely abolished acid secretion, increased secretion of mucus and significantly elevated the level of protein, fucose and sialic acids. These levels were,however, not significantly altered during the period of sepsis.

In a study on rats, Bolton, Palmer and Cohen (346) found out that the total amount of mucus produced was significantly increased by $DMPGE_2$. They suggested

that increased mucus production stimulated by the E_2 prostaglandins may contribute to their cytoprotective action. This suggestion may only be partially true. We have been able to achieve complete protection with $DMPGE_2$ at a dose (0.2 µg/kg QID) which did not significantly affect mucus production.

A pattern appears to emerge from our results: whenever there was acute gastric ulceration, there was an increase in the levels of free fucose and sialic acids in the gastric juice. It is difficult to make any deduction from the results obtained for sialic acids since we could not prevent contributions from saliva and the duodenum. The results for fucose, on the other hand, seem to link the free fucose level in gastric juice to acute gastric ulceration.

In a prospective study of gastric secretion composition in 50 combat casualties, Stremple et al (58) found that sialic acid output was higher in those patients who developed proven gastric ulcers. Fucose output, on the other hand, was not significantly different between those patients who developed proven gastric ulcers and those who did not. These authors did not make any mention of contribution of sialic acids from the mouth or the duodenum, but it can be assumed that, like us, they could not prevent this. We cannot reconcile their findings on fucose with ours. We can only suggest that, perhaps, the difference has been

caused by the time of collection of the gastric juice and the different modes of collection.

Fucose (a deoxy-sugar) and sialic acid (a derivative of neuraminic acid) are prominent oligosaccharide chains or branches of glycoproteins found in mucus secretions such as gastric mucus. They have been used as indicators of mucus production (58, 345), and the "health" of the "mucous barrier" (347, 348).

The place of mucus as an integral part of the defense mechanism of the stomach has been the subject of several studies (347, 348). It was Claude Bernard (1856), who, more than a century ago, held that the mucus lining of the stomach was like a "vase imperméable". The question of how mucus does function in this role is not yet answered.

In 1954, Hollander (143), enunciated the concept of a two-component self-regenerating mucous barrier. According to this hypothesis, the gastric mucous barrier is a composite of two integrated structural units comprising of 1) the layer of viscous mucus secreted by the mucous epithelium and 2) the layer of tall columnar cells immediately beneath this sheet of mucus, together with the low columnar and cuboidal cells which line the crypts of the gastric gland.

Based on experimental models, it has been hypothesized that diminished production of gastric mucus might make the underlying mucosa more vulnerable to H ions or that

alterations in the individual glycoproteins and muco-proteins might enhance the diffusion of H ions (350). This hypothesis has been difficult to prove and the exact mechanism by which mucus might protect the underlying epithelium remains to be defined. It has been suggested that "the mechanism lies in the lubricating action of the highly viscous and slippery mucus which should facilitate the passage through the proximal alimentary tract of undigested roughage in the gastric chyme" (347).

The importance of mucus in many gastric lesions has been demonstrated by extensive biopsy which have shown on histopathological examination considerable differences in the type and amount of mucus (351, 352).

A valid objection to the study of only the soluble gastric mucus is that information on the viscous insoluble "visible mucus" coating of the gastric mucosa is lost. Studies of the "barrier" function of mucus must also include studies of the visible gel function. Nevertheless, the studies of the soluble fraction reported herein indicate that useful information may be obtained relating mucus secretion to alterations of the gastric mucosa.

Even though the data reported herein do not prove the existence of the protective "mucous barrier", it is reasonable to consider these data as "circumstantial evidence" in favor of this hypothesis. It is likely, as with H ions and pepsin secretion, that the rate of secretion

and the composition of gastric mucus may reflect the functional state of the gastric mucosa in health and disease:

4.7 Sodium and Potassium Fluxes in Sepsis

The results presented indicate that there is significant increase ($p<0.01$) in the output of Na and K ions in the gastric juice when there is gastric mucosal damage in sepsis. The output of these ions returns to normal levels by the third day after induction of peritonitis when resolution of the peritonitis is taking place and when the gastric mucosa is healing.

Davenport (145, 149-151, 154, 353) has demonstrated several times that whenever there is a break in the mucosal barrier, there is increased back-diffusion of H ions into the gastric mucosa with a concomitant bidirectional increase in Na and K ion movement, the net flux being into the lumen. Damage to the mucosal barrier has therefore been portrayed as an increased mucosal permeability to these ions (154).

Impaired active ion transport has been suggested as the underlying mechanism responsible for the altered movement of H and Na ions. Decreased active transport of H ions would yield results indistinguishable from back-diffusion of this ion as measured by the usual collection procedure, and, decreased active transport of Na ion from lumen, to blood (354) would lead to accumulation of this

cation in the gastric juice after mucosal damage. Work by Shanbour and her colleagues (355-358) indicate that the initial response of the gastric mucosa to topical damage with ethanol involves impairment of active ion transport. The isolated dog gastric mucosa transports Na ions from mucosa to serosa (354, 359). If such a postulated Na ion transport is inhibited, it may appear as a net efflux of Na ions into the lumen, which has been observed and used as a criterion of mucosal damage (149).

Potassium fluxes across the resting gastric mucosa are very small under normal circumstances. However, when the mucosa is damaged by "barrier breakers" such as aspirin and acetic acid, there is a bidirectional increase in K ion movement with a net flux into the lumen, resulting in as much as 10-fold increase in lumenal K ion concentration. Potassium entering the gastric lumen after gastric mucosal damage may be derived from exfoliated mucosal epithelial cells as the result of either secretion of cellular disintegration. It may also come from extracellular fluid (360). When bleeding occurs, additional K ions come from plasma and erythrocytes.

Our results also show that Cimetidine and $DMPGE_2$ do not have any significant effect on the output of Na and K ions and therefore, when mucosal damage was not prevented by Cimetidine (6 mg/kg QID) there was increased output of these

ions in the gastric juice.

In a study of the effects of metiamide and $DMPGE_2$ on Na and H ion fluxes across the gastric mucosa, O'Brien and Carter (361) demonstrated that while $DMPGE_2$ causes profound inhibition when administered orally or intravenously, its effects on ionic fluxes across the mucosa are seen only after local application. When $DMPGE_2$ is given intravenously, however, there is no change in the ionic permeability of the mucosa. They could not demonstrate any effect of H-2 receptor blockade (using Metiamide) on the ionic fluxes before and after gastric mucosal barrier damage. They concluded that "it is unlikely that these receptors play a significant role in this process". Our results in the septic canine model support these findings.

Metoclopramide does not have any effect on gastric secretory activity (331, 336) and did not significantly influence the output of Na and K ions before and during the period of sepsis in our dogs. Since Metoclopramide could not completely prevent mucosal damage, there were significant increases ($p<0.05$) in the levels of Na and K ions in the gastric juice during the first two days after induction of peritonitis in our dogs.

CONTRIBUTIONS TO ORIGINAL KNOWLEDGE

Sepsis-related stress ulceration has been reported extensively in the literature but detailed investigation of the pathophysiologic factors involved has received scanty attention partly because of the poverty and limitations of previous experimental models.

The development of a reproducible septic canine model (in our laboratory) which presents most of the features found in the clinical situation has made it possible for us to take a closer look at some of the pathophysiologic factors involved in this condition.

Hitherto, acid secretory studies in sepsis have been difficult to control and have been limited to the vagal phase of acid secretion only. By creating total gastric fistulae in our model, it has been possible to study simultaneously variations in the vagal, parietal and antral phases of gastric secretion during the evolution of septic erosions. We have also shown that with resolution of sepsis, there is healing of gastric erosion and gastric secretory activity returns to normal.

Cimetidine and 16,16-dimethyl PGE_2 have been used successfully to prevent stress ulceration in our septic canine model. It has been established that Cimetidine acts through its antisecretory effect whereas the PGE_2 analog acts through a cytoprotective mechanism independent of acid inhibition. Metoclopramide will only prevent stress ulceration if it

can completely abolish regurgitation of duodenal contents into the stomach; otherwise, it will only reduce the severity of the gastric lesions.

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