CHAPTER

II

REVIEW OF LITERATURE

CHAPTER

IIa

AYURVEDA AND PEPTIC ULCER

The history of medicine in India can be traced to the remote past. The earliest mention of the medicinal use of plants is in the Rigveda, which is one of the oldest, having been written between 4500 and 1600 B.C. In this work mention has been made of some plants and their effects on man. Ayurveda, in fact, is the foundation stone of the ancient medical science of life and the art of healing.

AMLAPITTA AND PARINAMSHOOL are the two diseases described in the literature which are similar to peptic ulcer. The elaborate description of amlapitta in Kashyapasamhita (600. B.C.) is one of the most ancient reference . In the Ayurvedic text books namely, Yogratnakar and Madhavnidan have given a similar type of narration subsequently.

The word amlapitta denotes amla-sour and pitta- a type of secretion in the stomach. Hypersecretion of the sour acid secretion in the stomach seems to be the main pathogenetic mechanism in amlapitta, whereas parinamshool is the disease of stomach. Parinamshool is a condition in which the patient suffers from (shool) pain in abdomen during the process of digestion of food. Pain is relieved by vomiting or at the end of the digestion. It is aggravated by chillies, spices, rice etc.

The clinical symptoms are sour and bitter regurgitation (Tiktoamlodgar) and heart burn. Other symptoms include dyspepsia,nausea, heaviness in the abdomen, lassitude, anorexia, distension of the abdomen, gurgling, unformed stools, headache and piloerection.

AETIOLOGICAL FACTORS

These include, incompatible food, eating before the earlier ingested food is digested and emptied from the stomach, post-lunch sleep, intake of water in the middle of the meals, stale food, incompletely cooked food, unboiled milk, food prepared from finely ground grains, roasted food grains, horse gram, preparation from sugar cane, precursor of jaggery, and heavy food. Sour food and liquids can also create the acid pepsin disorder.

TREATMENT

Treatment of Amlapitta consists of emetics, medicated enema, and blood-letting. Drug treatment includes single plants, combinations of plants, medicated ghee, various formulations containing bhasmas and plants.

Treatment of parinamshool consists of emetics, various enemas, plant treatment, medicated ghee and numerous complex formulations.

Alcohol, salt, pungent food, black gram, sour food, suppression of natural urges, hot sun and anger should be avoided by the patient of parinamshool.

CHAPTER

IIb

GASTRIC SECRETION

The stomach, like most of the portions of the gastrointestinal tract, has four coats, the mucosa, submucosa, muscular coat and serosa. The surface area of the gastric mucosa in man is about 800 cm^2. The epithelial layer invaginates below the surface (0.5 to 2 mm) to form pits or foveolae, which communicate with the gastric glands and occupy 25-50% of the mucosal surface. There are about 100 pits per mm^2 of surface and 3 to 7 tubular glands empty into the bottom of each pit.

Three kinds of tubular glands are present namely, cardiac, gastric and pyloric. The cardiac glands are coiled and lined by mucus producing cell and are confined to the cardiac orifice region. The gastric glands are straight and simply branched, they occur in the fundus and over the greater part of the body of the stomach. The pyloric glands in the pyloric and antral regions are short and tortuously coiled with branched ends. A few argentaffin cells containing serotonin lie scattered on the basement membranes of the pyloric glands.

The secretion from cardiac, antrum and pyloric regions consists of an alkaline viscid mucus which prevents epithelium from attack by pepsin and acid secreted from the main region of the stomach. The rate of secretion from the cardiac and antrum are not affected by feeding or by substances that control the secretion of the gastric gland. The antral mucosa also secretes gastrin.

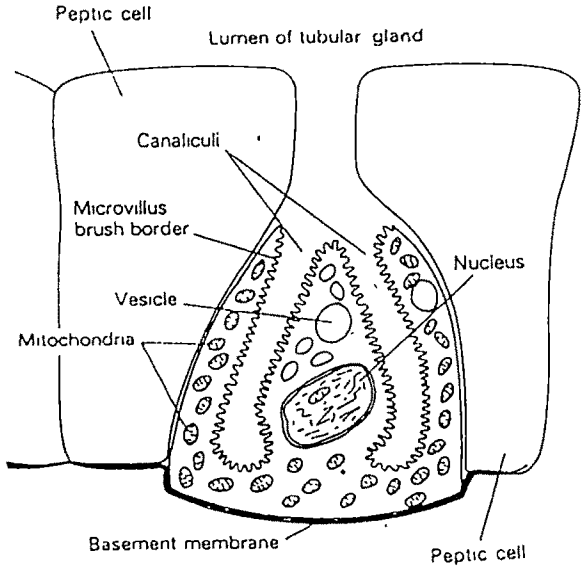
The epithelial cells of the mucosal surface and gastric pits also secrete an alkaline mucus. The gastric glands contain three types of cells which have different secretory functions.

Mucus cells, located mainly at the neck of the glands near the base of the gastric pit, secrete a soluble acidic mucopolysaccharide; they are stimulated to secrete by vagal impulse, and by direct chemical and mechanical stimuli. These cells are also thought to secrete intrinsic factors. Peptic cells are serous cells which elaborate granules containing pepsinogen.

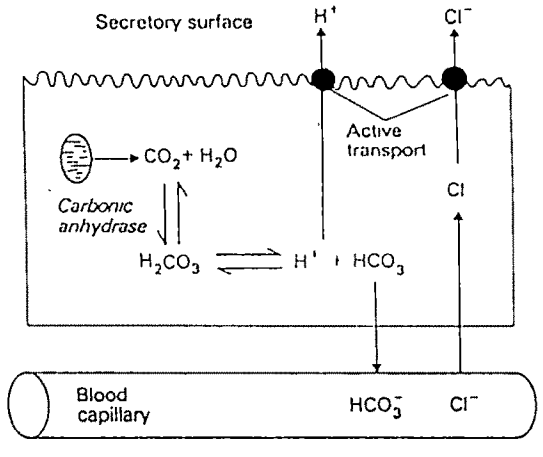
Parietal cell or oxyntic cells lie slightly behind the peptic cells. The secretory surface is covered with microvilli and is deeply invaginated to form channels termed canaliculi. The parietal cells secrete hydrochloric acid with a strength of about 150 mmól/l. The secretion is formed by the metabolic activity of the parietal cells (Fig.1). The parietal cells are rich in mitochondria and have a high rate of oxidative metabolism when in an active state. They are rich in the zinc-containing enzyme, carbonic anhydrase, and the carbon dioxide produced by mitochondrial metabolism is rapidly converted to carbonic acid. Bicarbonate ions produced by dissociation of carbonic acid are exchanged for chloride ions in the blood plasma. The hydrogen and chloride ions are actively transported by separate system through the microvilli brush border of the canaliculi of the parietal cells.

REGULATION OF GASTRIC SECRETION

Gastric acid secretion is commonly divided into basal or fasting and stimulated or postprandial phases. Basal secretion varies considerably over time and usually represents



Structure of Parietal Cell



Mechanisms involved in acid secretion

Fig. 1

5-10% of maximal rates. The mean rate of secretion in the basal state is reduced by vagotomy (Anita et al., 1951; Gillespie et al., 1960). Vagotomy does not completely abolish the basal secretion. Stimulated secretion is commonly subdivided somewhat arbitrarily into cephalic, gastric, and intestinal phases. The cephalic phase begins with the sight, smell, taste, and chewing of appetizing food; the gastric phase begins when food enters the stomach; and the intestinal phase begins when food components begin to enter the intestine. Obiviously these phases overlap. The mechanisms that mediate these phases are multiple, and several mechanisms may be operative during the same period.

CEPHALIC PHASE

The Cephalic phase appears to be mediated by different impulses transmitted through fibres of the vagus nerve to the stomach. The sensory receptors for cephalic stimulation have not been identified, nor have the pathways been mapped in the central nervous sytem (Brooks, 1967; Ramamurthi et al., 1977). Cephalic stimulation is abolished by vagotomy (Tepperman et al., 1973). The cephalic phase probably makes a significant contribution to the overall response to a meal. In humans, the acid response to an eaten meal is significantly greater than the response to the same meal infused directly into the stomach (Richardson et al., 1977). Sham feeding in humans also increases the acid responses to gastric distention with glucose or saline solutions (Richardson et al., 1977) The increased acid responses to sham feeding in humans are accompanied by greater increases in serum gastrin than those achieved by introduction of food directly into the stomach.

GASTRIC PHASE

The two factors known to be operative when food is present in the stomach are distention of the stomach and chemical stimulation of the gastric release.

DISTENTION Distention of the intact stomach results in a small but significant stimulation of acid secretion. Presumably this results from activation of reflexes, since serum gastrin concentrations are not increased. Distention may also activate a mechanism for inhibition of acid secretion. In some human subjects, balloon distention of the fundus decreased the acid response to maximal doses of pentagastrin (Grotzinger et al., 1977 a). The response to fundic distention in humans is markedly inhibited by atropine or by proximal gastric vagotomy; this agrees with the concept that the acid response is mediated by an atropine-sensitive chlorinergic reflex conveyed by both short intramural and long vago-vagal pathways (Grotzinger et al., 1977 b).

CHEMICAL STIMULATION

When various food components were studied for acid-stimulating activity in humans, amino acids and partially digested protein were found to be effective while glucose and fat caused no stimulation (Richardson et al., 1976). Amino acid phenylalanine and tryptophan are the most potent releasers of gastrin in dogs and humans and are the most potent stimulants of acid secretion in man (Byrne et al., 1977; Strunz et al., 1978). Gastric administration of calcium salts also causes stimulation of acid secretion, not associated with an increase in serum calcium (Levant et al., 1973). Caffeine stimulates acid secretion in humans without an increase in gastrin (Walsh and Grossman, 1975).

INTESTINAL PHASE

Food substances entering the intestine may cause stimulation or inhibition of gastric secretion. Gastrin is present in the proximal duodenum in relatively high concentrations, but it is not known whether or not duodenal gastrin is released by a normal meal. There is some evidence that the acid response to peptides in the small intestine may be due atleast in part to effects of absorbed amino acids, since intravenous administration of amino acids in humans caused significant stimulation of acid secretion (Isenberg and Mexwell, 1978).

Introduction of fat into the intestine produces marked inhibition of gastric acid secretion (Christiansen et al., 1976; Sachmidt-Wilcks et al., 1975). The agent responsible for this inhibition has been called "enterogastrone". Many peptides isolated from the mucosa of the gut and pancreas can produce inhibition of acid secretion when administered in large doses (Baron 1976). However, none of these has been shown to meet the criteria required for identification as the major enterogastrone. The two inhibitory peptides released by fat are cholecystokinin (Brooks and Grossman, 1970) and gastric inhibitory peptide (Pederson and Brown. 1972). The doses of both required to produce inhibition are probably larger than the amount released by fat in the intestine. Both of these hormones are released by amino acids in the intestine as well as by fat. However, intestinal amino acids do not inhibit acid secretion. Hypertonic glucose is a moderately potent inhibitor of acid secretion but is effective when given intravenously as well as orally or intraduodenally (MacGregor et al., 1976; Ward et al., 1969). Acidification of the duodenum, especially the duodenal bulb, inhibits gastric secretion (Berstad and Petersen, 1972; Uvnas,1971). It is unlikely that the amount of secretion released is sufficient to account for this effect, since relatively high doses of secretion are needed to inhibit acid secretion (Dalton et al., 1976).

It is possible that a major part of the effect of intraduodenal administration of acid and other inhibitory substances is due to stimulation of an inhibitory reflex (Konturek and Johnson,1971).

It is quite evident that multiple and overlapping regulatory mechanisms act on the parietal cell to control the rate of secretion of hydrochloric acid. Acid secretion is regulated by several chemical messengers that appear to act separately on the parietal cell but have important interactions in the overall regulation of acid secretion (Grossman, 1978; Soll and Grossman, 1978). The well defined chemical messengers are acetylcholine (Ach), histamine and gastrin. Recently prostaglandins have also been reported to affect gastric secretion.

ACETYLCHOLINE

The neurotransmitter released by muscarinic nerve endings of the parasympathetic nervous system in the gastric mucosa is acetylcholine (Ach). The nerves that innervate the gastric glands are postganglionic fibres that originate in ganglia located in submucosal and muscular layers of the stomach. Most of the preganglionic fibres that synapse in these ganglia have their cell bodies in the plexuses of the stomach and form the local reflex arcs within the wall of the stomach. The remainder of the postganglionic cells synapse with preganglionic fibres from the vagus nerve and are part of the vagal reflex system.

The transmitter impinging on the terminal neurone in both the central and local reflexes is Ach and reflex gastric secretion is suppressed by ganglion blocking drugs. Ach is also the transmitter of terminal axons impinging on the effector cells and its action is blocked by atropine. Ach and other agonists with muscarinic activity are direct stimulants of the gastric secretory cells. However, they also act indirectly by liberating a polypeptide hormone, gastrin from the mucosal cells of the antrum. Maximal stimulation of gastric secretion requires the conjoint action of the cholinergic nerves to the secretory cells and gastrin.

HISTAMINE

Histamine is present in large quantities, about 40 micrograms per wet weight, in the oxyntic mucosa of humans and other mammals (Reite, 1972; Troidl et al., 1975). The development of a series of histamine antagonists that act on H_2-receptors distinct from those antagonized by ordinary antihistaminic drugs has made it clear that histamine plays an important role in physiologic stimulation of parietal cell (Black et al., 1972). The cellular source of histamine in the gastric mucosa is not known and the chemical and physiological mechanisms for the synthesis and release of histamine in the gastric mucosa are unknown (Beaven, 1978). Histamine diffuses through the lamina propria

to reach the parietal cell and combine with H_2 receptors present there and trigger gastric acid secretion. The ultimate mediator is through the second messenger 'cyclic AMP'.

Acid secretion from the parietal cells is strongly stimulated by histamine; this action of histamine is exerted through H_2-receptors. Gastric acid secretion in response to exogenous histamine or pentagastrin is blocked due to specific blockade of the H_2-receptors and not due to non specific effect on mucosal blood flow.

GASTRIN

Gastrin is the peptide hormone most clearly identified as an important stimulant of gastric acid secretion. The highest concentration is found in the mucosa of the pyloric antrum; smaller but still appreciable amounts are present in the mucosa of the proximal duodenum. The normal plasma level of gastrin estimated by radio-immunoassay, is 30-60 pg/ml in the resting state; after feeding it increases to 200-400 pg/ml, the peak being reached 20-45 minutes after the start of the meal. The two principal biologically active forms of gastrin in pyloric gland mucosa and in the ciruclation are little gastrin (G-17) and big gastrin (G-34) (Walsh, 1977). The potency of G-17 is 6-8 times that of G-34 and it appears that G-17 is the principal biologically active circulating form. Both G-17 and G-34 exist in sulfated and non-sulfated forms, but sulfation does not affect acid-stimulating activity. G-17 is the most abundant form in pyloric gland extracts while the reverse is true for circulating gastrin, probably because of the slower disappearance rate of circulating G-34. Gastrin is released by amino acids and peptides bathing the pyloric gland mucosa. The specific amino acids that are the most potent gastrin releasers in human are tryptophan and phenylalanine; these two amino acids are the most potent stimulants of acid secretion (Byrne et al., 1977). The effect of vagal and cholinergic stimulation on the release of gastrin are confusing (Walsh and Grossman, 1975). Many observations suggest that there is a vagal, cholinergic mechanism for release of gastrin.

The only known physiological inhibition of gastrin release is caused by acidification of the gastric contents below pH 3 (Walsh et al., 1975). Thus there is an inhibitory feed back (autoregulation) control on gastrin mediated acid secretion. During achlorhydria the plasma levels of gastrin are higher than normal. The half-life of gastrin in the circulation is 2-3 min. Several peptides present in the gut have the ability to inhibit gastrin release when administered in large doses exogeneously, but none appears to inhibit at concentrations likely to exist in the circulation under

normal cirucmstances (Baron, 1976). Somatostatin, which is present in large quantities in the pyloric mucosa, is a potent inhibitor of gastrin release (Philip et al., 1977; Vatn et al., 1977). Somatostatin may modulate gastrın release by local action on gastric cells. The same possibility exists for vasoactive intestinal peptide, which is found in nerve fibers in the stomach (Pearse et al., 1977). It is apparent that vagal inhibition of gastrin release is more sensitive to low doses of atropine than vagal stimulation of gastrin release (Soll and Walsh, 1979).

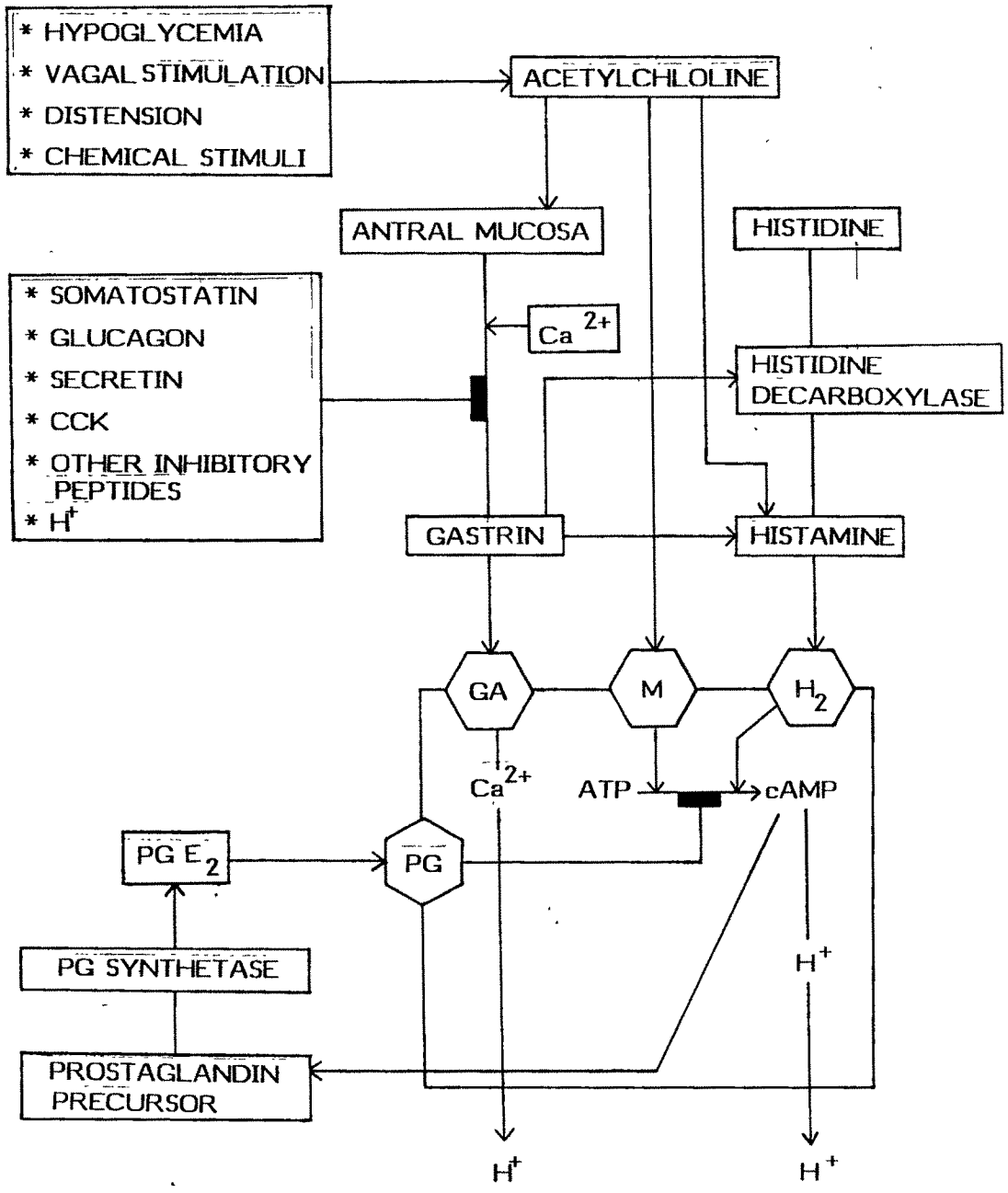
Until recently, gastrin was regarded as a direct stimulant of gastric acid secretion; however the ındirect effect through release of histamine has also been suggested. Gastrin released histamine in the gastric mucosa, increases the rate of histamine formation by the glandular region of the gastric mucosa and ıncreases the amount of histamine and its metabolites excreted in the urine. The simplest interpretation of the experimental findings is that the acid secretion from parietal cells in response to gastrin is mediated by histamine released from, or in the vicinity of parietal cell. It has been shown that acid secretion can be directly stimulated by Ach and other cholinomimetics which act on atropine-sensitive muscarinic cholinoceptor but the maximal secretory response is due to an indirect action whcih involves release of gastrın, and hence is ultimately mediated by histamine (Fig.2).

However, it has been reported that H_2-receptor antagonist metiamide does abolish acid secretion in response to cholinomimetic drugs or vagal stimulation. Since metiamide does not have atropine-like activity, the finding raises the possibility that histamine has an obligatory role in the secretory response, and acts either as the final mediator of cholinergic stimuli, or as essential adjunct to cholinoceptor agonists. Furthermore, it has been demonstrated that vagal stimulation releases not only Ach, but also directly releases histamine in the gastric mucosa (Fig.2).

PROSTAGLANDINS

Prostaglandin is widely distributed throughout the body. Prostaglandın is present in large quantity in the mucus membrane of the fundus, body and pylorus of the stomach and duodenum (Konturek, 1981). Prostaglandin E_1 and E_2 inhibit basal histamine and pentagastrin stimulated acid secretion in humans and other species (Becker et al., 1973; Ippolity et al., 1976 and Robert, 1976). Synthetic analogs have been developed that are resistant to intestinal ınactivation and are effective orally. One of these analogs 16, 16-dimethyl prostaglandin E_2 was found to produce almost

Fig.2


* HYPOGLYCEMIA
* VAGAL STIMULATION
* DISTENSION
* CHEMICAL STIMULI
ACETYLCHLOLINE
ANTRAL MUCOSA
HISTIDINE
* SOMATOSTATIN
* GLUCAGON
* SECRETIN
* CCK
* OTHER INHIBITORY PEPTIDES
* H+
Ca 2+
HISTIDINE DECARBOXYLASE
GASTRIN
HISTAMINE
GA
M
H2
Ca2+
ATP
cAMP
PG E2
PG
PG SYNTHETASE
PROSTAGLANDIN PRECURSOR
H+
H+
H+

complete inhibition of meal stimulated acid secretion in humans when administered into the stomach and lesser inhibition when given intraduodenally (Ippolity et al., 1976). A parellel inhibition of gastrin release was also observed with this drug. Parenteral prostaglandin E_1 was found not to inhibit gastrin release in the dog (Becker et al., 1973) presumably this inhibition is caused by a local effect on the gastric mucosa (soll and Walsh, 1979).

Preliminary studies in man showed that orally active prostaglandins accelerate healing of gastric and duodenal ulcer (Gibinski et al., 1977). Diarrhoea is however, a problem. PGE_2 is liberated during gastric acid secretion and it has been shown that PGE_2 is liberated from gastric mucosa by cyclic AMP. PGE_2 is formed from endogenous substrate in the gastric mucosa and is present in gastric juice (about 2 ng/ml). Study with isolated parietal cells indicate that prostaglandin stimulates cyclic AMP production by nonparietal cell, with little or no stimulation of cyclic AMP production by parietal cell itself (Soll and Wollin, 1977). It has been suggested that prostaglandin was acting by means of blocking histamine activation of adenylate cyclase.

PGE_2 inhibit gastric acid secretion in response to histamine and pentagastrin, this action may be due to inhibition of formation of cAMP. Thus cyclic AMP and prostaglandin system of parietal cells may interact to form an inhibitory feed back loop (Fig.2). Aspirin and other antiinflammatory drugs having an inhibitory effect on prostaglandin synthesis would disrupt the inhibitory loop and increase acid production; this effect has been implicated in their ulcerogenic action (Bowman and Rand, 1980).

CALCIUM

Intravenous infusion of calcium salts is usually associated with an increase in gastric acid and pepsin secretion as well as in the serum gastrin level. The gastric secretory response to acute hypercalcemia is usually greater in duodenal ulcer patients than in normal subjects, while the responses in Zollinger Ellison Syndrome (ZES) patients are in excess of those seen in hypersecreting duodenal ulcer patients without the ZES (Basso and Passaro, 1970). The mechanism responsible for the stimulation of gastric secretion by calcium remains unexplained. Probably the chief mediator of the increased secretory response is the release of the gastrin. It appears, that the intact antrum is not an indispensable condition for the stimulation of gastric secretion

by calcium because induced hypercalcaemia has been found to be an effective stimulant of gastric secretion in patients after antrectomy and vagotomy without any change in serum gastrin level; further, atropine which abolishes calcium-stimulated gastric secretion, does not affect calcium-induced gastrin release (Konturek, 1979).

An increased prevalence of peptic ulcer in patients with hyperparathyroidism (about 30 per cent of cases) is well recognised. In addition the coexistence of hyperparathyroidism, pancreatic islet tumor (gastrinoma) and peptic ulcer disease has been described by several authors (Barreras, 1973).

Hypocalcaemia inhibits gastric secretion in all species. Hypoparathyroidism in man results in achlorhydria and diminished secretion of pepsin and intrinsic factor when the serum calcium is less than 3.5 mmol/l. The correction of hypocalcaemia by the administration of calcium salts and vitamin D causes an increase of gastric acid secretion (Konturek, 1979).

Studies with isolated parietal cells indicate that histamine, gastrin and acetylcholine each appears to act at separate receptor on the parietal cell (Fig.2). Evidences for this conclusion comes from study of the effect of cimetidine and atropine on stimulation of both oxygen consumption and aminopyrine accumulation by carbachol, gastrin and histamine (Soll, 1977 and 1978a). Anticholinergic agents specifically prevent the cellular action of Ach, cimetidine specifically inhibits stimulation by histamine and neither inhibitor blocks the small direct response to gastrin. Furthermore potentiating interactions occur between histamine, gastrin and cholinergic agents, which may account for the interdependence of secretogogue action observed in vivo. Direct potentiating interaction occur between histamine and gastrin and carbachol but not between carbachol and gastrin;however in the presence of histamine, carbachol and gastrin a three-way potentiation does occur (Soll, 1978b, 1978c).

By interfering with the potentiating interaction between stimulants, anticholinergic agents and cimetidine display an apparent cross-specificity in vitro that resembles the effects of these agents in intact mucosa.

The mechanisms underlying these interactions are unknown. The potent acid secretogogues, histamine and pentagastrin, increase mucosal cylic AMP (Nakajima et al., 1971; Domschke et al., 1973). The role of cAMP in the response of the parietal cell to

stimulation has been controversial (Jacobson and Thompson, 1976), largely because of the complex mixture of cell types in the intact mucosa. In the isolated parietal cell preparation, histamine but neither carbachol nor gastrin stimulates cAMP (Soll and Wollin, 1977). The action of histamine appears to be mediated through increased production of cAMP and cyclic AMP analogs, which mimic the interaction involving histamine itself.

It is clear that the actions of carbachol and gastrin are mediated by intracellular effectors different from those mediating the actions of histamine. Only histamine stimulates cyclic AMP production in parietal cell. Alteration of calcium fluxes across the plasma membrane or alteration in the membrane cellular calcium may play a role in the responses to carbachol and gastrin (Soll and Walsh, 1979). It has been suggested that part of the stimulant effect of cholinergic and gastrin on gastric secretion may be related indirectly to histamine (Fig.2); hence histamine may function on the final chemostimulator of the parietal cell in all models of activation.

CHAPTER

IIc

PATHOPHYSIOLOGY OF ULCER

Peptic ulcer is a general term used to cover both gastric and duodenal ulcer; this also includes oesophageal ulcers, stomal ulcers and ulcers associated with Meckel's diverticulum. Gastric and duodenal ulcers are different but there is much common in relation to treatment. Gastric ulcer seems to be a disorder of wear and tear and is associated with gastritis and atrophic changes of the gastric mucosa. Duodenal ulcer, on the other hand, seems to be associated with a tendency to hypersecretion of acid and pepsin.

Gastric ulcer tends to occur on the lesser curve of the stomach at the junction of normal and atrophic mucosa (fig.3). The normal gastric mucus membrane produces hydrochloric acid so that there is less of this acid if the area of integrity of the healthy mucosa appears to be the susceptible area (Croft, 1978).

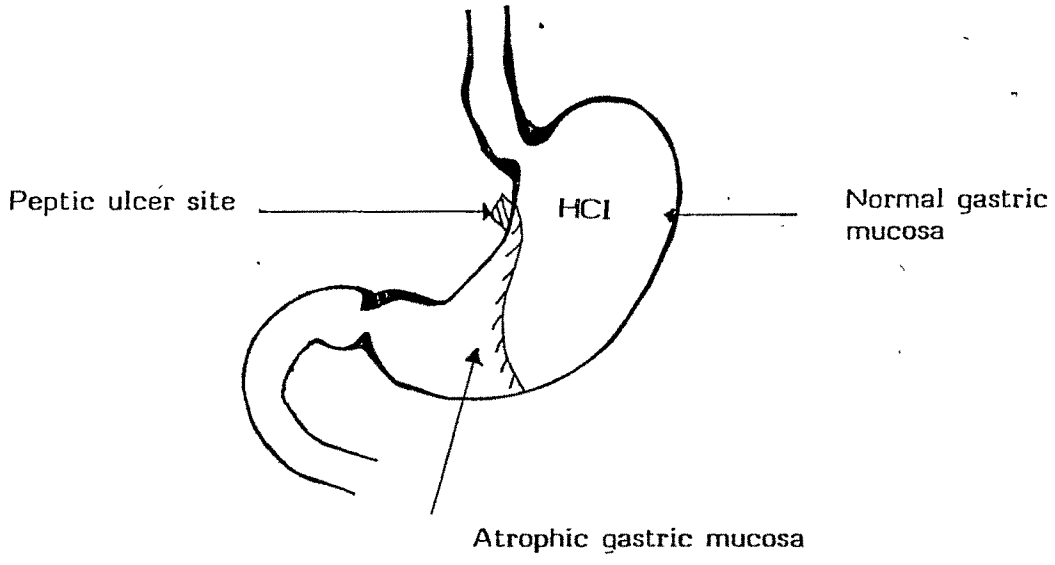


Fig. 3

The aetiology of peptic ulcer remains unknown. There is an interplay between environmental factors and the susceptibility in ulcer disease (Francis Avery Jones and Sullivan, 1972).

(A) Constitutional factors

Sex
Age
Temperament
Family history
Gastric mucous
Acid
Pepsin

(B) Environmental factors

Social Class
Changing incidence
Geographical difference
Occupation

Over the years, the pathophysiological basis of erosions or ulceration has been considered to depend on imblance between a number of factors. Abnormally destructive 'aggressive or offensive' factors, or abnormally impaired 'defensive' factors or a combination of abnormally impaired offensive and defensive factors permit developme or prevent healing of the chronically ulcerated mucosa. The state of gastric mucosa is the result of balance between the following aggressive and defensive factors.

(A) Aggressive factors	(B) Defensive factors
Physicochemical trauma	Inadequate blood flow
Hydrochloric acid	Mucus barrier
Pepsin	Mucosal barrier
Refluxed bile	a. Mitosis
Pancreatic proteolytic enzymes	b. Life span of the cell.
Ingested irritants	
Bacterial toxins.	

Table.1

AGGRESSIVE FACTORS

EXCESSIVE PRODUCTION OF GASTRIC JUICE: The gastric hypersecretion is considered characteristic and causally important in the pathogenesis of duodenal ulceration. Two different processes of gastric hypersecretion with quite different functional and aetiological base have been reported in duodenal ulcer. Patients with duodenal ulcer secrete gastric juice persistently and inappropriately when the stomach is empty between meals and at night. Information about the overall incidence of such secretion and its cause is much controversial and has been reemphasized (Leya & Danilans, 1974).

It has been reported that the magnitude of the basal secretion of acid is correlated with the basal levels of gastrin in the blood (Royston et al., 1974), and the old hypothesis (Dragstedt et al., 1951) of basal vagal 'hyperactivity' in duodenal ulcer has been reexamined (Lam and Sircus, 1975; Sircus, 1975), although the evidence currently available for abnormal vagal tone (Wormsley, 1975) is not conclusive.

The second type of hypersecretion in patients with duodenal ulcer involves the excessive secretion of acid and pepsin in response to various stimulants like histalog (Sperenza et al., 1972) and histamine (Jablonska et al., 1974). The degree of acid hypersecretion

in response to pentagastrin was reported to relate to the endoscopically-assessed depth of the duodenal ulcers (Moshal et al., 1974). Hydrogen ions appear to be necessary for the formation of nearly all benign ulceration and this plays atleast secondary role in pathogenesis. The Zollinger-Ellison Syndrome illustrates how extreme over-production of acid by the stomach leads to a greatly increased incidence of ulceration, although these are usually extragastric. Some patients with duodenal ulcer may have parietal cells that react more vigourously than normal to stimulants (Isenberg, 1975). The proteolytic enzyme pepsin which is pH dependent with a pH of 3.5 is another aggressive force at play.

ABNORMAL RELEASE OF GASTRIN

The parietal cells of the stomach of some patients with duodenal ulcer appear to be more sensitive than normal to stimulants, similarly the gastric endocrine cells producing gastrin (G Cell) apparently secrete abnormal amounts of gastrin and seem to continue to secrete gastrin under circumstances when 'normal' G cell cease to secrete.

There have been number of reports confirming that although the basal concentration of gastrin in the blood is not different from normal in patients with duodenal ulcer (Arnol et al., 1974 ; Gedde-Dahl, 1974; Wesdrop and Fischer, 1974; Malagelada et al., 1975), there is significant increase in blood gastrin after meal in the patient with the duodenal ulcer (Arnold et al., 1974; Gedde-Dahl, 1975). Arnoldet al (1974) showed that no significant differences from normal in the antral content of G cell or in the antral content of gastrin in the patient of duodenal ulcer, although the G cell of the patients were interpreted as indicating persistently excessive functional activity after electron microscope observation. The cause of this increased secretion of G cell may be either because of more G cell than normal or because the G cells are more sensitive to stimulants than normal.

Patient with duodenal ulcer also appears to suffer from an abnormally impaired regulation of the release of gastrin from 'G' cells.

It has been shown that gastrin is released not only from the antrum but also from the upper small intestine (Hausamen et al., 1974). Many evidences suggested that there must be some defect in the 'autoregulatory negative feed back' control of gastrin release in patients with duodenal ulcer (Wesdrop & Fischer, 1974; Gadde-Dahl, 1975; Malagelada et al., 1975; Walsh et al., 1975).

DEFECTIVE INHIBITION OF GASTRIC SECRETION

Inhibition of gastric secretion in dogs has been demonstrated after introducing acid into the duodenum and following the parenteral administration of secretin (Johnson and Grossman , 1971). Similar gastric inhibition is much more difficult to demonstrate in man and requires infusion of large amounts of acid into the duodenum (Wormsley, 1970) or administration of large amounts of secretin (Berstad et al., 1972). The role of defective duodenal inhibitory mechanisms in the pathogenesis of the hyper-secretion of acid in patients with duodenal ulcer is controversial (Wormsly, 1974).

ABNORMALLY RAPID GASTRIC EMPTYING

Evidences showed increase in the gastric emptying in some patients with duodenal ulcer (Wormsley, 1974; Moberg et al., 1974; Moberg, 1974; Malagelada et al., 1975). It can be concluded that patients with duodenal ulcer receive a greater than normal duodenal acid load (Caro and Isenberg, 1975).

ABNORMAL MOTOR ACTIVITY OF THE DUODENUM

Excessive amounts of acid can accumulate in the proximal duodenum either from failure to remove the acid containing luminal contents by means of antero or retrograde peristalsis or because there is failure of 'neutralization' or buffering with secreted bicarbonate within the duodenum. Reflux of duodenal contents into the stomach, is excessive in patients with duodenal ulcer (Fiddian and Green, 1974; Vitebsky, 1974; Kallner, 1975).

It has also been proposed that secreted bicarbonates are distributed within the duodenum under normal circumstances, but in patients with duodenal ulcer a motor defect prevents uniform distribution. The motor function of the duodenum in duodenal ulcer really does require sophisticated analysis.

FAILURE TO SECRETE BICARBONATE NORMALLY INTO THE DUODENUM

One of the features of the pathophysiology of duodenal ulceration which has been appreciated, though neglected, for a long time is that there is a defective secretion of bicarbonate into the duodenum in response to duodenal intraluminal acid (Morton, 1929), and duodenum in duodenal ulcer remaining 'dry' in response to intraluminal acid.

It has recently been shown that the basal secretion of acid in patients with duodenal ulcer is much greater than the basal secretion of bicarbonate, while the two values are virtually identical in control subjects (Gutierrez and Baron, 1974), perhaps because the pancreas of patients with duodenal ulcer is less sensitive than normal to stimulation with secretin (Berstad et al., 1974).

It is not possible to infer whether defective inhibition of release or an excessive stimulation to release of the gastrin is being involved in duodenal ulceration. There may be abnormalities of the secretion of gastrin in patients with duodenal ulcers; neither the phenomenon itself nor its significance nor the pathophysiological basis have been defined.

DEFENSIVE FACTORS

INADEQUATE BLOOD FLOW: Ischaemia as a cause of ulcer genesis is the oldest idea. Blood supply to the mucosal cell is presumably important in maintaining cell integrity and the presence of hypoxia or hypovolemia probably plays a role in the pathogenesis of some types of stress ulceration and erosions, but the absence of end arteries reduced its importance (Palmer and Sharman, 1958). However, the concept was given renewed interest with the recognition of arterio-venous shunts which arise from each mucosal artery either just before or after the artery pierces the muscular layer of the mucosa. Thus, despite the absence of end arteries, it is possible that a shunt mechanism could deprive a section of mucosa of sufficient oxygen and start a process of cellular damage and necrosis.

PROTECTIVE MUCUS BARRIER

Mucus is of great interest as a protective factor. In man the entire alimentary tract is covered with a layer of protective mucus. The mucus barrier is the first line of defence and is mainly physical, consisting of a viscous mucosubstance which clings tenaciously to the mucosa, provides lubrication and separates the mucosa from the digestive juice. It protects the epithelial cell against sudden osmotic change and in stomach it prevents the corrosive effect of acid and pepsin. This substance also provides some degree of chemical protection as it is alkaline and is capable of neutralizing considerable amount of acid (Davenport, 1966). However, the mucus itself is not a barrier to diffusion of acid, and hydrogen ions can diffuse through it rapidly (Heately, 1959).

Mucus consists of glycoproteins synthesized by goblet cells, protein, mucopoly saccharide and blood group substances (Horwitz, 1967). The glycoprotein molecules have got a protein chain to which several disaccharide side chains are attached. Depending on the presence of sialic acid residue, glycoprotein may be acidic or neutral. The principle glycoproteins of human gastric juice contain carbohydrate components composed of mainly galactose, galactosamine, glucosamine, fucose and protein which contains chiefly the amino acids serine, threonin, proline and alanine (Scharger, 1969; Allen and Shary, 1972). Altered synthesis of hexosamine containing compound have been shown to influence gastroduodenal ulcer (Kent 1962). Factors which impair the integrity of this mucus barrier form a vital link in the pathogenesis of gastric ulceration.

PROTECTIVE MUCOSAL BARRIER

The real barrier to acid pepsin digestion is the mucosal barrier. The concept of this barrier and its importance in gastric disease has been described by Davenport (1967a, 1970, 1972). It is a complex physico chemical substance residing in the gastric epithelial cell. These cells are fused together at their apices forming tight junctions and preventing hydrogen ions penetrating into the mucosa beneath. The integrity of this barrier is the most important protection the stomach has against attack by acid and pepsin. When this barrier is broken, a chain of events ensues, starting with a rapid penetration of hydrogen ions into the mucosa which leads to the release of histamine, which inturn induces inflammation and oedema. Also the acid may damage blood vessels leading to haemorrhage and stimulates nerve in the stomach wall, leading to increased muscular contraction. Thus the back diffusion of hydrogen ion from the lumen of the stomach into the mucosa initiates the series of events that leads to erosion and frank ulceration. Many substances attack the mucosal barrier. These include physiological substances like bile, drugs like salicylates and substances like alcohol in the diet.

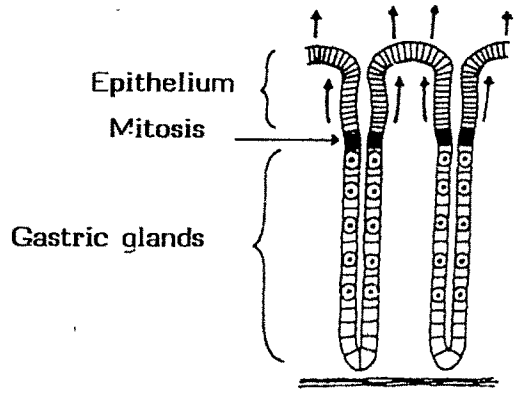
Reflux of bile and associated pancreatic secretions from the duodenum into the stomach is of much importance. The presence of bile allows the back diffusion of hydrogen and sodium ions from the lumen into the cells which may result in injury or necrosis of cells. Some contribution to the mucosal barrier is made by a layer of mucus that consist of glycoproteins and mucopolysaccharide.

MUCOSAL CELL KINETIC

Recent studies have demonstrated a dynamic and rapid life cycle of the mucus producing gastric epithelial cell in man. Normal epithelial cell proliferation and life span of these cells plays most valuable role in ulcergenesis. Mackay and Hislop (1966) reported that, chronic atrophic gastritis is also involved in the genesis of gastric ulcer.

MUCOSAL EPITHELIAL CELL REPLICATION

Mucosa is generally composed of glandular portion. The surface epithelium represents only a fraction of the total thickness. It is from this layer that most of the production and loss of cell occurs. The first parietal cell is found at the base of the pit where the surface epithelial cells are produced by mitosis; these cells then migrate up the wall of the pit and are lost after 2 to 3 days, at the mucosal surface. The loss in the normal subjects has been estimated to be the order of half a million cells every minute.



The above figure is the diagramatic representation of zone of mitosis, the migration of the surface epithelial cells to the lumen and in the glandular portion proper, the parietal and chief cells which are relatively static in terms of cell turnover.

A new and important concept has been introduced by Lipkin (1971) that the erosions are preceded by an inhibition of DNA synthesis, this means a decrease in the production of the protein moiety needed for mucoprotein synthesis.

This epithelial cell turnover may have a special significance in relation to the development or persistence of ulceration. Thus, if the normal epithelial cell proliferation does not occur, repair of break in the epithelial barrier cannot occur and small erosion become large ulcers. It seems that in gastric ulcer subjects there is a high rate of turnover of the gastric mucosal epithelial cells which are lost before they can reach maturity. Thus, as these cells generate the protective mucus, secretion of these substances is diminished and the mucus itself is perhaps of poor quality. Finally adequate blood flow and nutrition are necessary for the protection, repair and renewal of the mucosa.

OTHER CONSTITUTIONAL AND ENVIRONMENTAL FACTORS

Sex Feminity protects against peptic ulcer, and atleast twice as many men as women have gastric ulcers, and four to five times as many men have duodenal ulcers. Evidence suggest that oestrogen plays a protective role in ulceration. Jorden in 1966 reported that symptoms of peptic ulcer is aggravated during menstruation when oestrogen titre is least and ameliorated during pregnancy when there is increased oestrogen titre. Moreover in females, incidence of peptic ulcer is greatly increased after menopause. Lordon and Wild (1970) reported decreased acid secretion in denervated gastric pouch in dogs during oestrus cycle. Oestrogen is reported to increase mucus secretion (Prabhoo and Johnston, 1966), mucus cell renewal and healing (Lohery and Creamer, 1969; Kelly and Robert, 1969).

AGE In the population at anyone time approximately twice as many new chronic gastric ulcers per thousand population occur at the age of 40 than the age of 20, and twice as many again at the age of 60.

TEMPERAMENT Individual temperament may be a significant constitutional factor, and those who cannot cope with nervous stress may be more likely to suffer from the complications and chronicity of ulcer than those who make light of their stresses. In human also gastric ulcers are often seen in acute stressful conditions like severe physical injury, head injury, burn etc. The exact mechanism of stress ulcer is not clear but probably it involves central and peripheral neuro-humoral substances and psychosomatic factors.

FAMILY HISTORY The first degree relatives of patients with gastric or duodenal ulcers are more prone than the rest of the population. This is more likely to be due to inheritance than to enviromental factors.

The incidence of peptic ulcer is higher in people of blood group O than in those of blood groups A and B. Gastric ulcer occurs to an equal extent in men and women and between all socioeconomic groups; however, duodenal ulcer occurs more commonly in men than in women, and is most common in the professional and executive groups.

ENVIRONMENTAL FACTORS

High incidence of peptic ulcers are observed in the lower social strata of society, amongst the labouring classes. The increased incidence has not been limited to the metorpolitan sectors, with all its attendant rush and hurry, but there are peaks of incidence in rural areas, where the slower tempo of life might well be thought to be associated with low incidence. The occupational incidence of ulcer has been found highest in doctors, foremen and business executives.

CHAPTER

IId

CLINICAL MANAGEMENT OF PEPTIC ULCER

Peptic ulcer is a common disease affecting and incapacitating men and women in the prime of their career. Its precise cause remains controversial.. Twenty years ago, medical treatment of peptic ulceration consisted of bed rest, a bland diet and antacids. Anticholinergics, antacids, carbenoxolone and colloidal bismuth were available in 1960's, but controlled evidence of their efficacy in healing duodenal ulcer was lacking. All that has been changed through the development of fibre optic endoscope and H_2 receptor (1972) antagonists in the last decade.

Approximately 20% of the ulcers fail to heal after one month of treatment with active drugs such as cimetidine, ranitidine, antacids, pirenzipine, tripotassium dicitrato bismuthate, sucralfate or carbenoxolone, The reasons for this resistance are ill understood and are likely to be multifactorial. In terms of potentially useful ulcer healing drug, omeprazole appears to have many distinct advantages over presently useful ulcer healing available drugs, but eight years (1975-1984) after the 'cimetidine revolution' there still seem to be more questions than answers for clinical management of the peptic ulcer (Pounder, 1984). It seems that appropriate drug in sufficient dose is necessary for the treatment of ulcer. Drugs which are effective can either prevent HCl formation or secretion, can neutralise the HCl or help in strengthening the mucosal barrier.

PREVENTION OF HCl FORMATION

Hydrogen ions are produced in the gastric mucosa by the oxyntic cell with the help of the enzyme carbonic anhydrase (C.A.)

$$CO_2 + H_2O \xrightarrow{C.A} H_2CO_3 \xrightarrow{C.A} H^+ + HCO_3^-$$

The hydrochloric acid formed in the oxyntic cell is secreted into the stomach, under normal physiological condition its back diffusion into the mucosa is prevented by the mucosal barrier. Carbonic anhydrase inhibitors block the catalytic action of the enzyme and therefore thought to be useful in peptic ulcer. It is now realized that at the doses commonly employed clinically, these drugs do not affect the formation of gastric juice and hence have no role in the prevention of peptic ulcers.

PREVENTION OF HCl SECRETION

ANTICHOLINERGIC DRUGS Since, stimulation of parasympathetic nerve evokes gastric acid secretion, it was reasoned that muscarinic blocking agents would be effective in blocking secretion of the many drugs faster. Only, few have been adequately demonstrated to block gastric acid secretion in humans, which include atropine sulphate and l-hyoscine. The gastric inhibitory effect of anti-cholinergic drugs is much less than the inhibition produced by H_2 receptor blockers (Richardson and Fordtran, 1975).

There is no evidence that any of these drugs significantly decreases the healing time for the ulcer (Piper, 1973). Traditional anticholinergics are limited by the widespread and unselective blockade of cholinergic receptors that they cause. All have to be given in doses that produce side effects, if any effect on gastric secretion is to be achieved. Anticholinergics on long term treatment cause urinary retention in prostatic hypertrophic patients, blurring of vision, dryness of mouth, precipitation of glaucoma, gastric retention and constipation. The consensus at the moment seems to be that these drugs are of limited use in the long term treatment of peptic ulcer. pirenzepine is claimed to be more specific for the muscarinic receptors associated with gastric parietal cell (Chierichetti et al., 1979), but unwanted effects do occur, although they tend to be less severe than those seen with other anticholinergics.

NON ANTICHOLINERGIC DRUGS

A number of new chemicals with inhibitory effects on the stomach have been described (Bass, 1974). Prolonged gastric inhibition in experimental ulcer was claimed for a piperazine derivative (Binachetti et al., 1975). Decreased secretion of acid and pepsin was also obtained with alpha and beta sympathetic blocking drugs (Lisovsky and Uspensky, 1974). The application of these drugs in the treatment of duodenal ulcer has not yet been defined.

The substituted benzimidazoles are new agents which are potent inhibitors of gastric secretion. They act by selective noncompetitive inhibition of the H^+/K^+-ATPase enzyme on the secreting membrane of the parietal cell (Fellenius et al., 1981). This enzyme is the active transport mechanism for hydrogen ion secretion in the stomach. One of these agents OMEPRAZOLE has been shown to suppress gastric acid secretion (Walt et al., 1983; Lind et al., 1983; Konturek et al., 1983; Londong et al., 1983 and Sharma et al., 1984).

Omeprazole (30 to 60 mg/day for 7 days) produced almost 100% inhibition of both basal and pentagastrin stimulated acid output and it caused significant decrease in the volume of gastric juice without affecting pepsin secretion (Howden et al., 1984), suggesting that other components of the gastric secretion are relatively unaltered by omeprazole, having highly specific site and mode of action.

Omeprazole caused median 24 hr pH to rise from 1.4 to 5.3, hence pepsin is stable but essentially inactive, the drug can control 24 hour acidity with one dose each day, which helps patient compliance and active for many days, (Sharma et al., 1984). Omeprazole has been reported to provide complete and rapid healing of duodenal ulcer (Gustavsson et al., 1983; Bergsaker - Aspoy et al., 1983 and Daly et al., 1983). Omeprazole has now been given to patients with Zollinger Ellison Syndrome with good therapeutic effect and without side effects (Blanchi et al., 1982 and Oberg and Lindstrom, 1983). It is of considerable interest that the drug had no observed haematological, biochemical or subjective side effects despite its extremely powerful action on gastric acid secretion (Howden et al., 1984).

H_2-RECEPTOR BLOCKERS

Two types of histamine receptors have been proposed, H_1-receptor for bronchial and vascular effect, and H_2-receptor which mediate histamine-induced gastric acid secretion. In 1972, a new group of drugs was discovered which produced an inhibition of gastric acid secretion lasting for several hours (Black et al., 1972).

H_2-receptor antagonists act on histamine receptors in the stomach to reduce acid secretion (Chand and Eyre, 1975). Clinically it has been observed that H_2-receptor blocking drugs inhibit the gastric secretion (Editorial, M.J. Auster., 1974). The first H_2-receptor antagonist found effective in suppressing acid secretion in human was BURIMAMIDE, which was poorly absorbed if administered orally and had to be given parenterally for maximal effectiveness. METIAMIDE is very effective in response to a variety of stimulants, histamine, pentagastrin, insulin and food (Pounder et al., 1975). Metiamide has been studied in more detail and has been shown to produce significant increase in the rate and incidence of healing the duodenal ulcer (Brabezat et al., 1974; Thjodleifsson and Wormsley, 1975) and in the rate of relief of symptoms (Pounder et al., 1975). Metiamide causes neutropenia, agranulocytosis and bone marrow depression in a small number of patients, perhaps because of the thiourea group in the side chain of the molecule, and was considered too dangerous for human use. CIMETIDINE, has cyanoguanidine group in metiamide side chain. It is effective by oral route and produces reduction

of gastric acid secretion that remains for several hours without any harmful side effect on bone marrow (Burland et al., 1975; Wormsley, 1976 and Brogden et al., 1978). Cimetidine has been shown to inhibit basal nocturnal and food stimulated gastric secretion (Henn et al., 1975; Hollander et al., 1975;Longstreth et al., 1975) as well as the secretion stimulated by exogenous stimulants (Barbezat et al., 1974).

Therefore, cimetidine appears to be a remarkably safe and effective drug for the short term treatment of duodenal ulcer and the management of such hyper-secretory condition of Zollinger Ellison Syndrome, systemic mastocytosis and multiple endocrine adenomas.

Cimetidine treatment for 4-6 weeks heals ulcer in 70-80% of cases compared to 30-40% of patients treated with placebo (Winship, 1978). The cure is not permanent and the patients relapse at the same rate as would be expected from the natural history of the disease (Haggi et al., 1976). It seems that this group of drugs exerts a direct action on acid and pepsin secreting cell (Wan et al., 1974).

RANITIDINE, is an H_2 antagonist in which furan ring has been substituted for the imidazole nucleus of cimetidine. It is some five times more potent than cimetidine on a molar basis, permitting a twice daily dose of only 150 mg. Ranitidine has greater antisecretory effect in comparison to cimetidine. In patients with duodenal ulcer ranitidine causes more rise in pH than cimetidine, and ranitidine causes ten-fold decrease in acidity whereas cimetidine causes only two-fold (Walt et al., 1981;1983). Ranitidine controls nocturnal acidity better than cimetidine if full dose is taken at bed time (Ireland et al., 1984).

Other H_2 antagonists such as oxmetidine, titotidine and etentidine have not at present been sufficiently evaluated (John Meyrick and George Misiewicz, 1984). Famotidine , another new H_2 receptor blocker is more potent than cimetidine and ranitidine, but more clinical experience is required with this H_2 receptor blocker (Ogle,1985).

Cimetidine or ranitidine, both are free of serious adverse reactions. Careful adjustment of the dose of cimetidine in the elderly and seriously ill, and in those with renal impairment or on other medication should ensure that unwanted effects are kept to a minimum..

One way of getting an extra antisecretory effect using an H_2 -antagonist is to add an effective dose of anticholinergics. Such combinations have been shown to produce excellent gastric inhibition for a prolonged period than individual drugs acting alone (Richardson and Fordtran, 1975). The basis for the combination of anticholinergic and H_2 -blocker is the apparently separate action of histaminergic and cholinergic pathways on the parietal cell (Thompson et al., 1975). Combination of the antacids and anticholinergic drugs have been used for many years. Anticholinergic drugs may prolong the buffering effect of antacids (Barger and Mitchell, 1975). Antacids may reduce the absorption of anticholinergic drugs when the latter is administred orally at the same time as the antacid (Littman and Pine, 1975).

The addition of PIRENZIPINE to an H_2 -antagonist could provide a potentially powerful antisecretory combination, which may be useful for patients who do not respond to conventional doses of H_2-antagonist (Feldman, 1974).Cimetidine and rantidine do not have antisecretory effect with time (Burland et al., 1975 and Peden et al., 1979) whereas OMEPRAZOLE produced a degree of inhibition of acid secretion in excess of that seen with H_2 blockers (Howden et al., 1984). Clinicial study shows omeprazole a powerful inhibitor of gastric acid secretion in man and a potentially useful agent in peptic ulcer.

The capacity of several PROSTAGLANDINS to suppress gastric ulceration in experimental animals is a property of potential therapeutic importance. PGEs, PGAs and PGI_2 inhibit gastric acid secretion stimulated by feeding histamine or gastrin or other secretogogue. (Robert, 1976, 1977;Becker et al., 1973; Ippoliti et al., 1976; Whittle et al., 1978). Certain methylated analogues of prostaglandin inhibit gastric secretion in man following oral or intravenous administration (Karim and Fung, 1976), raising the possibility of their therapeutic utility for peptic ulcer; 16, dimethyl PGE_2 has been reported to be antisecretory and have antiulcergenic action (Robert et al., 1976).

Volume of secretion, acidity and content of pepsin are all reduced probably by an action exerted directly on the secreting cell. In addition, these prostaglandins are vasodilator in the gastric mucosa and may be involved in the local regulation of blood flow (Jacobson, 1970).

NEUTRALIZATION OF HCl

Antacids have been used in the symptomatic relief of the pain associated with the ulceration (Piper, 1973). The antacids remove hydrogen ions from the gastric contents (Schnekenburger, 1974) and bring down pH to 6 at which pepsin is inactivated (Berstad, 1971). Antacids are to be taken after meals in order to achieve prolonged elevation of intragastric pH (Littman and Pine, 1975). Antacids have no marked effect on ulcer healing time. It is generally believed that to be effective, antacids must be given in large dose (1000 mmole or 200-250 ml daily) which is inconvenient and cause adverse effect. Many antacids exert an action on the bowel, some have mild laxative effect (magnesium hydroxide) and some are constipating (calcium hydroxide preparation). Systemic alkalosis may be produced if the cation is absorbed. This is particularly in the case of sodium salts as antacids with the less absorbable cations (Ca^{2+}, Mg^{2+}, Al^{3+}, Bi^{3+}) the problem is still one of the toxicity of cation; thus calcium may produce hyper calcemia, and magnesium as well as aluminium cause precipitation of phosphate in gastrointestinal tract and thus produce depletion of phosphorous. Antacid therapy may affect the absorption of other drugs by adsorption of the co-administered drug or by altering the pH of the gastric contents, thereby delaying the absorption of basic drugs. Concomitant administration of antacids decreases the absorption of tetracycline, ferrous sulphate, chlorpromazine, isoniazid and digoxin and increases the absorption of anticoagulants (Green et al., 1975). Aluminium hydroxide may be therapeutically more important as it possesses buffering capacity and anti peptic activity (Littman and Pine, 1975).

STRENGTHENING THE MUCOSAL BARRIER

The mucosal barrier is the physiological barrier that resists back diffusion of hydrogen ions (Davenport, 1967a). It protects the stomach against attack by pepsin and acid. There is a group of drugs that have the effect of strengthening the mucosal barrier. These are mainly based on liquorice, which has been reported to have healing property (Adamaska et al., 1975). The therapeutic effect is associated with glycerrhizinic acid fraction. This is a very sweet substance present in large quantity in liquorice root, which on hydrolysis yields an aglycone, enoxolone; CARBENOXOLONE is the carboxypropionyl derivative of enoxolone. Thus although, carbenoxolone is synthesized from precursors present in liquorice, it is pure crystalline, water soluble powder and is not in any way similar pharmacologically or therapeutically to extract liquorice(Frank'Sullivan, 1972).

It can be concluded that carbenoxolone reduces toward normal the rate of cell-loss from the gastric mucosa in high turnover states such as atrophic gastritis and benign gastric ulcers. Carbenoxolone probably exerts this effect by increasing the life span of the surface epithelial cell and allowing it to survive longer in the gastric mucosa (Lipkin, 1970). This effect of carbenoxolone is responsible for the healing action of the drug in gastric ulceration. Carbenoxolone is reported to increase mucous production (Goodier et al., 1967; Goodier, 1968). After carbenoxolone therapy the epithelial cells last longer in the mucosa, they become more natural and thus produces more mucus. Carbenoxolone also reduced back diffusion of hydrogen ions (Colin-Jones and Taylor, 1973). A recent study indicates that carbenoxolone action is prostaglandin • mediated (Yagamata et al., 1970; Levine, 1970;Whittle, 1976).

Carbenoxolone is now seldom used because its aldosterone-like effects can be troublesome, particularly in older patients and in those with cardiorespiratory insufficiency. In about one third of patients it produces hypertension, fluid retention and potassium loss. In man it has been suggested that the side effect of sodium and water retention and potassium loss may be due to prolongation of aldosterone by carbenoxolone (Baron and Nabarro, 1968; Hausmann and Tarnoky, 1968). Carben-oxolone has mineralo corticoid like activity and has been shown to decrease aldosterone secretion in human (Baron et al., 1969). It is of particular interest to note that spironolactone must be used, as this neutralizes the healing effect of carbenoxolone. Thiazides will have the desired effect in healing with the water retention. Carbenoxolone is also reported to possess anti-inflammatory activity (Finny and Somers, 1958; Khan and Sullivan, 1968).

Controlled clinical trials indicate that in ambulatory patients this drug significantly increases the rate of healing of peptic ulcers, especially gastric ulcers (Davies and Reed, 1977).

Recently aluminium salts of sucrose sulphate (sucralfate) have been reported superior to cimetidine in ulcer healing property (Martin, 1982). It was first reported by Nagashima and Yoshida (1979). Sucralfate is claimed to inhibit peptic activity. It has got specific affinity for ulcer and protect the ulcer as natural mucus does.

Tripotassium dicitrato bismuthate has been used clinically in duodenal ulcers refractory to cimetidine. Unfortunately it is uncertain how it works. Although it does adhere to the raw surface of an ulcer (Koo et al., 1982), this 'Band-Aid'

action seems unlikely to protect from acid and peptic attack. Under the influence of bismuth, the microvilli of epithelial cell in the duodenal mucosa return to their normal height whereas cimetidine has no such action (Moshal et al., 1979). Bismuth is reported to lower ulcer relapse rate more than cimetidine. It is difficult to understand how a Band-Aid action would provide long term protection from recurrent ulceration. It is possible that bismuth has a role in the maintenance of mucosal repair and a short course of treatment may provide depot of bismuth, which gives some months of protection aqainst relapse (Pounder, 1984). Suppression of colloidal bismuth appears to be safe, but it colours the stool black and has an unpleasant ammoniacal odour.

Beside these above mentioned drugs, following few drugs have also enjoyed a brief spell of popularity in the clinical management of peptic ulcer.

METOCLOPRAMIDE is more effective than placebo in prevening symptomatic relapses of old duodenal ulcer (Moshal, 1973). GLIPTIDE, a glycopeptide, has been used in the treatment of duodenal ulcer and claimed to have significant healing and protective effects (Consiglio et al., 1972); Magarci, 1972 and Fazzaani et al., 1974). PROGLUMIDE, a polypeptide containing the tetrapeptide terminal of gastrin has been proved excellent for the treatment of duodenal ulcer (Geoffroy et al., 1974). A number of uninterpretable reports have appeared claiming that the use of OXYFERRISCORBON (Dunayerskya et al., 1974), AMEDIN and D,1-DOPA (Anichkow et al., 1974; Schedrunov et al., 1975), VICALIN (Ljobojevic et al., 1974), VITAMINE U (Varga, 1974) and IPRONAL (Gamaski and Tyminski 1975) has resulted in improvement in upto 91.5% of patients with duodenal ulcer.

Sulphasalazine antagonizes stress ulcers in rats (Ogle et al; 1985). Verapamil, a calcium antagonist has also been reported to be effective in stress-induced gastric ulcer (Koo et al., 1985), and cysteamine-induced duodenal ulcers (Sainath et al., 1985). Morphine has also been reported to decrease acid secretion and gastric lesions in rats (Ho.A et al., 1985 a, b).

A large number of drugs with widely dissimilar pharmacological properties are apparently equally effective in the short term treatment of duodenal ulcer. The choice of a therapeutic agent should therefore depend on factors such as safety, unwanted effects, cost and acceptibility to the patient. Although other treatments are available, the H_2-antagonist remains the most thoroughly investigated, specific and convenient drug for the treatment of duodenal ulcer, although such treatment may be expensive. Their safety record is good and in general unwanted effects are trivial.

CHAPTER

IIe

EXPERIMENTAL ULCERS AND ULCEROGENIC DRUGS

Experimental ulcers are known to be caused by various chemical substances and drugs. Clinically these ulcers differ considerably from human ulcers. The rat is the most commonly employed laboratory animal for investigation of the pathogenesis of gastric ulcer and evaluation of antiulcerogenic agents. It is well known however that the duodenum of the rat is resistant to an induction of ulcer by chemical agents There are several chemicals which cause duodenal ulcer in rats, most involve complicated procedure or reveal low incidence of ulceration when used for a routine evaluation of anti-ulcerogenic agents.

Prolonged pyloric ligation (18-24 hr.) has been reported to produce gastric damage (Shay et al., 1945), and prolonged immobilisation or stress produces restraint ulcers (Fregly, 1953). It has been pointed out that the ulcers produced in dogs by burns are the nearest analogue to acute human stress ulcers of the duodenum; that ulcer produced by deficiency of pantothenic acid, or by direct topical application of acetic acid as well as by administration of cinchophen to dogs and mice (Obuoforibo, 1973) most closely resemble chronic duodenal ulcer in man; that Mann-Williamson ulcers (Tasse et al., 1975) resemble human ulcers and that secretogogue induced ulcers resemble the Zollinger Ellison syndrome in human subject.

Selye and Szabo (1973) reported an experimental model for acute perforating duodenal ulcers in rats by a single administration of cysteamine hydrochloride (β-mercaptoethylamine). Recently cysteamine has been reported to produce acute and chronic duodenal ulcers in rats (Groves et al., 1974; Rebert et al., 1974). Oral or parenteral administration of cysteamine causes rapid duodenal ulcer with pathophysiological changes similar to human chronic duodenal ulcer (Szabo, 1978).

Robert et al (1974) reported severe duodenal ulcer in rats by subcutaneous infusion of gastrin for 48 hours, either alone or in combination with histamine or carbachol, suggesting gastric hyper secretion alone can produce lesions in the duodenum of the rats. Fujii and Ishii (1975) reported similar type of ulcer with cysteamine. Acidity of the gastric juice was increased after cysteamine in a dose dependant manner with significant decrease in volume. The ulcer index of cysteamine-induced duodenal ulcer was markedly attenuated by atropine methylbromide or pyloric ligation and aggravated by tetragastrine and bethanecol, suggesting that the presence of gastric juice in the duodenum is a sine qua non for the production of duodenal ulcers (Fujii and Ishii, 1975). It has been concluded that gastric secretogogue action was not responsible for the development ofulcer,since cysteamine was anti secretory in pylorus ligated rats (Robert et al., 1974; Fujii and Ishii, 1975).

However, potent and sustained gastric acid stimulating action of cysteamine was observed in dogs and rats with various other methods (Fujii and Ishii, -unpublished- Groves et al., 1974). Many studies have shown that in patient with duodenal

ulcers there is characteristically excessive amount of gastric juice. Therefore the production of experimental duodenal ulcer by means of hypersecretion of gastric juice appears quite feasible and this may be an excellent model for the study of the pathogenesis of duodenal ulcer in humans. This procedure is superior to other techniques previously reported because of the simplicity and high incidence of ulceration.

The structure activity relationship of the compound shows that duodenal ulcerogenic property is associated with carbon (-C- -C-) groups containing reactive radicals of -SH, -CH, $-NH_2$, $-CH_3$ and Cl. The importance is that many chemically related substances are present in different food stuffs and environment.

The bacterial endotoxins, also produce acute duodenal ulcers (Greenberg and Himala, 1974). Propionitrile has been reported to produce acute perforating duodenal ulcers in rats when given subcutaneously or orally, though it has little effect on the secretion of acid and its mode of action in causing the ulceration is not known (Robert et al., 1975). The related compound butyronitrile was found to be less potent in producing perforating duodenal ulcers, although up to 80% of the treated rats developed ulceration of the duodenum. Butyronitrile stimulates the gastric secretion of acid (Szabo and Reynolds, 1975). Individual reports have mentioned the production of experimental duodenal ulceration by acetic acid (Takagi et al., 1974); cinchophen (Obuoforibo, 1973) and secretogogues (Joffe et al., 1975a; 1975b). The experimental methods and screening of anti-ulcerogenic agents have been reviewed comprehensively (Lee and Ranchi, 1971).

ULCEROGENIC DRUGS

(1) GLUCOCORTICOSTEROIDS It is generally accepted that administration of corticosteroids is associated with an increased incidence of gastric ulceration. Robert and Nezamis (1958) reported that daily subcutaneous administration of cortisol (Δ - Cortisol) to rats for 4 days resulted in the regular development of gastric ulcer. Evidence indicates that patients of rheumatoid arthritis treated with corticosteroids have an increased rate of developing ulcer. Steriod associated ulcers tend to be gastric rather than duodenal. These ulcers tend to be insidious

in their development, with few if any symptoms until a major complication occurs. There is high incidence of complications such as haemorrhage, perforation and penetration, the latter sometimes resulting in fistulous tracts (Jacobson and Price, 1969). Steroid associated ulcers tend to show very little inflammatory reaction or surrounding induration.

Normal endogenous corticosteroids appear to be necessary for normal acid production, as patients with Addison's disease are usually hypochlorhydric (Engel, 1955)). There is as yet no good evidence that the acute administration of steroids increases acid output. However, chronic steroid administration clearly increases acid output in dog and may do so in man (Cook, 1967; Strickland et al., 1969). There is no evidence that steroids act on gastric secretory process via any primary change in the gastric mucosal circulation (Jacobsan and Price 1969). There is very little evidence that chronic steroid administration predisposes to ulcer by affecting any of the aggressive forces (Fredrick, 1973).

There is considerable evidence in experimental models that steroids have qualitative and quantitative effect on mucus production (Desbaillets and Menguy, 1967; Menguy and Masters, 1963; Sun, 1969). Mucosal cell renewal is modified by steroid, with decreased exfoliation of surface cell and decreased mitotic activity (Clarke, 1972; Max and Menguy, 1969). Steroids alter mucosal defence mechanism; hence the gastric ulcers are soft, without much of a fibrotic ability of the mucosa to renew and repair itself. Corticosteroids also produce ulcer by inhibiting prostaglandin synthesis (Robert and Nezamis, 1964).

(2) ANTI INFLAMMATORY AND ANALGESIC AGENTS Salicylates and NSAID cause ulceration (Davenport, 1967b; Brodie and Chase, 1967). Similar to aspirin, indomethacin is well known to evoke gastrointestinal damage in animals (Cioli et al., 1967; Djahanguiri, 1969; Kent et al., 1969; Sopmogyi et al., 1969; Brodie et al., 1970) and human (Lorgreen and Allander, 1964; Katz et al., 1965; Beirne et al., 1974). Indomethacin has been reported to reduce the rate of mucus (Park et al., 1975).

Green et al. (1981) reported that indomethacin (15 mg/kg, s.c.) produces constant and severe gastric damage with the significant decrease in mucus. The location and type of lesion with indomethacin are dependent upon the feeding condition

in rats; in fasting rats lesions occur only in the gastric corpus (Somogyi et al., 1969; Brodie et al., 1970 and Hiroshi et al., 1981). Phenylbutazone and oxyphenbutazone produce gastric irritation and bleeding and may induce ulcer or exacerbate an existing ulcer. Penicillamine in a dose of 7.5 and 15 mg/kg for 7 days induces significant ulceration (Gupta et al., 1980).

(3) HISTAMINE. produces gastric and duodenal ulcers in experimental animal when given in repeated doses (williams, 1951; Eagleton and Watt, 1965). Histamine selectively produces gastric ulcer by its musculo-vascular phenomenon whereas duodenal ulcer probably through the H_2-receptors in guineapigs (Eagleton and Watt, 1967). In man the histamine released by severe injuries, especially burning, may induce the formation of gastric ulcer. BETAHISTINE, which has histamine-like activity, is used in the treatment of 'Meniere's disease' and may produce peptic ulcer as a side effect.

(4) RESERPINE is a potent ulcerogenic agent in experimental animals. Reserpine i.p. 20 mg/kg given in three doses at three hours intervals in conscious rats produces severe ulcers in 24 hours (Al-Joboory, 1985). But it is less well established that it has this action in man, even though it increases gastric acid secretion and motility. The effect of reserpine may be partly due to vagal hyperactivity, and possibly partly due to serotonin depletion. XANTHINES, including caffeine stimulate parietal cell secretion; it has been suggested that this may lead to the development of an ulcer, but direct evidence is lacking (Bowmen and Rand., 1980).

(5) GASTRIN, is secreted in large amounts due to pancreatic tumor in patients with Zollinger-Ellison syndrome, characterized by a high incidence of multiple and persistent peptic ulcer.

(6) VASODILATOR DRUGS Nicotinic acid and its derivatives, the α-adrenoreceptor antagonists tolazoline and phentolamine and β-adrenoreceptor agonist buphenine have a stimulant action on gastric acid secretion and are contraindicated in patients with peptic ulcer.

(7) DISCRETE vermal lesions of cerebellum have been shown to produce gastric ulcers in cats and rats (Maiti and Guha, 1977).

(8) CENTCHROMAN a postcoital antifertility agent has been reported to induce gastric ulcers in rat (Gupta et al., 1976).

(9) N-METHYL-4-PHENYL-1,2,3,6-TETRAHYDROPYRIDINE in 5 mg/100 gm of body weight of female albino rats, either p.o. or s.c. daily for 4 days produced severe duodenal ulcers (Szabo et al., 1984).

CHAPTER

IIf

PREPARATION OF TAMRABHASMA

The TABH used in the present study was obtained from Gujarat Ayurveda Vikas Mandal Pharmacy (GAVMP), Junagadh. The details of the method used by GAVMP for preparing TABH is given below. Their method of preparation is as per the reference of Ayurvedic Pharmacopoeia, Drug Committee, Ministry of Health, Government of Gujarat, Ahmedabad, Gujarat State, 1966.

The metals or metallic compounds are always subjected to a special process called 'SHODHAN' or purification before using it as a medicine. Our ancient scholars were much conscious about the heavy metal toxicity. The use of copper as an internal medicine is highly toxic. If copper is not purified and incinerated it gives rise to perspiration, loss of consciousness, nausea, vomiting, diarrhoea and colic.

SHODHAN

Thin copper leaves (sheets) are heated and immersed in the juice of VITEX NIRGUNDO LINN (Nirgundi), then smeared with the milk of EUPHORBIA LINN (Thor), CALOTROPIS PROCERA (Arka), common salt and butter milk. This process is to be repeated 12 times. Alternatively process of 'shodhan' can also be carried out by smearing the copper leaves with chalk and common salt, rubbed with butter milk, heated and while still hot, to be immersed in the juice of VITEX NIRGUNDO LINN (Nirgundi), and rubbed with sour vegetable juice. This last process is to be performed six times. Thus the copper is 'purified'.

After purification of special process called "Maran" is to be performed, so that the metals lose their identity and converted chemically into the fine powder of copper oxide or sulphide.

MARAN

Purified thin copper leaves, which can be pierced through by means of thorns, are to be smeared with an equal quantity of sulphur, previously rubbed with sour vegetable juice. They are then to be dried and subjected to "Gajput", a special process for heat and then powdered. The powder is now mixed with one-fourth its quantity of sulphur and rubbed with the juice of lime fruit, or juice of CYNODON DECTYLON LINN PERS (Durva) and then subjected to "Gajput". The last process is to be performed four times, after which the powder is rubbed with the juice of CITRUS MEDICA LINN (Bijaura) and once agains subjected to "Gajput", then the powder is rubbed with equal quantity of sugar and then subjected to "Gajput" and this is how copper is reduced to ash.

The process of 'Maran' converts the metals into such forms which can be acted upon by the gastric juice and intestinal juice, so as to be rendered absorbable. This preparation is absorbed very slowly and in this way minute concentrations having a stimulant action on the tissue are obtained and higher toxic concentrations are avoided.

GAJPUT

A special process for heat is followed by keeping material in an earthen vessel, and covered with another basin, the joint being tightly cemented with mud, cloth etc. It is then to be heated by a fire made of cowdung cakes.

A cubical pit, 24 inches in length, breadth and height, each, is to be filled with cowdung cakes upto the brim. An earthen vessel containing the copper is to be placed upon the heap of cowdung cakes. Half the number of cakes, required for filling up the heap, which is next to be set fire to. Heating in this way is called burning by 'Gajput'.

IMPORTANCE OF "GAJPUT"

The excellence of the preparation of metals depend upon the prescribed number of 'puts' (heat); a medicine must not be subjected to a greater or less number of 'puts'than are actually necessary for its efficaciousness. The 'puts' (heat) reduces a metal to state of incineration, from which it cannot be restored to former condition. It is 'put' which causes the excellence in the quality of metals, the ability of metals to enter into the plasma, and the ability of the metals to increase the power of digestion.