INTRODUCTION

I N T R O D U C T I O N

Peptic ulcer, because of its frequency and worldwide distribution, continues to be the subject of numerous investigations both experimental and clinicopathological. In this respect peptic ulcer occupies a place secondary to carcinoma in the field of gastroenterology. Quincke[1] was probably the first to use the term 'peptic ulcer' which is an excoriated area of gastroduodenal mucosa caused by the digestive actions of gastric juice.

PATHOGENESIS OF PEPTIC ULCER

Physiologically, peptic ulcer results from the inability of the localised area of gastroduodenal mucosa to withstand the digestive action of acid-pepsin of gastric content. Quincke[1] stressed the importance of acid and pepsin in the aetiology of peptic ulcer. Schwarz[2], Kahn[3], Palmer and Nutter[4] suggested that peptic ulcer does not occur in absence of acid. Menguy[5] as well as Glass[6] described the

importance of mucus in preventing the gastric mucosa from forming ulcers. Clinical experience has suggested that the cause may be multiple and may include anxiety, smoking and fatigue as enviornmental factors with the parietal cell mass and the blood groups as helping to determine the hereditary tendency[7]. In addition to these factors there are many other important factors which need consideration in the pathogenesis of peptic ulcer, viz., mucosal blood flow[8-10], neurohumors and autocoids[11-14], autonomic nervous system[15,16], gastro-intestinal hormones[17-20] and central nervous system[21,22]. Thus it signifies that the pathogenesis of peptic ulcer has long been a matter of investigation and debate, nor has any agreement yet been reached in spite of extensive research in this direction.

EXPERIMENTAL ULCER

So far as experimental ulcer is concerned, it was Seyle[23] who for the first time developed gastric ulcer in albino rats subjected to different types of noxious stimuli. Brodie and Hanson[24] produced stress induced gastric ulcers in various experimental animals and implicated increased acidity in the pathogenesis of these ulcers. Bonfils and Lambling[25] as well as Guth and Hall[26] suggested the importance of disturbed circulation in experimental restraint ulcer. Now-a-days, it is well known that ulcer can be produced in rats, guineapigs and mice by injecting various drugs viz. analgesic, antipyretic, antiinflammatory, steroids, ACTH, histamine etc.[27,28]

ASPIRIN INDUCED GASTRIC ULCERATION

Anderson[29] and Davidson *et al.*[30] have demonstrated that parenteral administration of aspirin does not produce

gastric haemorrhage in animals or man, while other workers have shown that direct contact of aspirin with gastric mucosa is not necessary for the production of gastric bleeding[31-33]. Brodie and Chase[34] and Djahanguiri[35] reported that subcutaneous or intraperitoneal injection of aspirin produced 90-100% ulcerogenic response in rats. Furthermore, Brodie and Chase[34] showed dose dependent response of aspirin by oral or intraperitoneal route.

The literature on the effect of aspirin on gastric secretion was reviewed by Lynch et al.[36], who reported an increase, no change or a decrease in gastric secretion by salicylates depending upon the preparations and species studied. Paul et al.[37] and Lish et al.[38] have reported that aspirin caused decrease in volume and acidity of the gastric secretions in rats. Winkelman and Summerskill[39] reported that aspirin given by mouth in customary doses has no effect on hydrochloric acid secretion. Soluble aspirin acted as a weak stimulus whereas sodium salicylate solution appeared to inhibit secretion. Furthermore, they suggested that in the pathogenesis of aspirin induced gastric ulceration factors involved in mucosal damage and resistance seem to be more important than hydrochloric acid secretion. Aspirin may also increase epithelial cell exfoliation[40], reduce the secretion of mucus[41] and alter its composition[42] and physiochemical properties[43].

Davenport[44-45] has presented a hypothesis on mechanism of aspirin induced gastric damage. He suggested that aspirin alters the gastric mucosa in some way which permits the back diffusion of hydrogen ion through the normally impermeable mucosa into the interstitial space, where it causes capillary breakdown and haemorrhage. Thus the low gastric acidity by aspirin is due to loss of hydrogen ion

through the gastric mucosa rather than to a suppression of parietal cell activity.

Aspirin has also been shown to reduce the rate of synthesis and secretion of mucus[41,42]. It seems possible as Menguy[41] suggested that it is the loss of mucus 'barrier' that permits the back diffusion of hydrochloric acid into the aspirin-damaged gastric mucosa. Davenport[44] showed that aspirin damaged gastric mucosal barrier which allows back diffusion of hydrogen ion. When the mucosa is damaged by salicylates histamine is released and capillary permeability increases which is followed by bleedings.

Brodie and Chese[34] observed that aspirin-induced gastric ulcerations were significantly reduced by anticholinergic, antacids, a ganglion blocking agent and vagotomy but not by central nervous system depressants. Djahanguiri[46] reported the involvement of catecholamines in aspirin-induced gastric ulceration. Caravati and Cosgrove[47], Dodd et al.[48] have suggested central role of salicylates induced gastric ulceration and haemorrhage by hypothalamic-pitutary-adrenal system. Salicylates mimic in many respects the pharmacological properties of cortisone[49], but the evidence is conflicting regarding the release of cortisone by the action of salicylates on the pitutary-adrenal axis[50]. Smith[50], in a comprehensive review of the subject, has concluded that the majority of effects of salicylates are due to their intrinsic properties rather than to secondary endocrine influences.

ANALGIN AND PARACETAMOL INDUCED GASTRIC ULCERATION

Peracetamol (acetaminophen) and analgin (metanizol or dipyrene or sodium noramidopyrine methanesulphonate or noraminopheno-

-zone) are generally thought to be safe antipyretic and analgesic having antiinflammatory activities too. Paracetamol was originally used in the late 19th century, but only in the last few years it is again widely used as an antipyretic and analgesic agent. Adverse effects following therapeutic doses have rarely been recorded. Proudfeet and Wright[51] studied 41 cases of acute paracetamol poisoning in which only one died of gastrointestinal haemorrhage and acute massive necrosis of the liver, which on autopsy showed massive upper alimentary bleeding due to hypoprothrombinaemia. However, analgin has been shown to cause agramulocytosis as a serious toxic effect[52,53].

GLUCOCORTICOIDS INDUCED GASTRIC ULCERATION

Numerous reports are there showing glucocorticoids, viz. hydrocortisone, cortisone, prednisolone and ACTH produce gastric ulceration in normal rats[54,55], the shay rats[56], dogs[57,58] and in man[59,60]. Kahn et al.[61] have reported extension and perforation of the ulcers as well as reulceration of a healed ulcer area in rats receiving cortisone.

Several theories have been proposed to explain the pathogenesis of glucocorticoid induced gastric ulceration. Robert and Nezamis[54] have found that anticholinergic drug methscopolamine bromide prevents the steroid induced ulcers. Robert and Nezamis[62,63] suggested that the antipolgistic property of steroid may be concerned for gastric ulceration. Seyle[64] suggested the diminution of tissue resistance related to the anti-inflammatory action of corticosteroids in the genesis of ulceration. Foley and Glick[65] and Robert and Nezamis[62,63] have suggested the role of histamine release in corticoid induced gastric

ulceration. Levis and Beerseerts[66] observed vascular dilation resulting in localized haemorrhagic thrombosis in corticoid induced gastric ulceration. Sanyal and coworkers[28,67] reported that anti 5-HT agent (Cyproheptadine) failed to prevent prednisolone induced gastric ulcers, whereas banana extract reduced the incidence.

INDOMETHACIN INDUCED GASTRIC ULCERATION

Indomethacin was introduced in 1962 as a synthetic non-steroidal, anti-inflammatory, analgesic and anti-pyretic agent for the treatment of rheumatoid arthritis, degenerative joint-disorders and other inflammatory conditions. Reported observations suggested that patients taking indomethacin sometimes developed gastrointestinal symptoms[68-70].

That indomethacin caused peptic ulcer in human subjects was reported by Wanke et al.[71] and Kais et al.[72] while Ballabio[73] found no evidence of ulcer but only bleeding in patients taking indomethacin as therapeutic agent, although the site and the pathogenesis of haemorrhage remains a mystery.

In animal experiments, Djahanguiri[74] and Lee et al.[75] showed that indomethacin caused gastric, duodenal, antral and jejunal ulcerations, haemorrhage and perforation in rats and guineapigs. On studing this ulcerogenic property, Nocolff[76] showed that ulcerogenic effect of indomethacin did not seem to be related to acid hypersecretion Menguy[41], however, while studing the mucus secretion in vagally denervated gastric antral pouch of dogs during administration of indomethacin for 21 days showed that indomethacin lowered the rate of secretion of gastric antral mucus and diminished the amount of

carbohydrate incorporation into the mucosubstance.

PHENYLBUTAZONE AND OXYPHENBUTAZONE INDUCED GASTRIC ULCERATION

A non-steroid, synthetic compound 'phenylbutazone' was introduced in 1949 for the treatment of rheumatoid arthriti musculoskeletal diseases and allied disorders. Mauer[77] in a survey of 3934 patients treated with phenylbutazone reported 40 proved cases of peptic ulcers, 9 cases of haemorrhage and an additional 424 individuals also developed gastrointestinal symptoms including epi-gastric pain. Others who reported development of peptic ulcer after constant use of phenylbutazone were Leonard[78], Deseze and Levernievx[79], Kern et al[80] and Kirsner[81].

Animal experimental studies also showed that mice, rats, guineapigs and dogs were vulnerable to peptic ulceration after phenylbutazone treatment administered either orally or parenterally.[82-84]

A casual relationship between phenylbutazone ulcers with gastric secretion and acidity was observed by various workers. Schimid et al.[85] reported that phenylbutazone stimulated both gastric acid secretion and peptic activity of the gastric juice, oxyphenbutazone, by contrast, lacked these effects. Bonfils[86] observed that there was no change in gastric acid secretion after oral or parenteral administration of the drug. Number of workers, however, have given importance to the mucus barrier whose absolute or relative deficiency acts as a factor in the production of ulceration[87-90]. Zaidi et al.[91] observed a steady decrease of mucin in the gastric juice after 30 days of phenylbutazone treatment in guineapigs.

STRESS INDUCED GASTRIC ULCERATION

Several studies in human subjects have demonstrated that emotion can cause increase in gastric acidity. On this basis 'emotional stress' has been considered as an important factor in the etiology of peptic ulcer. James[92] discussed the work of Wolf and Wolf on fistulous patient. He showed that when the patient was subjected to acute or chronic periods of emotional stress there was an increase in the gastric acidity. Shay and Coworkers[93] demonstrated that the emotional stress increased the total acid output to over four times the basal levels. Eichhorn and Trackfier[94] observed alteration in acid secretion in patients with hypnotically-induced emotions. Thus it appears that emotional stress can be a factor in the etiology of peptic ulcer.

Seyle[23] was the first to report the experimental peptic ulcer in rats subjected to different types of noxious stimuli such as immobilization, injection of drugs, exposure to cold or surgical trauma. Since then many other workers reported the restraint ulcers in rats by immobilization[24,95]. These stimuli were classified as nonspecific stressee. It was postulated that nonspecific stresses produced certain emotional disturbances in the animals, which increase adrenal function and resulted into the appearance of 'neurogenic' ulcer in 85-100% animals. Behavioral techniques for the production of neurogenic ulcers have been described in rats by Weisz[96] and in monkey by Porter et al.[97] They used conflict situation in the animals by electrical shock, anxiety, punishment and condition avoidence situation.

Numerous studies have been undertaken to

investigate the mechanism underlying the stress induced gastric ulceration[27,93]. Menguy[27] was first to demonstrate the effects of restraint on gastric secretion in the pyloric-ligated rats. He demonstrated that restraint significantly decreased free acid output in these animals, although vagotomy prevented the restraint ulcers. Thus, he concluded that acid-pepsin digestion was not the basic mechanism in the production of restraint ulcers. The protection provided by vagotomy was due to an alteration in gastric mucosal blood flow or delayed gastric emptying. Brodie et al.[24,98] studied the effects of restraint on gastric secretion in the chronic fistula rat. They found increase in the concentration of free and total acid. It is not necessary, James pointed out[92], that stress alters gastric secretion mediated through vagus nerve. Gray[99] has reviewed the effects of endocrine changes on gastro-intestinal tract and indicated that gastric acidity can be increased by adrenocortical stimulation. Bonfils and Lambling[25] and Guth and Hall[26] suggested the importance of disturbed circulation in restraint rats. Nylander and Olerud[100] observed the accumulation of blood vessels just beneath the surface of epithelium after 6h restraint. 'The vascular engorgement and ulceration were prevented by vagotomy' - observed by Guth and Kozbur[101] who demonstrated that buffering of intraluminal contents does not prevent microcirculatory and mast cell changes associated with restraint, but produces a decrease in the incidence of ulceration. However, Goldman and Rosoff[102] showed that the vascular changes occur before the appearance of gastric lesions. Hase and Moss[103] studied the microvascular changes in gastric mucosa in the development of stress ulcers in the rats. They suggested that mucosal ischaemia is caused by contraction of connecting arterioles and that persistent local ischaemia of gastric mucosa triggers tissue damage and development of stress ulcers.

Sharma et al.[104] suggested that hypothalamus may be concerned in relaying effects of stress to stomach both by neural and hormonal routes. Several investigators have demonstrated that vagotomy reduced the incidence of restraint ulcers[24,95,105]. Furthermore, Hanson and Brodie[24] and Hanson[106] showed that pretreatment with anticholinergic drugs, viz. atropine or scopoeminemethylbromide prevents the ulcer formation in restrained rats.

There are reports that stress induced gastric ulceration is primarily due to excitation of sympathetic nervous system which leads to increase in the turnover rate of catecholamines in the gastric mucosa[46]. Okabe et al.[107] and Djahanguiri et al.[46] have reported that alpha adrenoceptor blockers (phentolamine, phenoxybenzomine dibenamine and yohimbine) and beta adrenoceptor blockers (propranolol and aleprenol) reduce the incidence of gastric ulceration induced by stress. On the contrary, Djahanguiri et al.[35] reported that beta adrenoceptor blockers failed to prevent stress induced gastric ulcers. However, Takagi et al.[108] showed that propranolol in doses of 1 mg/kg aggravates stress ulcers but when the dose of propranolol was increased to 10 mg/kg it blocks the ulcers. It has also been shown that the drugs bretylium and alpha methyl dopa which deplete or alter the synthesis of catecholamines block stress ulcer[46]. However, these workers failed to protect stress-induced gastric ulceration by 6-hydroxydopamine which causes chemical denervation of sympathetic nerves. 'Stress ulcer is due to central sympathetic activation', Fledmen et al. suggested[109]. Corrodi et al.[110] have demonstrated that the stressful stimuli increase brain noradrenaline turnover and ACTH secretion. Recently, Bhargava et al.[111]

reported the involvement of catecholamines in the release of ACTH. There are many reports showing an increase in corticoids secretion during stress[112,113] and corticoids do cause gastric ulceration[55,56]. However, bilateral adrenalectomy failed to prevent restraint ulcers[24,46].

Many workers have attributed the role of histamine in restraint ulcers. Singh et al.[114] demonstrated increased level of blood histamine during stress. Alphin and Ward[115] failed to prevent stress induced gastric ulcers by classical antihistaminics (H_1 receptor blockers. Bugajski et al.[116] showed that restraint ulcers are blocked by metiamide which is an H_2 receptor blockers). Cyproheptadine which is an anti 5-HT failed to prevent restraint ulcers[67]. There are many reports that psychotrophic drugs prevent restraint ulcers. Bonfil and Lambling[25] showed that metaminodiazepoxide, thioproperazine and reserpine were ineffective in restraint ulcers. Imipramine in doses of 5 mg/kg failed to protect restraint ulcers but when the dose was increased to 10 and 20 mg/kg, the protection was proportional to the dose.

Thus, it seems that both local and systemic factors are involved in stress-induced gastric ulceration. In the local factors, gastric environment, mucus secretion, vascular alteration and cellular resistance are important[117,118]. Systemically, the stimulation of CNS , presence of high level of catecholamines and histamine may play an important role during stress.[46,114,119]

TREATMENT OF PEPTIC ULCER : ROLE OF INDIAN MEDICINAL PLANTS

Due to scant and contradictory knowledge about the cause of peptic ulcer, its treatment is still unspecific. Apart from the successful intervention of surgical means, drugs most frequently

used are either antacids, anticholinergics or the pro-mucus secreting drugs depending on the type and sign-symptoms of the ulcers. At present prostaglandin E_1 shows some therapeutic importance in peptic ulcer although it is still under trial[120].

Treatment of peptic ulcer with Indian medicinal plants and fruits is now attaining considerable interest to researchers. Senyal et al.[28,121] showed both the prophylactic action and the curative value of unripe vegetable banana in different types of experimental ulcers. Elliot and Heward observed[122], unripe banana prevents histamine induced gastric ulcer in mice. Recently, Varma et al.[123] demonstrated that amlaki rasayana, an indigenous medicine main ingredient of which is amlaki, is efficacious in patients suffering from gastritis and hyper acidity.

We in our laboratory when screened a number of indigenous plants and fruits for their antiulcerogenic activity[124-126] noticed that amlaki (Emblica officinalis Linn.) exerted antiulcerogenic effects in experimental ulcers as induced by

a. Aspirin

b. Restraint stress.

Since two experimental models are not sufficient to evaluate the antiulcerogenic activity of amlaki, it was thought worthwhile to study the same in more experimental ulcer models. The present work, thus, was an attempt to evaluate the antiulcerogenic property of amlaki and its effect on various biochemical profiles in experimental ulcers.