# INTRODUCTION

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Peptic ulcer is an excoriated area of gastroduodenal mucosa caused by digestive action of gastric juice.Quineke (1) was probably the first to use the term "Peptic ulcer". Because of its frequency and world wide distribution, peptic ulcer continues to be a subject of numerous investigation, both experimental and clinico pathological. In this respect peptic ulcer occupies a place secondary to carcinoma in the field of gastroenterology.

## EPIDEMIOLOGY OF PEPTIC ULCER

Duodenal ulceration is common. It is told (2) that 15% of the population will suffer from a duodenal ulcer at some time.They are two to three times commoner than gastric ulcer. Duodenal ulcer is commoner in male than women (4 :1) and both gastric and duodenal ulcer are more common in elderly people, is an age related incidence. There is considerable geographical variation. Duodenal ulcer is common in nothern England and Scotland than in other parts of the U.K. (2).

In India duodenal ulcer is very common among rice eating South Indian (Tamil Nadu, Kerela and Bengal), while less common in northern India where people are mainly wheat eater (3).

## AETIOLOGY AND PATHOLOGY OF PEPTIC ULCER

### AETIOLOGY

The peptic ulceration is caused by an imbalance between

Acid and pepsin and

Mucosal defences – mucus, bicarbonates, and prostaglandins, H. pylori plays a central role in both gastric and duodenal ulceration, although the mechanisms are unclear. Genetic susceptibility may also play a role, particularly in patients who do not secret blood group 'O' antigen into gastric secretions.

Possible Pathogenetic factors of H. pylori infections are

1. An increase in fasting and meal - stimulated gastrin release.
2. A decrease in somatostatin (D Cells). in the antrum.
3. An increase in parietal cell mass.
4. An increase in pepsinogen I.
5. An alteration in the mucus protective layer
6. Cytotoxin release.

All these affect acid secretion or the mucosal barrier.

The only other important cause of gastric ulceration is non steroidal anti inflamatory drugs. Peptic ulceration is also seen in hyper parathyroidism (since calcium stimulates acid sceretion) and in the Zollinger-Ellison syndrom (2).

### PATHOLOGY

Gastric ulcer can occur in any part of the stomach, but is most commonly found on the lesser curve. Most duodenal ulcers are found in the duodenal cap with the surrounding mucosa appearing inflamed, haemorrhagic and friable (duodenitis).

Histologically there is a break in the superficial epithelium penetrating down to the muscularis mucosa with a fibrous base and an increase in inflamatory cells. The ulcer may heal with fibrosis (2).

## FACTORS CAUSING PEPTIC ULCER

Various factors like tobacco smoking, tobacco chewing, spicy food, hot food,

improper chewing habit, mental stress, too much tea or coffee drinking are blamed for the causation of peptic ulcer. Drugs like, steroid, aspirin, aminophyllin, non steroidal anti inflamatory and analgesic drug play a significant role in the development of peptic ulcer. Strong alcoholic drink when gulfed without food develops peptic ulcer (3).

## EXPERIMENTAL ULCER

Seyle (4) for the first time developed gastric ulcer in albino rat subjected to different types of noxious stimuli. Brodie and Hanson (5) produced stress induced gastric ulcer in various experimental animals and implicated increased acidity in the pathogenesis of these ulcers. Bonfil and Lambling (6) as well as Guth and Hall (7) suggested the importance of disturbed circulation in experimental restrain ulcer. Now-a-days it is well known that ulcer can be produced in rat by injecting various drugs like, analgesic, antipyretic, anti inflamatory, steroid, ACTH, histamin etc. (8,9).

## *INDOMETHACIN INDUCED GASTRIC ULCERATION*

In 1962 indomethacin was introduced as a synthetic, non steroidal anti inflamatory, analgesic and antipyretic agent for the treatment of rheumatoid arthritis, degenerative joint disorder, and other inflamatory conditions Wanka et al (10) and Kaig et al (11) for the first time reported that indomethacin caused peptic ulcer in human subject. There are also reports (12,13,14) suggerting that the patients taking indomethacin sometimes develop gastrio intestinal symptoms. Ballabio (15), however, found no evidence of ulcer but only bleeding in patients taking indomethacin as drugs. In animal experiment it was noted (16,17) that indomethacin caused gastric, duodenal, antral and jejunal ulceration, haemorrhage and perforation in rats and guniapigs. While studying this ulcerogenic properties Nocoloff (18) showed that ulcerogenic effcet of indomethacin did not seem to be related to acid hyper secretion.

Menguy (19), however, while studying the mucus secretion in vagally denervated gastric antral pouch of dog during administration of indomethacin for twenty one days showed that indomethacin lowered the rate of secretion of gastric antral mucus and diminished the amount of carbohydrate incorporation into the mucus substance.

## *ANALGIN AND PARACETAMOL INDUCED GASTRIC ULCERATION*

Analgin and paracetamol are generally thought to be safe antipyretic and analgesic having anti inflamatory activity too. Paracetamol was originally used in late 19th century and in the last few years it is widely used as an antipyretic and analgesic agent. Adverse effect following therapeutic dosages have rarely been recorded. There

is, however, a study on 41 cases of acute paracetamol poisoning in which one died of gastro intestinal haemorrage and acute massive necrosis of the liver (20). Analgin, on the other hand, has been shown to cause a granulocytosis as a severe toxic effect (21,22).

## ASPIRIN INDUCED GASTRIC ULCERATION

It was demonstrated (23,24) 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 production of gastric bleeding (25,26,27). Brodie, Chase (28) and Djahanguiri (29) reported that subcutaneous or intraperitonial injection of aspirin produced 90-100% ulcerogenic response in rats. Furthermore, dose dependent response of aspirin by oral or intraperitonial route was also demonstrated (28).

Effect of aspirin on gastric sceretion was reviewed by Lynch et al (30). He reported an increase, no change, or a decrease in gastric secretion by salicylates depending upon the preparation and species study. There are reports that aspirin caused decrease in volume and acidity of gastric secretion in rat (31, 32). There is also a report that aspirin given by mouth in customary dosage has no effect on hydrochloric acid secretion (33). In the report the author suggested that in the pathogenesis of aspirin induced gastric ulceration factors involved in mucosal damage resistance seems to be more important than hydrochloric acid secretion. Other reports indicated that apirin may increase epithlial cell exfoliation, reduced the secretion of mucus and alter its composition and physico chemical properties (34,35,36).

A hypothesis on the mechanism of aspirin induced gastric damage was presented by Davenport (37, 38). Davenport suggested that aspirin alters the gastric mucosa in some way which permits the back difusion of H-ion to the normally impermeable mucosa into the interstitial space where it causes capillary breakdown and haemorrhage. Thus, low gastric acidity by aspirin is due to loss of H-ion through the gastric mucosa, rather than to a suppression of parietal cell activity.

Menguy (19) suggested that aspirin reduces the rate of synthesis and secretion of mucus. He told that it is the loss of mucus barrier that permits the back diffusion of hydrochloric acid into the aspirin damaged gastric mucosa. Davenport (37) showed that aspirin damaged gastric mucosal barrier allows back diffusion of H-ion.

There was observations (28) that aspirin induced gastric ulcerations were significantly reduced by antacids, anticholinergic, ganglion blocking agent and vagotomy, but not by central nervous system depressant. Catecholamines, however, were involved in aspirin induced gastric ulceration (39). There were suggessions (40, 41) that hypothalamic pituitary, adrenal system is involved in salicylates induced gastric

ulceration. Salicylates mimic in many respect the pharmacological properties of cortisone (42) but the evidence is conflicting regarding the release of cortisone by the action of salicylates on the pituitary adrenal axis. In a comprehensive review of the subject Smith (43) has concluded that the majority of effects of salicylates are due to their intrinsic properties rather than to secondary endocrine influences.

## GLUCOCORTICOID INDUCED GASTRIC ULCERATION

There are numerous reports showing the production of gastric ulceration in normal rat, the Shay rat, dog, and in man by glucocorticoid namely hydrocortisone, cortisone, prednisolone and ACTH (44-50). Khan et al (51) have reported extension and perforation of the ulcer as well as reulceration of a healed ulcer area in rat receiving cortisone. Several mechanisms have been put forward to explain the pathogenesis of glucocorticoid induced gastric ulceration(52-55). Some where it was considered that anticholinergic drug, methapopolamine bromide prevent the steroid induced ulcer, while somebody suggested that the anti polgistic properties of steroid may be concerned for gastric ulceration. There were also suggetions that diminution of tissue resistance related to the anti inflamatory action of corticosteroid is responsible in the genesis of ulceration. Histamine is also considered involved in corticoid induced gastric ulceration.

Levis (56) observed vascular dilatation resulting in localized haemorrhagic thrombosis in corticoid induced gastric ulceration. Sanyal and co-workers (57) reported that anti 5 HT agent (cyproheptadine) fail to prevent prednisolone induced gastric ulcer.

## PHENYLBUTAZONE INDUCED GASTRIC ULCERATION

Phenylbutazone is a good example in which dosages level employed are of utmost importance. Low dosages appear to be well tolerated. A high dosage of the same compound have been observed to produce gastroduodenal ulceration both in experimental animals and in human.

Epigastric pain, nausia, vomiting, acute ulcer, activation of pre exsisting peptic ulcer or development of peptic or duodenal ulcer in a number of cases (58 - 62) ulcerogenic effect has been observed after both oral and parenteral route of administration of phenylbutazone. Bonfils et al (63) were first to administer phenylbutazone orally to rats in a dosage 100mg / kg body weight, in 88% of the animals ulceration of the glandular stomach was observed (64 - 66).

## HISTAMINE INDUCED GASTRIC ULCERATION

Of the many substances that have been used to the experimental production of ulcer in laboratory, histamine is perhaps one of the most physiological. Popielski

in 1920 (67), demonstrated that histamin is a powerful stimulator of gastric secretion. Injected intravenously it stimulates acid secretion not only from the intact stomach but also from totally denervated gastric pouch. Evidence has been accumulating that it might even be physiological stimulant of the acid secreting parietal cell.

More recently in the investigation of the so called histamine releasor, experimentalist have noted the occurance of gastric ulceration in the cat (68) and also in some small animals such as rats (69,70). Ulcerogenesis has been attributed to the endogenous histamine released from the tissue.

Similarly, following injection of gastrotoxin and its anaphylaxis due to horse serum, endogenous histamine is held responsible for the production of ulcer in the stomach (70).

## ACETIC ACID INDUCED CHRONIC GASTRIC ULCER

Of the various problem, relating to human peptic ulcer disease, one of the least understood aspects is the chronicity of the disease. A number of models of chronic gastric ulceration have been tried using submucosal injection of silver nitrate, formalin, nicotine and epinephrine in cats and dogs. These experimental lesions grossly and histologically resembled human gastric ulcer, however they healed rapidly and completely within 2-3 weeks. Two simple methods for the production of the clearly defined deep, gastric and duodenal ulcers in rats have been describe by Okabe and Pfeiffer (71). These methods have been successfully used by a number of workers to screen newer anti-ulcer agent (72,73,74).

In as much as the chronicity of the experimental acetic acid ulcer model in the rat uniquely resembles human peptic ulcer, this model may be quite useful for the study of human ulcer and the evaluation of pharmacological agents used for this disease (75).

## RESERPINE INDUCED SOLITARY CHRONIC GASTRIC ULCERS

Reserpine produces severe haemorrhagic glandular ulceration of the stomach which has been attributed to significant degranulation of gastric mast cell and consequent liberation of histamine. These events are thought to be cholinergically mediated (76). The morphological changes in gastric mucosa are very similar to the destructive changes found in the mucosa of human gastric ulcer (77).

## SEROTONIN - INDUCED GASTRIC MUCOSAL LESIONS

Serotonin ulcer, one of the chemically induced experimental gastrc ulcer, has

been described by Wilhelmi (78), Hedinger and Veraguth (79). Since then it has been widely used for the investigation of the atiology of peptic ulcer disease and as a tool in the search for new anti-ulcer drugs.

## DIMAPRIT INDUCED GASTRIC ULCER

On the basis of universally recognized hypothesis about the involvement of $H_2$ receptors in the pathogenesis of peptic ulcer, an appropriate rat model has been designed with dimaprit as specific $H_2$ receptor agonist. Dimaprit was administered intraperitonialy I.P. or I.V to 24 hours fasted rats and the animals were sacrificed four hours after the injection. The drugs for studying their gastroprotective effect were given 30 min. before dimaprit. The procedure is extremely simple and rapid. Its feasibility and spceificity are added advantage. It is very useful for evaluating not only the absolute potency of a drug given by any route but also of other pharmacodynamic parameter, particularly the duration of action which seems to be an important criterion in selecting new potentially $H_2$ antagonistic drugs (80).

## ENDOTOXIN (LIPOPOLYSACCHARIDE B) INDUCED GASTRIC MUCOSAL DAMAGE

Gastric mucosal ischemia is recognised as one of the major factor in the pathogenesis of acute gastric ulceration. Consequent to the impaired gastric blood flow during shock, the clearances of back difusing $H^+$ ion is reduced, the intramural pH decline and ulceration occurs. These observation based on the experiment in anaesthetised rat following the withdrawal of blood from the circulation (81) have led to development of another gastric ulcer model using endotoxin shock (82). Administration of endotoxin (20 mg / kg,i.p. ) produced a moderate degree of gastric mucosal damage in rats. The lesions remained confined to the glandular mucosa and consisted of small punctiform lesions, erosions and petechial haemorrhages. The characteristic feature of these lesions was a typical submucosal ecchymosis in the glandular stomach observed in about 30% of the animals. Pretreatment with ranitidine, pirenzepine, proglumide, sucralfate, and naloxone provide significant protection.

## CYSTEAMINE (MERCAPTAMINE) INDUCED DUODENAL ULCERS

Experimental duodenal ulcers in rats induced by cysteamine hydrochloride were first described by Selye and Szabo (83). The pathogenic mechanism leading to ulceration have not yet been fully explained, but both protective and aggressive factor influencing the resistance of the duodenal mucosa seen to be involved. Cysteamine inhibits the alkaline mucus secretion from the Brunner's gland in the proximal duodenum and stimulates gastric acid scerction rate. Gastric emptying is also delayed and serum gastrin concentration is increased. Cysteamine induced duodenal ulcer in the rat is

widely used as a model of peptic ulcer disease. This chemically induced ulcer resemble duodenal ulcer in man to its location, histopathology and some aspcets of pathophysiology. The development of duodenal ulcer in response to cysteamine is inhibited by the anticholinergic agent, antacid, prostaglandin, and $H_2$ receptor antagonist. Since multiple dosing is necessary to prevent cysteamine induced ulcers, the usefullness of the model in a screening programme is limited by the large quantity of drug required. Hence, cysteamine has also been used in mice to produce duodenal ulcer which can be used for the evaluation of antiulcer drug overcoming the above mentioned drawback seen in rats.

## DULCEROZINE INDUCED DUODENAL ULCER IN RAT

Kurebayashi et al (84) reported that acute perforating duodenal ulcer can be produced in rat following single oral administration of dulcerozine, a compound structurally related to non steroidal anti-inflamatory drug such as phenylbutazone and other known to cause gastro intestinal damages in man and in animals. It has been proposed that prolonged gastric hyper secretion might be an important factor contributing to the pathogenesis of duodenal ulcer in this species. The dulcerozine-induced duodenal ulcer in rat is a useful model for studying the pathogenesis of duodenal ulcer and testing the antiulcer drug from the practical and pathogenic standpoint because

1) The lesions develop are analogous to the clinical disease with respect to location and histology.
2) The factor producing the pathologic changes is similar in man and animals used.
3) The drug treatment and a surgical operation effective in animals could be clinically useful .
4) It is extremely simple to perform the massive production is feasible and the results are obtained within 18 hours.

## DIMAPRIT INDUCED DUODENAL ULCER

Recently Del Soldato et al (85) have used the model of dimaprit induced duodenal ulcer in the guineapig to study the anti-ulcer activity of some $H_2$ receptor antagonists.

## MPTP INDUCED DUODENAL ULCER IN RATS

Szabo et al (86) have shown that the parkinsonism inducing agents 1-methyl-4-phenyl-1,2,3,6,-tetara hydro pyridine (MPTP) given in multiple daily doses, either P.O. or S. C. induces solitary or doubled ("kissing") duodenal ulcer in a rat in

a dose dependent manner. MPTP decreases the gastric secretion of acid and pepsin as well as pancreatic bicarbonate, trypsin and amylase. Thus, it produces duodenal ulcers that are possibly associated with impaired defence in the duodenal bulb (e.g. decreased availability of duodenal and pancreatic bi-carbonate). However, there is very limited experience with this model as yet in order to establish its suitability for routine use in the evaluation of anti-ulcer drugs. Only some dopamine agonist like bromocriptine and lergotrile and monoamine oxidase inhibitors like pargyline and deprenyl have been shown to prevent MPTP induced duodenal ulcers in rats.

## STRESS ULCERS

Gastrointestinal erosion is one of the consistent findings in man and in experimental animals subjceted to different types of stress. These ulcers appear to be the experimental counterpart of curlings ulcer or human stress ulcer. The major advantages of the preparation over pylorus ligation are that they are technically simple, they do not require anaesthesia or surgery, they bring central nervous system-into play and the lesions produced by the method are located in the glandular region of the stomach, whereas in the pylorus ligated rat the lesion occours mostly in the rumen of the rat's stomach. The following method have been commonly used (87,88).

### *RESTRAINT ULCERS*

The method discribed by Brodie and Hanson (5) is used for the production of restraint ulcers.In a series of similar investigation Brodie and co-workers systemetically examined the restraint technique and popularised its use in North America (89, 90). Brodie (91) concluded that the technique was a useful one but that several disadvantages were still present, including the fact that the lesions did not penetrate the muscularis mucosa and as such were not ulcers in true sense and the fact that the technique appeared to be somewhat species specific. Hence the restraint method has been modified by suming, less cumbersome and more reproducible. This method has been excellently reviewed by Glavin (92) some of the commonly used modifications are described here.

### *WATER IMMERSION - INDUCED RESTRAINT ULCER*

It has been shown that exposure of rats to restraint stress significantly decreases gastric acid secretion (93), but there occurs an increase in gastric acid secretion towards the prestress level for a few hours when the restrained animals are subjected to additional water immersion (94). Since the development of gastric lesions during stress was significantly enhanced by exposure to water immersion, the rise in acid secretion may be important in the aggravating process of lesions during water immersion.

## COLD AND RESTRAINT ULCERS

In 1997 Vincent et al (95) devised a method of restraining animals which

(1) Did not require an extensive period of starvation prior to use.

(2) Did not require, that the animals be restrained for lengthy period of time.

(3) Restricted virtually all the movements of animals without respiratory or circulatory trauma.

(4) Rapidly produced very high and very reliable degree of gastric glandular restraint ulcers in rodents.

This model, later reffered to as hypothermic restraint ulcer represents a useful experimental ulcer model and a valuable research tool for use by psychologist, physiologist and pharmacologist in examining the cause, course, consequence and treatment of peptic ulcer disease.

## ACTIVITY STRESS ULCERS IN RATS

If young adult rats are individually housed in running wheel activity cage (Wahmann manufacturing Co, Baltimore, Maryland, U.S.A.) allowing continuous access to the wheel, and fed only one hour each day, some of these animals will die within 4-16 days. An interesting feature of the phenomenon is that rat, demonstrating high activity level which die, reveal extensive lesion in the glandular stomach. Since this glandular lesion resembled the 'Stress ulcer' reported by other worker and since the activity was shown to be instrumental in their development, these lesions have been designated as 'activity stress ulcer'.

The method has been described in detail by Pare (96) and is of limited value in the evaluation of anti-ulcer activity of new drug as it is time consuming and needs continuous supervision of the animals in the activity cages. Interestingly, animals developing activity - stress gastric lesion are hypo-secretors of gastric acids (97) and do not respond to histamine $H_2$ blockers (98). Activity stress gastric lesions are, however, reduced by centrally acting agent such as diazepam and imipramine suggesting that aberrations in central neurotransmission play a role in their development (99). However, some local factors also contribute to activity-stress gastric damage (100).

## HAEMORRHAGIC SHOCK INDUCED GASTRIC ULCERS IN RATS

Bleeding acute gastric erosions have now become the second most common cause of upper gastrointestinal haemorrhage (101). The increase use of alcohol, NSAIDs, as well as the increased incidence of major trauma, burns and surgery, has resulted in a great increase in the frequency of gastric erosions.

## TREATMENT OF PEPTIC ULCER

In gastric ulcer, treatment is given to ensure ulcer healing which must be checked with follow up endoscopy and biopsies at 6 weeks. Failure to heal raises the question of malignancy and further treatment and followup endoscopy is required. There are a number of approaches to treatment.

1. $H_2$ recepter agonistic have been the most common agent used for treatment, but omeprazole is being incresingly used as an initial therapy as symptom relief is rapid, follow up with endoscopy and biopsis at 6 weeks.
2. Eradication of H. pylori. Eradication treatment should be given to all patients with a gastric ulcer; usually the presene of H. pylori has been documented at endoscopy. If the patient is taking an NSAID when the ulcer is discovered, eradication therapy should still be given if H. pylori is demonstrated.
3. Smoking should be strongly discouraged. Dietary changes are unneccessary.
4. Attempt should made to stop NSAID's in patient with peptic ulceration. This may be difficult in those with severe arthritis and if it is essential to continue NSAID's either misoprostol or ranitidine should be prescribed concurrently.

### *SURGICAL MANAGEMENT*

Since the introduction of $H_2$ receptor antagonist , surgery for peptic ulceration is rarely performed. In the past, two types of operations were performed.

(1) Partial gastrectomy

The principle in both type of gastrectomy performed for peptic ulcer disease is to remove the antral area that secrets gastrin, since this, in turn, stimulates acid production.

(a) Billroth I partial gastrectomy. The lower part of the stomach is removed and the stomach remnant is connected to the duodenum.

(b) Billroth - 11 (Polyagastrectomy) The stomach remnant is collected to the first loop of jejunum (a gastro enterostomy) and the duodenum is closed.

(2) Vagetomy

a) Truncal vagotony plus gastroenterostomy / pyloroplastey

b) Selective vagetomy (Preserving the hepatic and coeliac branch of vagus) plus gastroenterostomy / pyloroplasty

c) Highly selective vagotomy a proximal gastric vagotomy in which only the nerve supplying the pariectal cells are transceted, and therefore no drainage

is required. With this type of operation there is little diarrhoea, but the recurrance rate is still 5 to 10% .

### *CURRENTLY SURGERY IS RESERVED FOR COMPLICATION*

1. Recurrent uncontrolled haemorrhage when the bleeding vessels is ligated.
2. Perforation which is overshown (for both these condition and other procedure such as a gastrectomy or vagotomy is required ).
3. Out flow obstruction which requires gastric resection (102).

## TREATMENT OF PEPTIC ULCER – ROLE OF INDIGENOUS PLANT

Treatment of peptic ulcer with Indian Medicinal plant and fruits is now attaining considerable interest to researcher. Sanyal et al (103) showed both the prophylactic action and the curative value of unripe vegetable banana in experimental ulcer of rat and guineapig which was subsequently confirmed by Elliott R.C. and Heward G. J. F (104) in mice.

Verma et al (105) demonstrated that Amlaki Rosayana - an indigenous medicine main ingrediant of which is amlaki, is efficacious in patients suffering from gastric and hyperacidity. Mitra et al (106) also showed the anti ulcerogenic effect of amlaki in different experimental ulcer models. Anti ulcerogenic activities of Piper longum Linn. (107,108), Ul-409 a multiconstituent herbal preparation (109), black tea extract (110), Symplocos racemosa (111) were also studied and reported in the literature. According to available literature, the anti ulcerogenic role of vegetable banana was studied only on phenyl butazone, aspirin and restraint stress induced gastric ulcer in rats and histamin induced duodenal ulcers in mice. The precise mechanism of the anti ulcerogenic effect was not explored.

Since four experimental models are not sufficient to evaluate the anti ulcerogenic activity of vegetable banana it was thought worthwhile to study the same on more experimental ulcer models. The present study was, thus, aimed to evaluate the anti ulcerogenic property of vegetable banana and its effects on various biochemical profiles in experimental ulcers.