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INTRODUCTION

A) Peptic Ulcers

1) Definition and Distribution:
   i) A peptic ulcer can be defined as 'Mucosal hole' in any portion of the upper gastrointestinal tract exposed to acid pepsin secretion. The major forms of peptic ulcer are chronic duodenal and gastric ulcer. At least 98% peptic ulcers are located either in the first portion of the duodenum or in the stomach. About 5% individuals with gastric ulcer develop duodenal ulcer, but 20% of those with duodenal ulcer develop gastric lesions.

   Duodenal ulceration is an acute and chronic recurrent disease. The ulcer is usually deep and penetrates through submucosa and often on to muscularis propria. More than 95% duodenal ulcers occur in the first portion of the duodenum and approximately 90% of these are located within 3 cm of the junction duodenal and pyloric mucosa. The duodenal ulcers are usually round or oval, but they may be irregular or elliptic and small or large, sometimes extremely large, 3 to 6 cm in diameter. There are many complications of this disease which are at times fatal and the prolonged use of drug causes many side-effects.
ii) The actual prevalence of duodenal ulcer in the population is not known; estimates have range from 6 to 15%. It is a striking fact that duodenal ulcers are more common in males than in females. It is also known that this immunity in females increases during pregnancy, so much so that ulcer may heal up during this period, but reappears at the end of the pregnancy (Culmer, et al., 1939; Gray et al., 1939; Truelove, 1960; Dey and Dey, 1974). Not only is duodenal ulcer much less common in women, but it also appears to run a less severe course, at any rate judged by the liability to perforation. It was shown that the chance of man developing duodenal ulcer remains remarkably constant between ages of 20 and 65. By contrast, the chance of a woman developing duodenal ulcer remains relatively low throughout the whole of her active reproductive life, but increases sharply at the time of menopause (Truelove, 1960).

Genetic factors appear to be important in the duodenal ulcerations. Patients with duodenal ulcers have increased frequency of blood group 'O'. An increased incidence of HLA-B5 antigen in white male subjects with duodenal ulcers has also been shown. Elevated serum pepsinogen-I level have been found in approximately 50% of patients with duodenal ulcers.
Increase in serum pepsinogen appears to be inherited as an autosomal dominated traits. Individuals with this traits have frequency of duodenal ulcers eight times greater than the general population.

Cigarette smoking has been associated with increased duodenal ulcer frequency, decreased response to therapy and increased mortality (Gray, 1929; Hammond, 1966; Friedmann et al., 1974; Paffenbarger et al., 1974; Doll and Peto, 1976; Peterson et al., 1977; Doll et al., 1978; Taylor and Walker, 1980; Sonnenberg et al., 1981; Kurata and Haile, 1984; Harrison et al., 1984; Hull and Beale, 1986). It has been suggested that the duodenal ulcer among cigarette smoking is due to inhibition of pancreatic bicarbonate secretion and or acceleration of gastric emptying of acid into the duodenum. Chronic administration of smoking doses of nicotine increases the volume of gastric acid and pepsin out-put through vagal pathway (Thompson et al., 1970; Thompson and Angulo, 1971 and Thompson and George, 1972). The incidence of duodenal ulcer has been reported to be increased in patients with chronic renal disease, alcoholic cirrhosis, renal transplantation, (Timoney et al., 1989) hyperparathyroidism, systemic mastocytosis, chronic obstructive pulmonary disease and chronic pancreatitis (Lesur et al., 1991).
The importance of psychological factors in the Pathogenesis of duodenal ulcer remains controversial. There is no single characteristic duodenal ulcer personality. There is no identifiable difference in frequency of duodenal ulcers among different socioeconomic classes or occupation groups; chronic anxiety or psychological stress may, however, be factors in exacerbation of ulcer activity.

2) Etiology and Pathogenesis

i) The etiology of duodenal and gastric ulceration has been a matter of dispute for many years. Much evidence has accumulated from epidemiological, clinical, genetic and pathophysiological studies to support the concept that the duodenal ulcer is a heterogeneous condition (Lam and Sircus, 1975; Rotter and Rimoin, 1977). Although the pathogenesis of duodenal ulcer is not clear, according to some, inappropriate acidification of the duodenum is a fundamental factor and acid secretion by the stomach is essential for the production of duodenal ulcer. Abnormally large meal stimulates acid secretion and nocturnal acid hypersecretion (Lam, 1984). It is also possible that hyperacidity occurs as a temporary phenomenon and is associated with stressful life events. Duodenoulcerogenicity may also be due to reduced blood
flow (Harjlola and Sirula, 1966; Cheuna and Chang, 1977; Leung et al., 1985; Tasukamoto et al., 1991), and decrease in alkaline secretion in the duodenum (Ohe et al., 1988). According to Chirkov (1989), that in complicated course of ulcer, there was a tendency to increase acid-pepsin aggression and inhibition of glycoprotein mucosa product. The hyper-secretion is related to an abnormally large total mass of parietal cells in the gastric mucosa or either increased responsiveness of parietal cells to secretory stimuli or lack of normal regular control.

ii) Patients with duodenal ulcer have an increased vagal drive leading to augmented histamine release and a decreased mucosal histamine; vagotomy abolished and vagal drive decreased the histamine release and increased histamine content in the mucosa of stomach which led to reduction in stimulated gastric acid secretion (Lorenz et al., 1981; Vatier et al., 1991). Gastric hyper-secretion in duodenal ulcer caused by either increased vagal drive or hypergastrinaemia leads to an increased back diffusion of hydrogen ions in the stomach and duodenum. This may lead to histamine release and decrease histamine stores. The release of histamine from gastric mucosa caused by acid back diffusion, particularly in the presence of bile salts
or aspirin, has been documented (Davenport, 1966; Johnson and Overholt, 1967).

Most of the people interpret the hypersecretion of acid in the stomach with duodenal ulcer is of etiological significance. But a view has also been put forward, that duodenal ulcer is a 'tryptic' rather than 'peptic' ulcer. Gastric ulcer is in some way related to wear and tear of the gastric mucosa, whereas the duodenal ulcer is due, particularly, to excessive vagal activity leading to hypersecretion of acid in stomach (Jones, 1977), and inappropriate acidification of the duodenum may be fundamental factor (Baron, 1982). In case of duodenal ulcers, the stress produces hypermotility and hypersecretion by the over stimulation of vagus, which is the secretomotor nerve of the stomach. The hypermotility helps to propel a larger quantity of acid gastric juice into the empty duodenum, the mucous membrane of which is irritated predisposing ulcers (Dey and Dey, 1974).

iii) It is also generally believed that histamine is a mediator for gastrointestinal ulceration (Schwartz, 1971; Ogle and Cho, 1977; Guth and Code, 1978; Cho et al., 1979). There is an evidence which suggests that histamine activates vascular changes and induce ischemia during gastric ulceration (Cho and

Chronic administration of smoking doses of nicotine increases gastric juice volume, acid and pepsin output (Thompson et al., 1970) through vagal pathway (Thompson and Angulo, 1971; Thompson and George, 1972). Lam and Koo (1985) reported that some duodenal ulcer patients with normal maximal acid output might have increased sensitivity to gastrin. The elevation of serum gastrin which leads to increased gastric secretion of acid and increased duodenal acid load, is very probably an important component of the pathogenesis for ulcer formation (Briden et al., 1985).

Acid, though an absolute requisite for ulcer development, is unlikely to be the only pathogenetic factor (Barnades et al., 1978; Wormsley, 1979). Most of the discussions about the etiology of duodenal ulcer depict the duodenal bulb as a battle field on which aggressive and defensive factors wage a continuous and continuing campaign for the integrity of bulbar mucosa. The so-called aggressive factor is usually considered to be gastric juice eroding or digesting its way into (and through) the duodenal mucosa while defensive
factors are bicarbonates, which neutralize acid and inactivate the pepsin (from gastric juice) in the duodenal lumen; and mucus which acts as a barrier to acid and pepsin. The duodenal mucosa is considered to be important, as duodenal ulcers may effect presumed inadequacy of the mucosa, if no other reason can be found for the ulcer. Schulze et al. (1983) reported that the individuals are at risk, when their defenses are defective as they secrete too little bicarbonate or have diseased duodenal mucosa.

3) Pathogenesis of Drug Induced Ulcer

The study of physiological and biochemical mechanisms involved in ulcer formation and pathogenesis of ulcer in human being is not possible except some biochemical studies on gastric and duodenal juice. Therefore, to study pathogenesis of ulcer, it is necessary to induce the particular ulcers. Most of the epidermal ulcers are acute, non-penetrating, rapidly healing and non-scarring lesions while some others heal up with a scar. Despite of these limitations, it is possible to evaluate the therapeutic agents with reasonable predictability for their therapeutic usefulness, using experimentally induced models of gastric and duodenal ulcers and hyperacidity states.
Hartalia et al. (1950) found that cinchopen caused a depression of both spontaneous and food-induced secretion from Brunner's glands fistulas together with formation of ulcer in that area of duodenum of dogs. Selye and Szabo (1973) induced duodenal ulcers in rat with administration of 3-4-toluendiamine which is believed to inhibit the secretion of Brunner's glands (Perkins and Green, 1975). Kurebayashi et al. (1984) reported that acute perforating duodenal ulcers can be produced in rats following single oral administration of dulcerozine. Delsoldato et al. (1985) have used dimaprit to induced duodenal ulcers in guinea-pigs by significant increase in gastric volume and acid content. Szabo et al. (1985) have shown that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) given in multiple daily doses induced duodenal ulcers in rat probably due to decreased availability of duodenal and pancreatic bicarbonates. Szabo et al. (1985) have described lesions at the opposite side of mesenteric attachment in proximal duodenum in rat after the administration of indomethacin and subsequent dosing with histamine. The detailed results indicated that the development of duodenal lesions was due to both increase in gastric acid secretion and an impairment of acid induced duodenal HCO₃⁻ secretion. The bicarbonate secretion by the duodenum plays an important protective
role for the duodenal mucosa (Silen et al., 1986). Not only prostaglandins stimulate bicarbonate secretion when given exogenously but, perhaps more importantly, the normal flow of acid over the duodenum also stimulates the local release of bicarbonates. This physiological role of endogenous prostaglandin is supported by several studies showing that effect was blocked by pretreatment with either indomethacin or aspirin, known blockers of prostaglandin synthesis. It was also suggested that a reduction in prostaglandin synthesis by the gastric and duodenal mucosae is associated with ulcer formation in animals.

ii) Histamine was first used as ulcerogenic agent by Code and Varco (1940) since then it has been used as gastric acid secretagogue and ulcerogenic agent by various workers employing various routes of administration and species of animals. Eagleton and Watt (1967) described satisfactorily the ulcer model to induce acute duodenal ulceration in guinea pigs by repeated intramuscular injections of histamine acid phosphate (HAP), Hohnke (1974) tried to correlate between extend of duodenal damage, histamine dose and gastric acid output in HAP treated guinea pigs. Although the etiology of duodenal and gastric ulceration has been a matter of dispute for many years, it is
generally believed that histamine is a mediator for gastrointestinal ulceration (Schwartz, 1971; Ogle and Cho, 1977; Guth and Cole, 1978; Cho and Ogle, 1978, 79; Manekar and Waghmare, 1980). There is an evidence that histamine increases gastric secretion associated with duodenal ulceration (Pfeiffer and Watt, 1967; Cho and Eagleton, 1981). These changes if present would likely contribute to eventual gastric and duodenal necrosis. However, it is believed that the final mediator for tissue damage might be the lysosomal enzymes released under these abnormal changes in the tissue (Duvo and Wattiaux, 1966; Guth and Code, 1978). Thus it is possible that histamine may labilize lysosomal membranes during pathogenesis in the gastrointestinal tract. In any case this agent may lead to gastrointestinal lesions.

iii) Exact mechanism of cysteamine-induced duodenal ulceration is not known, but both the protective and aggressive factors influencing the resistance of duodenal mucosa seems to be involved. Cysteamine-induced duodenal ulcer in rat is widely used as a model of peptic ulcer disease. This chemically induced ulcer resembles a duodenal ulcer in man by its location, histopathology and pathophysiology. The ulcers develop 2 to 4 mm away from the pylorus, on the anterior wall of the duodenum and frequently perforates or penetrates
the liver and pancreas. Kurebayashi et al. (1985) studied changes in duodenal mucosal blood flow which precedes the appearance of duodenal ulcers. The decrease in sialic acid glycoprotein in the duodenum is described by Vatier et al. (1987). The studies on cysteamine-induced duodenal ulcers have provided much information about Brunner's glands (Seley and Szabo, 1973; Szabo, 1978; Krikegaard et al., 1981; Poulsen et al., 1981, 1986). During cysteamine-induced duodenal ulceration in rat, the Brunner's glands function was impaired. Briden et al. (1985) suggested that cysteamine may interfere with ability of the duodenal mucosa to resist the action of the luminal acid. Depletion of mucosubstances and histological alterations, such as dilation of lumen in the Brunner's glands, are the adverse changes during cysteamine-induced duodenal ulceration. The effect of duodenal ulcerogen cysteamine and secretion of epidermal growth factor from Brunner's gland pouches was studied in the rat (Kirkegaard et al., 1983), total output of immunoreactive epidermal growth factor was reduced to approximately 55% compared with controls.

4) Protection of Gastroduodenal Mucosa

Bicarbonates and mucus contribute to form unstirred layer over the gastric and duodenal mucosa
and animal and human data were presented showing that this mucus carbonate gel serves as a mixing barrier to acid. A pH gradient was demonstrated through thick layer in human volunteers. Therefore, the secretion of bicarbonate and mucus may play an important role in protecting the stomach and duodenum. The duodenal mucus has viscoelastic properties characteristic of water insoluble viscoelastic gels. The mucus will flow and anneal if damaged, due to breaking and making of its elastic structure, the measured life time of which was 10-120 min. Mucus reconstituted by purified glycoprotein has the same viscoelastic properties as fresh mucus, giving evidence that glycoprotein alone will reproduce the rheologic characteristic of the mucus.

Mucosal gels were unaffected by several damaging agents like undiluted pig bile, 20 mM sodium taurocholate or 20 mM sodium glycocholate (all at pH 2, 6, 8). Higher concentrations of ethanol caused dehydration and denaturation of mucus proteolysis by pepsin and other enzymes resulted in solubilization of the mucus gel with complete change in the properties from an elastic gel to viscous gel to those of a "viscous" liquid.
The mucus is secreted as a water-insoluble gel adherent to the mucosal surface and is also present as viscous soluble form in the lumen. The adherent gel covering the mucosal surface is considered to have a protective role against acid by acting as

a) Stable mixing barrier (with the epithelial HCO₃ secretion) (Hollander, 1954; Heatley, 1954; Allen and Garner, 1980; Flemstrom and Garner, 1982);

b) Luminal pepsin by forming diffusion barrier (Allen, 1981 a,b);

c) Mechanical damage by acting together with soluble mucus as a lubricant (Florey, 1955). By direct examination of ex vivo sections of rat stomach and duodenum the adherent mucus gel is observed to be continuous layer of variable thickness 5 to 200 um and occasionally 400 um (Keress, et al., 1982).

Mucus glycoprotein is a covalent polymer of subunit (5 x 10⁵) joined together by disulfide bridges (Allen, 1981; Snary et al., 1970). These intersubunit disulfide bridges are located in the non-glycosylated parts of the protein core and it is these regions that are susceptible to proteolytic enzymes or reduction cleavage (Scawen and Allen, 1977). This proteolysis of reduction cleavage marked lower viscosity and loss of gel forming potential in mucus.
Mucus structure is mainly formed of glycoprotein. In dilute solution this mucus glycoprotein has a high viscosity and occupies large volume (Allen et al., 1976). As the concentration of mucous glycoprotein is increased the viscosity of the solution rises steeply and at a concentration above 5% by weight a reconstituted mucus gel is formed. Glycoproteins originate from secretory cells characteristicly fitted with secretory granules. In the duodenum these glycoproteins are mainly secreted by Brunner's glands, Crypts of Lieberkuhn and Goblet cells. (Allen, 1981; Allen et al., 1982; Fosterner et al., 1982; Sellers and Allen, 1984).

B) Glycoproteins

1) Structure of Glycoprotein:

Proteins which are covalently associated with sugars (Oligosaccharide chain) are commonly designated as glycoproteins. These are complex group of macromolecules which are widely distributed in nature. They have been found virtually in all forms of life, i.e., animals, plants and microorganisms and have been identified in the extra and intra-cellular fluids, connective tissues and cellular membranes. The carbohydrate content of glycoprotein ranges from less than 10 percent to over 80 percent of the molecule.
Three types of sugars commonly found in glycoprotein are:

i) Neutral sugars such as D-galactose, D-mannose, D-glucose and L-fucose

ii) Aminosugars as N-acetylglicosamine and N-acetylgalactosamine.

iii) Acidic sugars like sialic acid, glucuronic acid and L-Iduronic acid.

Other constituents which are common to most of the glycoproteins are sulfate groups linked by ester bond to the hydroxyl group of their monosaccharide constituents.

2) Covalent Linkage of Carbohydrate to the Peptide Chain in Glycoprotein:

The key-step in the conversion of protein into glycoprotein is glycosylation of peptide chain. Glycosylation occurs at specific sites on the protein molecule. Basically there are four types of glycopeptide bonds which have been found to occur among the glycoproteins studied. These can be differentiated strictly on the basis of attachment of a given sugar to a specific functional groups of amino-acid.

1) Oligosaccharides linked through N-acetylglicosamine or N-acetyl galactosamine to hydroxyl group of serine and threonine-O-glycosidic linkage.
2) Oligosaccharides linked to serine and threonine through sugars other then N-acetyl glucosamine-O-glycosidic linkage.

3) Oligosaccharides linked to the hydroxyl group of hydroxylamine and hydroxyl group of proline-O-glycosidic linkage.

4) Oligosaccharides linked through N-acetal glucosaminyl to aspargine N-glycosidically linked (Kornfeld and Kornfeld, 1980).

Most of glycoproteins contain a common core consisting of five saccharide residues of mannose (Man) and N-acetyl D-glucosamine (GlcNac).

\[
\text{GlcNac} - \text{GlcNac} - \text{Man} \quad \text{Man} - \text{R}
\]

This core is linked to a asparginyl residue in the protein, and sometimes to serine or threonine residues or also to hydroxyl group of hydroxylamine. Three molecules of mannose attach to each other and form 'core' having two side chains (R). Besides the core side chains contain galactose, fucose and sialic acid. The side chains differ in length and composition in various glycoproteins.
3) Synthesis of Glycoproteins

The polypeptide chain of glycoprotein is synthesized on rough endoplasmic reticulum (RER) and then released into membranous portion of the RER, where addition of sugars takes place from dolichol pyrophosphate sugar (carrying agent) and the enzyme involved in the transfer of sugar from dolichol pyrophosphate to the protein, would be found in rough endoplasmic reticulum (Lennarz, 1975). In glycoprotein-secreting cells probably N-acetyl galactosamine or N-acetyl glucosamine is transferred to the serine or threonine of the polypeptide by means of an enzyme N-acetylgalactosaminyl transferase or N-acetyl glucosaminyl transferase (Young and Van Lennep, 1978). Main oligosaccharide linkage to core occurs in the Golgi complex and possibly in the transitional vesicles and Golgi vacuoles. The carbohydrate chain ends with a terminal sialic acid, fucose or glucuronic acid. The enzymes involved in this stage are glycosyl transferases (Schachter, 1974, 1977; Phelps and Young, 1977; Carlson, 1977). The action of each of the glycosyl transferase appears to be specific for a particular sugar (Schachter, 1977). According to Candy (1980) glycoproteins are synthesized on endoplasmic reticulum and then transported to GERL region of endoplasmic reticulum located in the inner aspect of
the Golgi complex. In the GERL, concentration of glycoprotein in condensing vacuole takes place; these vacuoles later on unite to form secretory granules.

4) Isolation of Glycoproteins

Number of procedures have been employed for the isolation of glycoproteins. The commonly used methods include gel filtration ion exchange, chromatography using Dowex-1 and Dowex-50, paper chromatography and high voltage paper electrophoresis, for high molecular weight, it is preferable to use sephadex, cellulose and polyacrylamide based on ion-exchangers. Some of the other techniques are used in combination, since they are based on the difference in the various physicochemical parameters such as molecular size, charge and solubility. The approach that one follows for the isolation of the glycopeptides depends upon whether the glycoprotein contains one or more carbohydrate chains along the polypeptide chain. Proteolytic enzymes with broad specificity such as pronase, papain, subtilism and proteinase are also used for isolation of glycoproteins. Wagh and Bahl (1981) in their review article ‘Sugar Residues on Proteins’ discussed in detail about the isolation of glycoproteins.
5) Properties of Glycoproteins

Mucus glycoproteins may be soluble or insoluble in aqueous solution. Glycoproteins, together, form a gel-like structure; it has electrostatic properties. The viscoelastic gel formed of glycoprotein is stable and water-insoluble that adheres to the luminal side of the epithelial surface in contact with an 'external' environment. The major part of mucus is water and gel is formed by very large and structurally complex glycoprotein referred to as mucus glycoprotein or mucins. Bonafide glycoprotein is originated from secretory cells characteristically field with secretory granules.

By virtue of their sulfate and carboxyl group glycoproteins are highly charged polyanions and are called acidic glycoproteins. If at neutral pH the number of negative charges from carboxyl group (sialic acid) and sulphate groups does not exceed the number of positive charges from free amino groups, the glycoprotein is classified as neutral glycoprotein. If however, the number of negative charges noticeably exceed the positive charges then the glycoprotein is classified as acid glycoprotein. The acidity may be due to presence of sulfate group, sialic acid or uronic acid. Acid glycoproteins may therefore conveniently be
classified as sulfomucins or sialomucin according to the group which is mainly responsible for acidity. Spicer et al. (1965) pointed out that majority of carbohydrate protein complexes demonstrated histochemically were not defined biochemically. Periodic Acid Schiff (PAS) Stains all neutral glycoproteins and most acidic glycoproteins. Alcian blue at pH 2.5 stains acid mucopolysaccharides; sulfomucins are strongly stained with alcian blue pH 1 (Steedman, 1950; Scott and Dorling, 1965). In a mild acid hydrolysis most of the sialic acid get hydrolysed.

6. Different Sugars Found in Glycoproteins

1) D-Galactose: This neutral sugar is found in wide variety of mucosubstances. A disaccharide named N-acetylglactosamine (4-0-β-galactopyranosyl-2-acetamido-2-deoxy-D-glucose) was from hog gastric mucus (Yasizawa, 1950). D-galactose was also found in gastric mucosal scrappings and whole gastric secretions (Werner, 1953).

![D-Galactose structure]

\(\beta-D\)-galactose
ii) D-Manose: D-Manose is present in serum glycoprotein and in minute amounts in hydrolysates of gastric secretion, duodenal fluid, pancreatic juice, and mucosal scrapping. Dische (1965) suggested that manose may come from the secretions of serozymogenic cells found in human submaxillary glands.

iii) L-fucose: L-fucose is a prominent constituent of neutral mucosubstances. Fucose has not been found in mammalian acid mucopolysaccharides. Fucose is especially prominent as a terminal group of
oligosaccharide chains or side branches. The neutral sugar, which includes hexoses and L-fucose may account for or slightly more than half of the carbohydrate present in epithelial mucosae and in secretions. The amount of bound neutral sugar has been used as one of the indicators of mucus production.

\[ \text{a-L-Fucose} \]

iv) Sialic Acids: Neuraminic acid (C\(_9\)H\(_{17}\)NO\(_8\)) is the parent compound of a number of acetylated derivatives, the sialic acids. They are widely distributed as constituents of glycoproteins found in biological fluid and tissue (Coldberg and Wolf, 1965). One of the best sources of the sialic acids is the submaxillary gland. Extracts of submaxillary glands from various species have yielded five or more sialic acids differing in the substituent attached to the nitrogen and in the position of the O-acetyl group.
v) Hexuronic Acids: The hexuronic acids are 6-carbon-sugar acids which generally contain the carboxyl group of carbon atom six. The two hexuronic acids found in mammalian acidic mucopolysaccharides are D-glucuronic acid and L-iduronic acid. Observations recorded indicate that uronic acids are the minor contributors to the carbohydrate content of gastric secretions.
7) Functions of Glycoproteins

Interest in glycoproteins is mainly due to the diverse biological functions which they perform. Biological functions of glycoprotein are protection, lubrication and transport. Some well known glycoproteins with well defined functions include immunoglobulins (Kornfeld, and Kornfeld, 1976); ganadotropins (Lin et al., 1972 a,b; Bellisario et al., 1973; Carlsen et al., 1973; Rathnum and Saxena, 1975; Christakos and Bahal, 1979; Kessler et al., 1979a,b) thyroid-stimulating hormone (Liao and Perce, 1971); ribonuclease (Jackson and Hirs, 1970; Tarentino et al., 1970), antifreeze glycoprotein (Devrise et al., 1971), mucus glycoproteins (Horowitz and Pigman, 1977), avidin (Huang and Delange, 1971; Delange and Huang, 1971), proteolycans (Meyer, 1970), Collagen (Spiro, 1972) and Fibronectin (Yamada et al., 1972). They are also constituents of blood plasma which include protein, transferrin, ceruloplasmin; all known clotting factors, follicle-stimulating hormone and chorionic gonadotropin are also glycoproteins and also are the enzymes ribonuclease, deoxyribonuclease (secreted by pancreas) and α-amylase (secreted by salivary gland). Other glycoproteins are those which occur as integral components of the cell membrane.
8) Glycoproteins of Gastrointestinal Tract

In the gastrointestinal tract a thick mucus layer of variable thickness 5 - 20 μM and occasionally 400 μM forms physical barrier between cells and proteases and in duodenum between HCl and gastric juice coming in the lumen form from the stomach. In the duodenum these glycoproteins are mainly secreted by Brunner’s glands. Duodenal lumen also receives bicarbonates from pancreas and Brunner’s glands. The role of mucus material in the protection of gastrointestinal tract has been described in detail by Richard (1980); Hotta (1981); Allen (1982); Fosterner et al. (1982); Sellers and Allen (1984).

Azuum et al. (1986) showed a relation between gastric mucus glycoprotein and their role in protection of gastric mucosa from ulcer. In an extensive review Touber and Gerok (1987) reported that biosynthesis of mucus glycoproteins is decreased during ulceration, while breakdown is enhanced, this indicates that disorder of glycoprotein biosynthesis and degradation may contribute to the pathogenesis of ulcer. Okubo Takeshi et al. (1986) examined quantitative changes in gastric mucosal glycoproteins during restrain and water immersion stress in rats. The glycoprotein in the mucosa of corpus of stomach was isolated and analysed.
quantitatively. The hexose level decreased two hour after stress loading. It was further decreased to 75\% after 6 hour and 68\% after 8 hour. The decrease in galactose and fucose content of slycoprotein was also noticed. Morrissey et al. (1983) proved that in duodenal ulceration, the Alcian blue staining acid mucosubstances in goblet cells are reduced and goblet cells themselves disappear. At the same time, periodic acid–Schiff (PAS)–staining neutral mucosubstances appear in the cells of surface epithelium. They further observed that during healing the changes are reversed and these changes suggest a metaplasia towards a gastric type mucosa as a protective response to the presence of ulceration.

C) Histology and Histochemistry of Pyloroduodenal Junction

1) Pyloric Glands:

There are three types of glands a) gastric, fundic or oxyntic glands distributed through the greater part of the gastric mucosa, b) cardiac glands, found in cardiac region of the stomach near its junction with the cesophagus. The gastric glands produce the essential digestive elements of the gastric juice, and the cardiac and pyloric glands function largely as mucous glands and c) pyloric glands, confined to the region immediately above the pylorus.
The pyloric glands are simple, branched, tubular glands, several of which open into each of the deep pyloric pits. These pits occupy a much greater proportion of the thickness of the mucous membrane than do the pits of the gastric glands, and the proportionate depth occupied by the glands themselves is correspondingly less. The pyloric glands although short, are quite tortuous, so that in section the tubules are seen cut mainly transversely or obliquely. They differ morphologically from the neck cells in that they are taller and their ovoid nuclei are generally oriented parallel with the long axes of the cells. Parental cells are found occasionally in the pyloric glands. The transition from the gastric to the pyloric type of stomach gland is not abrupt but is marked by a "transitional border zone" in which gastric and pyloric glands are intermingled and in which are also found single glands which combine the characteristics of both types (Kelly et al., 1985).

1) Ultrastructure of Pyloric Gland Cell:
Cytologically, the mucous neck cells closely resemble the mucous cells of cardiac glands and pyloric glands (Ito, 1966). These are relatively small and have a broad base and narrow luminal border or a very narrow base and broad apical end. The cytoplasm contains a
Unlike the surface mucous cells, the cytoplasm of these cells contain abundance of free ribosomes and moderate amounts of granular endoplasmic reticulum. The prominent Golgi complex occupies the supranuclear and paranuclear regions. The lateral plasma membranes are joined to neighbouring cells by typical junctional complexes at the apical margin of the cell. Occasionally desmosomes are found along the lateral membranes, which are relatively smooth except for some interdigitating cell processes near the base of the cells. The pyloric mucous cell granules are large, spherical and are often found in the paranuclear or basal cytoplasm.

ii) Mucosubstances from Pyloric Glands: The study of pyloric glands shows species-variation and variation in some individual cases within the same species as regards the nature of these glands. The pyloric glands in the ferret contained neutral mucosubstances (Poddar, and Jacop, 1979); so also in the pyloric glands of man (Berger and Pizzolato, 1975; Sheahan and Jervis, 1976). The pyloric glands of all the species except man and ferret contained variable amounts of acid mucosubstances (Poddar and Jacob, 1979). Most of them contained sulphated mucosubstances. However, in the
rhesus monkey, they contained sialomucin only (Sheahan and Jervis, 1976). In the armadillo they contained neutral and carboxylated mucins (Carvalho et al., 1973). In guineapig, both carboxyl and sulfate groups were found (Spicer, 1963; Sheahan and Jervis, 1976). Jennings and Florey (1956) and Belanger (1963) demonstrated incorporation of $\text{S}^{35}$ in few cells by autoradiographic method. In mouse, Burkl (1950) did not find metachromasia, but the mucosubstances were sulphated (Jennings and Florey, 1956; Sheahan and Jervis, 1976). Rat contained 'weakly sulphated' (Spicer, 1963), and 'sulphated' (Sheahan and Jervis, 1976) mucosubstances. Jennings and Florey (1956) and Belanger (1954, 1964) showed the sulphated nature by means of autoradiography in rat. In rabbit pyloric glands were not metachromatic (Burkl, 1950) but they were acidic and weakly chromatropic (Casoni, 1952); sulphated (Sheahan and Jervis, 1976). Cat contained strongly acidic, metachromatic mucosubstance (Burkl, 1950); neutral but weakly metachromatic (Casoni, 1952); sulphated (Jennings and Florey, 1956; Sheahan and Jervis, 1976). Dog contained strongly acidic metachromatic mucosubstances (Burkl, 1950); neutral but weakly chromatropic (Casoni, 1952), sulphated (Spicer and Sun, 1967; Gerard et al., 1967); sialomucin with traces of sulphomucin (Sheahan and Jervis, 1976). Horse contained
acidic and weakly chromatoropic (Casoni, 1952). Domestic pig had both neutral and acidic mucosubstances (Burkl, 1950; Casoni, 1952). Sheep had acidic and chromotropic mucins (Casoni, 1952). Bovine had acidic and chromotropic (Casoni, 1952). Sheahan and Jervis (1976) demonstrated neutral and sulphomucins in hamster, while Belanger (1954, 1963) showed by autoradiographic method presence of sulphomucins.

The significance of these variations is not clear. It is considered probably to be related to differences in dietary habits (Burkl, 1950; Krause, 1973; Odour-Okelo, 1976; Sheahan and Jervis, 1976). Burkl (1950) observed that the carnivores form more neutral mucus, while herbivores produce more acidic mucus and omnivores produce more or less, one or the other type. Sheahan and Jervis (1976) also observed that the differences in the nature of mucosubstances between species appeared to be unrelated to diet. Later on Odour-Okelo (1976) lent support to this view. However, Krause (1973) reported this correlation as unsatisfactory.

2) Duodenal Villi and Crypts of Lieberkühn

The mucosa is composed of its lining epithelium, a lamina propria with its connective tissues and glands and a limiting muscularis mucosae below. The most
Characteristic feature of the small intestinal mucosa are the villi.

i) Structure - The villi are mucosal projections, situated close together and covering the entire mucosal surface. Each villus consists of a core of delicate, loose connective tissue and an epithelial covering. The connective tissue, the lamina propria, is infiltrated with lymphocytes to a variable extent and contains occasionally isolated smooth muscle cells.

Single small lymphatic vessel (lacteal) with definite endothelial lining traverses the centre of each villus. Observations of the villi in living condition have revealed that they continually change the length and undergo waving motions. This is possible because of the presence of smooth muscle in them.

The epithelium covering the villi is a single layer of columnar cells attached to a delicate basement membrane. The epithelium consists of mainly of two quite different kinds of cells, columnar absorbing cells and goblet cells. Enteroendocrine cells are also present in small number. The columnar absorbing cells have finely granular cytoplasm, with an ovoid nucleus usually situated in the lower half of the cell. By means of phase contrast and electron microscopy, it is seen that the striated free border is actually composed of great
many, very fine, closely packed microvilli.

The striated border region contains a number of enzymes, including alkaline phosphatase, maltase, adenosine triphosphatase and aminopeptidase. At least some of these enzymes appear to be integral components of the plasma membrane itself. Thus, the border not only provides an increase in the luminal surface of the cell but also contains enzymes of importance for the final stages of the digestive process.

The mitochondria are distributed above and below the nucleus. In both regions they are rod—shaped or filamentous. These, in the basal portion, are numerous.

The Golgi apparatus lies between the nucleus and free surface of the cells. The endoplasmic reticulum is chiefly of smooth variety in the apical part of the cell and mostly of rough variety in the deeper portion. Free ribosomes are fairly numerous in the basal part of the cell.

Goblet cells, unicellular mucous glands, are dispersed among the columnar absorptive cells. In the early stages of the secretory process, only a few mucigen droplets are present in the cytoplasm adjacent to the Golgi region. As more droplets form, the apical portion of the cell becomes distended to the typical...
goblet shape, and the nucleus, together with most of the cytoplasm, is displaced into the narrow basal region or stem. The mucigen droplets are dissolved by routine methods of preparing sections for light microscopy; thus, the upper portion of the goblet cell appears relatively empty. When the mucigen droplets are preserved by special methods, they are found to be basophilic, metachromatic and periodic acid-Schiff-positive. Electron micrographs show that microvilli are short and sparse on goblet cells. The number of goblet cells is small in the duodenum and becomes progressively greater in the jejunum, ileum and colon (Kelly et al., 1985).

**Crypts of Lieberkühn**

They occur throughout the small intestine. They are simple, tubular glands located in the mucous membrane that open between the villi and extend through the lamina propria to the muscularis mucosae. The epithelium of the crypt is continuous at its opening with the surface epithelium of the villi. In general, the columnar cells which lie near the base of the gland are less differentiated and somewhat shorter than the columnar absorbing cells of the villi. The striated border of the cells, deep in the glands, is poorly developed with microvilli less than 0.5 μm in length.
There is gradual increase in the height of the microvilli of the striated border on the columnar cells from the base towards the mouth of the crypt. This fact together with the presence of numerous mitoses in the crypts, correlates well with the results obtained by thymidine-labelling studies which show conclusively that the intestinal surface cells arise from cells in the crypts (Kelly et al., 1985).

Studies have elucidated the interrelationships of the various cell-types in the crypts and on the villi. Primitive cells (undifferentiated) located in the bases of the crypts are maintained as population of stem cells. These have the capacity to differentiate and form all of the other cell-types. Thymidine-labelling indicates that intermediate stages in formation of all the epithelial cell-types lie in the midcrypt region. Oligomucous cells that give rise to goblet cells, and the early absorptive cells, are still capable of mitosis, but their progeny are committed to their respective cell-lines. On the other hand, there are also coarsely granular cells in the bases of the crypts, the cells of Paneth, that differentiate from the primitive cells but remain in bases of the crypts. It appears that Paneth cells do not divide, but they degenerate and are replaced at about the same rate as the other cell-types. Paneth cells have prominent
acidophilic granules and appear secretory in organization but their precise function is not understood. There is evidence that they contain bacteriocidal enzymes and are phagocytic, at least in rats. The earlier speculation that they elaborate important digestive enzymes has not been confirmed. Their failure to migrate out of the crypts with other differentiating cells has not been explained.

Enteroendocrine cells also rise in the intestinal crypts. The suggestion by some investigators that these cells may be of neural crest origin has not been verified. They are most numerous in the proximal duodenum and the appendix, although they are present throughout the small intestine and colon. These cells are thought to produce the intestinal hormones important in controlling gastric and intestinal motility, release of stomach content, release of bile from gall bladder and release of pancreatic secretions (Kelly et al., 1985).

Lamina Propria

The loose connective tissue, besides forming the centres of the villi, fills in the spaces between the crypts and muscularis mucosae. It is composed of interweaving reticular and delicate collagenous fibres, with a considerable number of elastic fibrils. It also
contains fibroblasts, eosinophils, plasma cells, mast cells and some smooth muscle cells. Lymphocytes are abundant and in many places they are so numerous as to give the appearance of diffuse lymphatic tissue. Lamina propria of the intestine appears to be the prime site for production of secretory immunoglobulin (Kelly et al., 1985).

ii) Mucosubstances of Duodenal Goblet Cells:

Poddar and Jacob (1979) found that duodenal goblet cells of ferret fall into three groups: a) those which contain sialomucin which may be either sialidase-labile or sialidase-resistant, b) those which contain sulphated mucin and c) those which contain sialomucin and sulphated mucin (in the same cell). Sialomucin alone was present in man (Ganter and Marche, 1970; Sheahan and Jervis, 1976). It was present with neutral mucin and with foci of sulphomucin in the rhesus monkey and baboon (Sheahan and Jervis, 1976). Sialomucin was predominantly seen in the gerbil in variable proportion, with sulphomucin in both superficial and deep goblet cells of rabbit, and in a few deep cells of rabbit (Sheahan and Jervis, 1976). In dog, Sheahan and Jervis (1976) observed that both sialo and sulphomucins were abundant in the superficial goblet cells and in lesser amount in the deep cells.
In Kangaroo, the goblet cells contained carboxylated mucosubstances and some neutral mucosubstances (Krause, 1973). In armadillo, it contained all three types of mucosubstances, neutral, carboxylated and sulphated (Carvalho et al., 1970). In mouse, rat and guinea-pig the goblet cells were weakly sulphated (Spicer, 1963). Sheahan and Jervis (1976) found that they were sulphated with small amount of sialomucins. Jennings and Florey (1956) proved by using autoradiographic method that the goblet cells contained sulphated mucosubstances. In cat the mucosubstances were sulphated (Odour-Okelo, 1976), sulphated but some deeper cells devoid of stainable acid mucins (Sheahan and Jervis, 1976), sulphated by autoradiographs method (Jennings and Florey, 1956).

3) The Glands of Brunner

1) Topography of the Brunners glands :

The Brunner's gland are found only in mammals including primitive species, such as echidna and duckbilled platypus (Kuczynski, 1890; Bensley, 1903, Middeldorf, 1946; Florey, 1955; Grossman, 1958). The Brunner's glands in monotremes are unique, to other species reported, in that the glands are confined largely to the submucosa of the distal stomach (Krause, 1970,71). In echidna, few distal glands are found in the most proximal portion of the duodenum.
(Krause, 1970), whereas in the duck-billed platypus, the glands are confined exclusively to the stomach (Krause, 1971). These glands lie mainly in the submucosa of duodenum of most of the species. The distance they extend from the pylorus to intestinal mucosa is variable between and within species (Kuczynski, 1890; Grossman, 1958).

Kuczynski (1890) reported that these glands extended short in carnivorous, moderate in omnivores and long in the herbivores with some exceptions. There is no single criterion to which the interspecies variation in the extent of the Brunner's glands can be related. In species such as rabbit, cow and guinea-pig the glands extend to the level of the entry of the pancreatic duct, whereas in dog, cat and rat the lower limit of these glands is above the level of the entrance of the pancreatic duct. In some species, such as horse and pig, the glands extend below the entrance of the pancreatic duct (Bensley, 1903; Villemin, 1922; Landboe-Christensen and Boh, 1944; Grossman, 1958).

Landboe-Christensen (1944) studied in detail the distribution of Brunner's glands in man. The glands are located in the submucosa of the duodenum and a few in the lamina propria near the pylorus, in close relation to the transition from gastric to intestinal mucosa.
Islands of these glands become less closely packed as the distance below the pylorus increases. He also found that with advancing age the upper margin of the glands becomes irregular and they invade the gastric side with 'tongues' or islands of the glands extending into gastric mucosa. The lower limit of the continuous gland area did not extend below the interior papillae (minor pancreatic duct) in a few instances and in no instance did it fail to reach the superior papillae. The extension of Brunner’s glands into the first portion of the jejunum was found distinctly, more frequently in younger subjects than in the older. There is a tendency for the Brunner’s glands to extend a shorter distance with less densely packed glands during ageing.

In rat, the main bulk of the Brunner’s glands lies at the pyloroduodenal junction as a comma-shaped mass with a narrow tapering tail extending into duodenum (Chandrama Anand and Han, 1975). Treasure (1978) reported that a dense band of Brunner’s glands, immediately distal to the pyloric sphincter, tappers off within 1 cm in the rat.

ii) Microscopic Anatomy of Brunner’s Glands:
   a) Secretory End Pieces

The glands of Brunner consist of tubules and
acini, their ducts open into the base of the crypts of Lieberkuhn (in most of the species), or directly into the lumen of duodenum. The glands are generally arranged in groups and are interlocked with connective tissue.

The Brunner's glands are composed of ramifying tubules into which acini open (Schwalbe, 1872; Maziarski, 1901; Peiser, 1902). In the resting state the cells of Brunner's glands are full of stainable secretory material and nuclei are flattened against the base of the cell (Grossman, 1958). The Brunner's glands cells are of two types: serous and mucous. Most of the species depict neutral mucosubstances in the Brunner's glands. The Brunner's glands have been shown to consist of mucous cells in man, ox, sheep, deer, beaver, dog, goat, rat, pig and guinea pig (Florey and Harding, 1934; Florey, 1955; Jennings and Florey, 1956), whereas in horse and rabbit a serous component has been reported (Martin, 1954; Leeson and Leeson, 1967). The Brunner's glands of cat (Moe, 1960) and guinea-pig (Cochrane et al., 1964) have both mucous and serous cells. The mouse (Friend, 1965) and rat (Leeson and Leeson, 1966) were reported to possess serous type and mucous types of cells respectively. But Chandrama Anand and Han (1975) reported that the glands of Brunner in
rat showed all the characteristic features for serous cells than mucous cells. The Brunner's glands of opossum posses' features more characteristic of serous than that of mucous (Krause and Leeson, 1969).

b) The Ducts of Brunner's Glands:  

Microanatomical studies of Brunner's glands of various animals by various scientists showed that these glands drain into crypts of Lieberkühn (Cooke, 1967; Krause and Leeson, 1969; Ham, 1974; Bloom and Fawcett, 1975; Leeson and Leeson, 1976; Treasure, 1978). Electron microscopic studies also stated the same view (Grossman, 1958; Moe, 1960; Friend, 1965; Leeson and Leeson, 1966, 1967, 1968). Subsequent studies on the microanatomy of Brunner's glands describe more variability in the mode of drainage. In cat and opossum the ducts open into the lumen of duodenum (Kuczynski, 1890; Bensley, 1903; Treasure, 1978) and in human the ducts open at variable levels; some ascend through the mucosa and open between the villi, others, however, enter part way up the crypts (Treasure, 1978).

The duct cells of different species also show slight variations. The ducts of Brunner's glands of man and cat are lined with cuboidal epithelial cells which are PAS-positive (Treasure, 1978).
Brunner's glands of opossum are lined by columnar cells and are alcian blue-positive (Krause and Leeson, 1969). Presence of alcianophilic cells was also observed in the ducts of mouse Brunner's glands (Obouforibo, 1975). Treasure (1978) reported that the duct cells of Brunner's glands of rat were columnar and periodic acid-Schiff (PAS)-positive.

iii) Fine Structure of Brunner's Glands

Electron microscopic studies of all the species studies showed morphological evidence of high secretory potential with an elaborate endoplasmic reticulum and Golgi apparatus in the Brunner's glands. In cat, microvilli were seen in the luminal surface of Brunner's glands cells and these cells had endoplasmic reticulum with granules on the surface. Dense secretory granules and numerous mitochondria and Golgi apparatus were also found (Moe, 1960). The cells of Brunner's glands in guinea-pig contain large globules of secretory material of low density and relatively few mitochondria which are in association with rough endoplasmic reticulum. The cell surface bears a few short microvilli with no intercellular canaliculi (Cochrane et al., 1964). Friend (1965) reported that the cells of Brunner's glands of mouse are provided with microvilli and intercellular canaliculi are also seen. The presence of unusually extensive Golgi
apparatus and numerous smooth-surfaced evaginations of the rough-surfaced endoplasmic reticulum in relation to the Golgi complex were also observed in the mouse Brunner's glands. In the cells of Brunner's glands of rabbit, majority of the organelles are situated in the basal cytoplasm and apical cytoplasm is occupied principally by secretory material. The cell surface shows microvilli projecting in the lumen. Granular endoplasmic reticulum and Golgi complex are well developed and occupy extensive region (Leeson and Leeson, 1967).

In opossum the Brunner's glands cells surround a relatively small lumen into which a few short irregular microvilli project from the apical surface. The nucleus is situated towards the basal region of the cells. Granular endoplasmic reticulum is concentrated mainly in the basal and perinuclear regions, although several cisternae often extend into the apical region of the cell. The endoplasmic reticulum of the recently fed animals has markedly dilated cisternae, whereas endoplasmic reticulum is less extensive and less dilated in starved animals. The Golgi elements are well developed and extensive and are confined mainly to the supranuclear region and also associated with numerous secretory droplets. Mitochondria, spherical or elongated,
and are found mainly in the basal and supranuclear regions, associated with the endoplasmic reticulum and Golgi Complexes. Secretory droplets occupy a major portion of the apical cytoplasm (Krause and Leeson, 1969).

The fine structure of Brunner's glands of rat has been studied in detail by Leeson and Leeson (1966) and Chandrama Anand and Han (1975). In the rat the component cells of Brunner's glands are arranged around a wide lumen into which project short microvilli from the apical surface. In addition to the gland cells, argentaffin cells are also observed. The nucleus is located at the basal region of the cell with prominent nucleoli. The granular endoplasmic reticulum is located mainly in the basal and at perinuclear regions of cell. The close association of mitochondria with desmosomes was found by Chandrama Anand and Han (1975). Mitochondria of these cells are well developed, numerous and are concentrated in the basal and perinuclear regions. The Golgi complex is also well developed and the elements are located principally in supranuclear cytoplasm, where they are commonly associated with secretory droplets. There is no close association between the elements of Golgi apparatus and endoplasmic reticulum. Large secretory droplets occupy the apical cytoplasm which contains small vesicles and
these are associated closely with secretory droplets. Infrequently, small multivesicular bodies and pleomorphic osmiophilic bodies are also found. Those are presumed to be lysosomal in nature. Chandrama Anand and Han (1975) clearly reported the presence of lysosomes in these gland cells and were present in the region of Golgi apparatus.

iv) Mucosubstances from Brunner's Glands

Bensley (1903) reported that mucicarmine and mucihematin stained the secretory masses of the cells of Brunner's glands all of the nineteen species he studied, but Florey and Harding (1934) were unable to find similar results. According to Florey and Harding (1934) good staining occurred in some species (goat, pig, rabbit and guinea pig) whereas in others (cat, dog, rat) there was no staining. Metachromasia is associated with the presence of sulfated mucins. Jennings and Florey (1956) correlated metachromasia with uptake of $S^{35}$ labelled sulfate detected by autoradiography. Autoradiographic study showed that in rat, cat and mouse the uptake of $S^{35}$ by Brunner's glands is negative and is positive in case of guinea pig and rabbit. Lillie (1949) reported that the Brunner's glands of rabbit were metachromatic but contained variable distribution of neutral sialo and
sulfomucins.

The presence of neutral mucosubstance was reported in Brunner’s glands of rat (Spicer, 1960; Belenger, 1963; Sheahan and Jervis, 1976; Smits and Kramer, 1981), cat (Sheahan and Jervis, 1976). In the Brunner’s glands of man, sialomucins were reported to be present (Ganter and Marche, 1970). In mouse, besides neutral muco-substances in the acinar cells, a sialidase\textsuperscript{labile} sialomucin was also found by Obuoforbo (1975) and small amounts of both sialomucins and sulfomucins by Sheahan and Jervis (1976) in the duct cells. The acinar cells of opossum contained neutral mucin whereas the duct cells contained both neutral and carboxylated mucins (Krause and Leeson, 1969). The Brunner’s glands in echidna (Krause, 1970), Koala and Wombat (Krause, 1973) and horse (Odour-Okelo, 1976) contained carboxylated mucin. The glands of hamster and gerbil contained some sulfomucins in addition to neutral mucins, whereas in rhesus monkey and baboon they contained both sialo and sulfomucins (Sheahan and Jervis, 1976).

Smits and Kramer (1981) reported that the neutral mucosubstance of the rat Brunner glands is a mucus glycoprotein, with short oligosaccharide chains. The variability between and within the species in the
staining reactions of Brunner's glands seems to be related to chemical differences in the mucins.

**v) Functions of Brunner's Glands**

The secretion of Brunner's glands is believed to protect the mucosa in the first part of the duodenum, from the acid chyme ejected from the stomach (Florey and Harding, 1934; Florey et al., 1939; Griffith and Harkings, 1956). Florey and Harding (1934) reported that the Brunner's glands area was more resistant to the damaging effect of dilute HCl than the lower regions of the duodenum. Chronic drainage of gastric juice over the isolated Brunner's glands area of pig did not cause ulceration but that similar exposure of lower small bowel showed ulcer (Florey et al., 1939). Jervis et al. (1973) reported that the Brunner's glands of guinea-pig were devoid of mucosubstances following starvation, which ultimately led to formation of duodenal ulcers. Gysteamine-induced duodenal ulceration also showed depletion of mucous material in the Brunner's glands of rat, indicating the impaired function of these glands during ulceration (Kirkegaard et al., 1981 b; Poulsen et al., 1981, 1985, 1986). In support of Brunner's glands function as to protect the duodenum from gastric juice, the scientific evidences are advancing. A new protein, epidermal growth factor (EGF) has been found to be present in the
Brunner’s glands secretion. Intraduodenal as well as intragastric instillation of EGF prevents the development of experimental duodenal and gastric ulcers in the rat (Kirkegaard et al., 1983; Skov Olsen et al., 1984, 1985). All these observations throw much light on protective function of Brunner’s glands.