CHAPTER - IV

DISCUSSION

In the present study 20% mortality in sialoadenectomized as well as in cysteamine treated mice was observed, but it was increased 30% in sialoadenectomized, cysteamine treated mice. No ulcers were reported in sialoadenectomized and also in sialoadenectomized, cysteamine treated mice at the gastric region of the pyloroduodenal junction.

Gastric mucosa changes as well as glycoprotein contents were not significantly altered in gastroduodenal mucosa of sialoadenectomized mice. But in cysteamine administered and sialoadenectomized, cysteamine treated mice there are alterations in the structure of gastric mucosa as well as glycoprotein contents. Columnar epithelial cells showed decrease in the PAS reactivity may be due to inhibition of synthesis of PAS positive material or may be due to loss in number of epithelial cells. Under the normal conditions the cell populations within the gastric tract are maintained at a dynamic steady state because cell loss through exploitation of surface cells (resulting from frequent exposure of the gastric mucosa to substance with wide range of pH, osmolatory and temperature) is balanced by continuous cell renewal (Lipkin, 1987). These cells are coming from gastric pits. The balance between cell loss and cell renewal must be tightly regulated, if there is excessive loss, it can result in atropy or ulceration. In the gastric mucosa such an excessive

loss is not marked out because lesions at gastric region of pyloro-duodenal junctions are not observed in sialoadenectomized and cysteamine treated (administered) mice. This shows that neither salivary gland secretion nor Brunner's gland secretion are responsible in the protection of gastric mucosa.

Growth factors like epidermal growth factors are also located in the Brunner's gland, submandibular gland and kidney (Elder *et.al.*, 1978; Kirkegaard *et.al.*, 1984; Olsen *et.al.*, 1984). In the rat the secretion of EGF/ URO from the submandibular glands is mainly exocrine (Jones *et.al.* 1999) and oral administration of these peptides has been reported to prevent development of experimental gastric lesions (Olsen, *et.al.* 1984; Olsen, *et.al.* 1984). In their study the removal of submandibular and sublingual gland complexes in rat was associated with abolition or reduction of gastric mucosal protection produced by brief exposure of stomach to mild irritant (Tepperman, *et.al.* 1989). The damaging action of irritant is prevented in sialoadenectomized mice receiving salivary extract. There are evidences that saliva and salivary extract promote the healing of experimental wound (Niall *et.al.* 1982) and exert cytoprotection influence on gastric mucosa (Miyoshi *et.al.*, 1969; Pilot *et.al.* 1979).

The secretion from gastric mucosa itself may be protecting gastric mucosa as well as the proliferation and migration of epithelial cells may not depend on the secretion or growth factors secreted by

these glands but must be from the glands present in the gastric mucosa. Immunohistochemical studies have identified the epidermal growth factor receptors which are shared by both EGF and TGF-alpha in some gastric mucous neck cells (Tarnawski *et.al.*1991). In gastric mucosa the highest levels of its ligand-TCF-alpha are present in mucous neck cells. EGF is involved in maturation of gastrointestinal tract, but acute gastric mucosal injury is associated with expression of EGF-R and TGF and not EGF (Polk *et.al.* 1992). According to Wright *et.al.* (1990) mucosal injury results in appearance of novel cell lineage that produce EGF. Playford *et.al.* (1996) have suggested that EGF should be considered a luminal surveillance peptide and TGF-alpha as a mucosal integrity peptide. An observation that leads to intriguing hypothesis because, unlike EGF, TGF-alpha is produced within normal gastric mucosa (Beauchamp *et.al.* 1989). Evidence suggest that TGF alpha may not only modulate the repair of gastric injury but also protect against injury (Chen *et.al.* 1991).

A few studies have investigated the role of TGF-alpha is a mitogen for cultured canine fundic cultured cells (Chen *et.al.* 1991) and guinea pig gastric mucous cells (Rutten, *et.al.* 1993). TGF-alpha also is a potent inhibitor of gastric acid secretion (Rhodes *et.al.* 1986; Guglletta *et.al.* 1994). Because TGF alpha inhibits gastric acid secretion in gastric mucosa and levels of gastric mucins are enhanced.

Mucins are secreted by the gastroduodenal cells of epithelium. Goblet cells located in gastric epithelium, are responsible for mucin secretion and mucins especially acid mucins are secreted by pylaro gastric (pyloric) glands. This could be exhibited selectively by the help of AB at pH 2.5 staining technique. Alterations/ reduction in gastric mucins in the ulcerations have been reported earlier (Nadar and Pillai, 1985). The increase in mucous content in gastric pits and pyloric glands in sialoadenectomy may also be the cause of the protection of gastro-duodenal mucosa.

Though ulceration was not observed in the gastric part of the gastro-duodenal junction, it could formed in the duodenal part of sialoadenectomized and sialoadenectomized, cysteamine treated mice. In the sialoadenectomized mice severity of ulceration was more than the sialoadenectomized, cysteamine treated mice. Duodenal lesions upto submucosa could also observed in sialoadenectomized and also in sialoadenectomized, cysteamine treated mice. In fact, if the salivary secretion is protecting duodenal mucosa, more severity of ulcer formation should be there in the later case, but apparently ulcer index did not show such an expected result. This apparent result may be due to death of severe ulcerated mice, as we have seen increase in the mortality rate in the sialoadenectomized, cysteamine treated mice. Severe ulceration or whatever ulceration in the anterior part of the duodenum may be due to lack of exocrine secretory protein of

salivary gland as well as secretion from the Brunner's gland. Lack of secretion from both the glands may fetal in some cases. Epidermal growth factor/ urogastrone has been localized to the submandibular glands and Brunner's glands of rats, mice and human (Heltz *et.al.* 1978; Gresik *et.al.*, 1979; Kirkegaard *et.al.* 1984). Epidermal growth factor/ urogastrone has been produces variety of biological responses including enhance proliferation and differentiation of epithelial tissue (Guth, 1982). In the rat EGF/ URO increases the synthesis of DNA in the gastrointestinal mucosa and stimulates ornithine decarboxylase activity (Hollenberg, 1979; Elder *et al.,* 1978 and Kirkegaard *et al.,* 1984). In the protection of duodenal mucosa the secretions of Brunner's glands may be playing more role perhaps than that of submandibular gland. Brunner's gland secretion is mainly exocrine and secretory product is believed to protect the duodenal mucosa (Olsen *et.al.* 1984 and Okabe *et al.,* 1971). An unpaired exocrine secretion of EGF/ URO from Brunner's glands has been observed in rats during the development (Lane, *et.al.*, 1957). The synthetic human EGF/ URO also has an effect on healing duodenal ulcers (Olsen, 1986). Investigations suggest that oral administration of EGF/ URO play role in the protection of gastric duodenal mucosa (Olsen, *et al.,* 1984; Dembiniski *et al.,* 1982).

Because only small amount of EGF seem to be absorbed from the gastroduodenal tract, the peptide probably exert its biological

effect at the epithelial surface. Receptors for EGF/ URO have been found in the rat small intestine at the tip of the villi as well as in the crypts and most numerous in the proliferative part of the crypt (Forgue-Lafitte, *et.al.* 1982 and Hollenberg, *et al.*, 1981). The mechanism of action of EGF in the duodenum is unknown. After EGF binds to its receptor, many events take place. These comparised increased ribosomal activity, marked elevation of ornithine decorboxylase activity as well as change in cell surface proteins and induction of glucosamino glucagon synthesis (Stastny and Cohen, 1970; Chinkes, *et al.*, 1979; Chen, *et al.*, 1977; Lembash, 1976). Decrease in PAS positive material in the Brunner's gland and crypts in sialoadenectomized mice and increase in PAS positive material at above sites in cysteamine administered mice clearly indicates the role of salivary secretion ion these glands. Perhaps EGF secreted from the submandibular gland may be enhancing synthesis of PAS positive material in the Brunner's and other glands. The mucosal layer which was quite intact to that of controlled even in the cysteamine treated mice but that was altered in sialoadenectomized, cysteamine treated mice. This can also be observed at the posterior part of the duodenum where number of Brunner's gland was reduced. Regular leaf formed villi and PAS positive material in all Brunner's glands was uniform in controlled and cysteamine administered mice where submandibular gland was intact. But in sialoadenectomized, cysteamine treated mice

Brunner's glands were not intact and leaf formed villi disorganized. Ducts of Brunner's glands and crypts of Liberkuhn (intestinal glands) showed presence of acid mucoproteins, its concentration was increased in sialoadenectomized mice. It clearly indicated protection of pylaro-duodenal mucosa under the control of secretions of submandibular glands.