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CHAPTER NINE

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GENERAL DISCUSSION AND CONCLUSIONS

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### General Discussion

The glands of Brunner are present only in mammals and lie mainly in the submucosal region of the duodenum. It is believed that these glands play a very important role in the natural defence of the duodenal mucosa. The secretion of the Brunner's glands is alkaline in nature and this neutralizes the acid chyme ejected from the stomach. Impairment of Brunner's glands lead to ulcer formation in the duodenum.

The present investigation was taken upto understand the role played by the Brunner's glands in the natural defence of the duodenal mucosa. The experiments were set up with reference to normally occurring physiological disturbances. Table 19 shows the findings through various methods.

Rats fed with normal ration of food do not show any gastroduodenal ulceration. It has been already reported that rats do not show any ulcer either in the stomach or in duodenum (Robert 1971; Nadar and Pillai, 1986a). The pancreatic duct opens well below the pyloroduodenal junction at a distance of 20 to 22 mm<sup>4</sup>. The Brunner's glands are concentrated at the pyloroduodenal junction as a thick collar and tapers off within 6 to 7 mm. Chandrama Anand and Han (1975) reported that the main bulk of the glands lies at the pyloroduodenal junction. Treasure (1978) reported that these glands taper off within 1 c.m. in the duodenum of rats. The glands of Brunner consist of secretory units and ducts. The secretory end pieces are of acinar and tubuloacinar type. The ducts open at the base of

the crypts of Lieberkuhn. The secretory units show characteristic features of the secretory cells. The cells are PAS-positive and only neutral mucosubstances are present. The Brunner's glands of rat were reported to have only neutral mucosubstances/mucus glycoprotein (Spicer, 1960; Belenge, 1963; Sheahan and Jervis, 1976; Smits and Kramer 1981). Study of  $\beta$ -glucuronidase in the Brunner's glands was initiated in our laboratory only (Kurane 1984; Nadar and Pillai, 1985). This enzyme has been reported to be involved in the metabolism of glycoprotein, active secretion, removal of excess secretory granules (crinophagy), growth, repair etc. Brunner's glands of rat show rich  $\beta$ -glucuronidase activity.

Normal rats, the controls for starvation group, do not show any ulcer either in the stomach or in the duodenum. Since the normal rats of both the sexes had rich PAS-positive material in the cells of the Brunner's glands, this might indicate a spontaneous synthesis and secretion of mucus material. During this spontaneous secretion the lumen was narrow in the secretory units. The  $\beta$ -glucuronidase activity was rich and found throughout the cell. Starvation led to formation of forestomach ulcers only. Rats of both the sexes developed ulcers in the forestomach after 7 days of starvation. There was a slight difference in the ulcer index between male and female. Duodenal mucosa did not show any sign for ulcer formation. Early workers also reported only forestomach ulcers in the rat due to starvation (Robert *et al.*, 1963; Robert, 1974; Nadar and Pillai, 1986a). The Brunner's glands

showed PAS-positive material only at the luminal side of the secretory units. Depletion of PAS-positive material due to starvation has been reported in guinea pig Brunner's glands (Jervis et al., 1973). The  $\beta$ -glucuronidase enzyme activity was found only at the basal side of the cells of the Brunner's glands. Unbuffered gastric juice might have stimulated the glands and the glands got exhausted. The decrease in the  $\beta$ -glucuronidase activity might indicate that the synthesis of mucus material was not encouraged. Chandrama Anand (1979) reported a 'stand still' condition of the Brunner's glands of rat due to starvation.

The duodenal ligated rats of both the sexes developed ulcers in stomach and duodenum. There was a difference in the duodenal ulcer index between male and female. The accumulated gastric juice was the main factor for the formation of ulcer in the stomach and duodenum. Forestomach ulcer formation in the pyloric ligated rats has been reported by Robert and Nezamis (1958), Kowalewski et al. (1962) and Sheriff (1973). The Brunner's glands showed a complete depletion of PAS-positive material which might have been due to the stimulation by the unbuffered gastric juice. The lumen of the secretory unit was narrow which seems that the secretion was only spontaneous. The nuclei showed mitoses and the  $\beta$ -glucuronidase activity was enhanced. The enhanced  $\beta$ -glucuronidase activity might be due to growth, repair or proliferation of cells. The enhanced  $\beta$ -glucuronidase activity during growth or repair has been reported by Levvy (1956).

The control rats showed slight decrease in the PAS-positive material this might be due to the starvation for 66 hrs. The  $\beta$ -glucuronidase activity remained more or less nearer to normal ones.

Intragastric administration of HCl led to the formation of ulcer in the stomach and duodenum of rats of both the sexes. There was a difference in the duodenal ulcer index between male and female. The inappropriate acidification might be the major cause for the formation of ulcer. The Brunner's glands showed wide lumen in the secretory unit and the glands also showed degenerative changes. There was depletion of PAS-positive material and only a very weak staining was observed in the glands. The  $\beta$ -glucuronidase activity was reduced and was towards the basal side of the cells. The decrease in the enzyme activity was more significant in case of males than that of females. The control rats showed a slight decrease in the PAS-positive material. The  $\beta$ -glucuronidase activity was slightly elevated in male.

The cysteamine administered rats of both the sexes developed only duodenal ulcers. There was a difference in the ulcer index between male and female. Since the stomach did not show any ulcer, the hypersecretion of gastric juice causing ulcer is ruled out; although cysteamine was reported to increase the acid secretion (Poulsen et al., 1981). So, the duodenal ulcer formation should be due to the impaired function of the Brunner's glands. The PAS-positive material was observed only at the basal side of the cells of the glands. The secretory

units showed wide lumen. Degenerative changes were also observed in the glands. The  $\beta$ -glucuronidase enzyme activity was reduced. The enzyme activity was found towards the basal side of the cells. The reduction in the PAS-positive material and  $\beta$ -glucuronidase might indicate the inhibition of synthesis of mucus material in the Brunner's glands. Depletion of PAS-positive materials in the Brunner's glands of rats followed by cysteamine administration has been reported by Poulsen et al. (1981). Delayed gastric emptying also would lead to a sudden surge of acidic gastric juice into the duodenum. Delayed gastric emptying leading to duodenal ulcer formation has been reported by Lichtenberger et al. (1977b) and Poulsen et al. (1982). Reduction in the PAS-positive material accompanied by a reduction in the  $\beta$ -glucuronidase activity has been reported by Brown (1978). The control rats showed a slight decrease in the PAS-positive material, which might be the effect of starvation. The  $\beta$ -glucuronidase activity was slightly elevated in males.

Cysteamine-induced duodenal ulcers were cured both by spontaneous healing and by Ayurvedic treatment. The recovery rate was 3 fold more in case of rats treated with Ayurvedic mixture. The Brunner's glands of rats recovered from duodenal ulcer showed PAS-positive material and rich  $\beta$ -glucuronidase activity. The glands of Brunner of the rats received Ayurvedic mixture showed more healthier histological structure. The reappearance of the PAS-positive material and  $\beta$ -glucuronidase indicates that these glands play a very important role in the healing of duodenal ulcer. The Ayurvedic formulation was

so-made to decrease the acid load in the duodenum and to increase the cell proliferation together with astringent and antiseptic approaches. The female rats showed a faster recovery than that of males.

Electrophoretic study further supported the histochemical and biochemical observations made after cysteamine administration. Cysteamine administration led to reduction in the PAS-positive material and  $\beta$ -glucuronidase enzyme. The reduction in isoenzyme intensity of  $\beta$ -glucuronidase may indicate that there was some interference in the synthetic activity in the Brunner's glands. The loss in the enzyme intensity was striking in the microsomal forms. Some changes in the rough endoplasmic reticulum might have reflected the alteration on the microsomal enzyme pattern. Changes in the endoplasmic reticulum seems to be inhibition of synthesis of PAS-positive material.

Starvation did not lead to the formation of duodenal ulcer. The depletion of PAS-positive material in the Brunner's glands might be due to the fact that the glands were stimulated by the unbuffered gastric juice. The  $\beta$ -glucuronidase activity in the glands also showed a reduction. Duodenal ligation induced duodenal ulcers and the Brunner's glands showed a depletion of the PAS-positive material. A number of mitoses were observed in the glands and the  $\beta$ -glucuronidase activity was enhanced. This enhanced enzyme activity might indicate growth or repair. Growth or repair is further supported by the fact that the glands did not show disintegrated histological



duodenal ulcer is entirely due to the choice of medicines. The Ayurvedic medicine used in this investigation had a combination of Glycyrrizha glabra, Terminalia chebula, Piper longum and Shanka Bhasma. Such a combination would reduce the acid secretion, increase cell proliferation, neutralize acidic juice; and also provide astringent and antiseptic effects. Since, the healing rate dependent on the reappearance of PAS-positive material and  $\beta$ -glucuronidase enzyme activity, it becomes more clear that the regeneration of Brunner's glands plays a very important role in the healing of duodenal ulcer.

#### Conclusions

- 1) Normally rats of both the sexes do not develop any ulcer in the stomach or duodenum.
- 2) The glands of Brunner are rich with PAS-positive material and  $\beta$ -glucuronidase.
- 3) Stimulation by unbuffered gastric juice and acid lead to the depletion of PAS-positive material in the glands.
- 4) The glands of Brunner, synthesize and secrete out mucus glycoprotein to protect the duodenal mucosa.
- 5) At times when the glands get exhausted the duodenal mucosa becomes susceptible for ulcer formation.
- 6) Decrease in the enzyme  $\beta$ -glucuronidase activity in the Brunner's glands might indicate the passive synthesis or inhibition of synthesis of PAS-positive material.
- 7) Enhanced  $\beta$ -glucuronidase activity seems to be involved in the secretory activity and/or growth/repair, so also in proliferation of cells.

8) The reduction in the PAS-positive material and  $\beta$ -glucuronidase activity from the Brunner's glands during duodenal ulceration and the reappearance of these entities after Ayurvedic treatment indicate a relation between duodenal physiology and Brunner's glands.

9) Maintenance of Brunner's glands would keep the duodenal mucosa from ulceration.

10) Inappropriate acidification and failure of Brunner's glands to maintain the synthesis and secretion of alkaline material would expose the duodenal mucosa susceptible to ulcer formation.

11) Electrophoretic study showed that cysteamine administration led to reduction in the intensity of microsomal forms of  $\beta$ -glucuronidase. This might indicate that the cysteamine induced inhibition of synthesis of secretory material in the Brunner's glands.

12) The present investigation makes clear that the Ayurvedic mixture of such a combination might be of much valuable in the treatment of duodenal ulcer.

13) Treatment of duodenal ulcer should be approached taking into consideration of hypergastricsecretion, neutralization of acid gastric juice, impairment of Brunner's glands, astringent and antiseptic effects of drugs, proliferation of cells etc.

From this investigation some important suggestions can be made useful to human welfare. Habit of taking diet regularly, in time, is very important to maintain the alimentary tract free from ulceration. Hypersecretion of gastric juice

due to stress and strain, and drugs like analgen should be avoided. Chemicals responsible for the impairment of synthesis of mucus materials should not be ignored. Obstructions/narrowing in the alimentary tract should be given due care to eliminate at once. Treatment of duodenal ulcer should be choice oriented with reference to the pathogenesis of the ulcer.

#### Investigation in Progress

The present investigation opens several avenues for further research on this line and we feel that further work in the following problems may prove to be fruitful in understanding, in a better manner the importance of Brunner's glands so also the role played by these glands in the protection of the duodenal mucosa.

- I. Effect of antioxidants on the physiology of Brunner's glands.
- II. Effects of analgesic drugs on the gastrointestinal tract and Brunner's glands.
- III. Effects of hormones on induced duodenal ulcer and Brunner's glands.
- IV. Study of Brunner's glands in the healing process of duodenal ulcer.
- V. Study of protein, PAS-positive mucus glycoprotein and  $\beta$ -glucuronidase from the Brunner's glands with respect to characterization study employing electrophoretic technique.

- VI. Case report study on human beings with reference to normally occurring physiological disturbances would be important in the treatment of duodenal ulcer.
- VII. Standardization of Ayurvedic medicines for the treatment of duodenal ulcer.