EVALUATION OF THE ROLE OF GASTRIN IN COLORECTAL CANCER

Thesis

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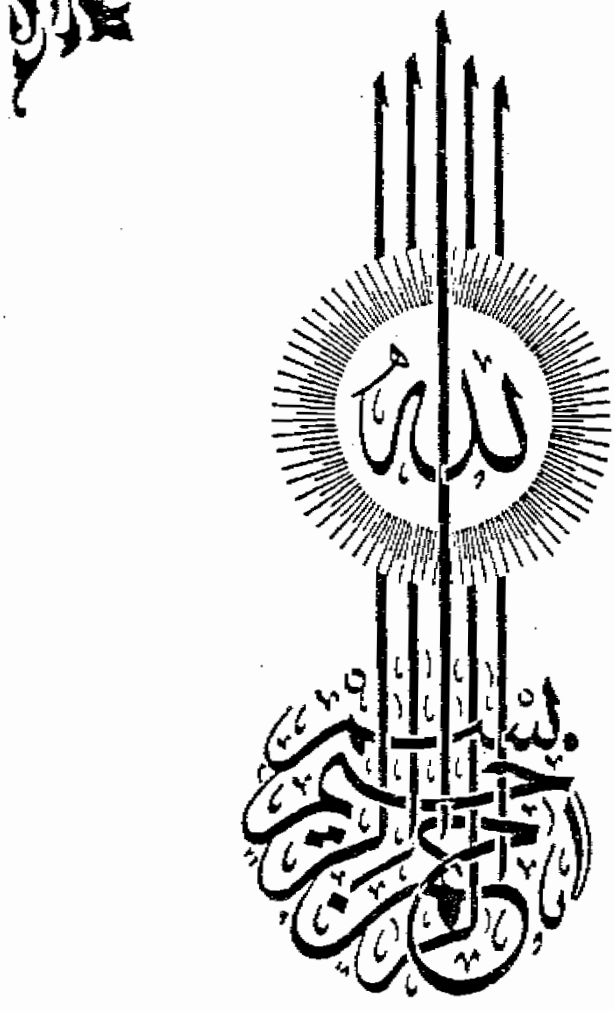

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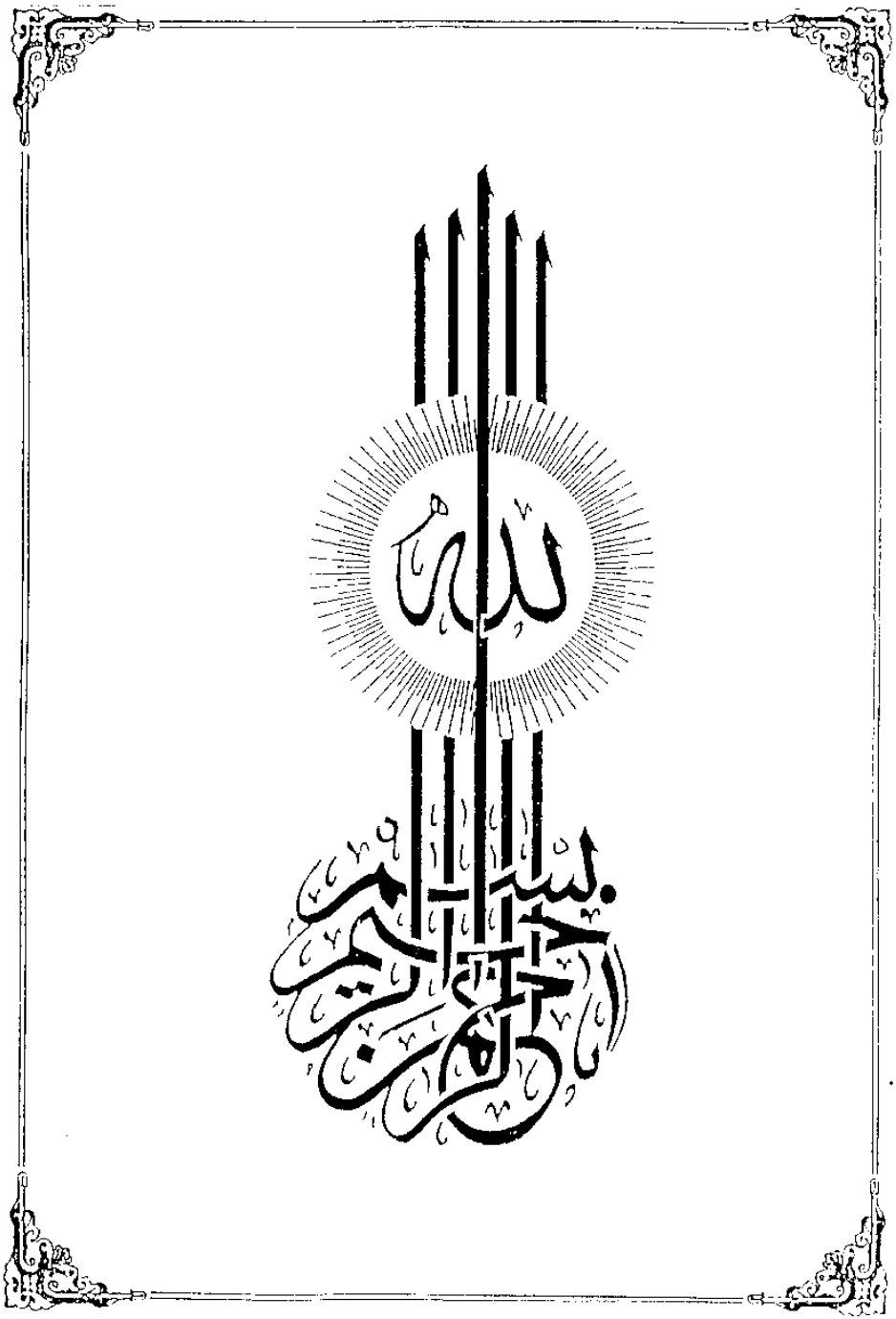

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INTRODUCTION & AIM OF THE WORK

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Gastrin is a hormone responsible for acid secretion. Protein in food is the most potent stimulant of gastrin release, but vagal Stimulation, calcium ion & other cations such as magnesium and aluminium, and alkalinization of the antrum also release gastrin. Gastrin release is inhibited by acid within the lumen of the antrum (Ganong, 1993)..

Gastrin and its analogue pentagastrin stimulate the growth of the human colon cancer cell lines in vitro (Kusky et al., 1986). Exogenously administered gastrin is trophic to colon cancer that possesses gastrin receptors (Winsett et al., 1986). Gastrin is an established trophic factor for benign and malignant colonic epithelial cells in vivo (Charnley et al., 1992). Antigastrin (proglumide) inhibits the growth of established colon cancer in mice (Beauchamp et al., 1985).

Wong et al, (1991) found that patients with colorectal cancer have significantly raised postprandial serum gastrin values compared with the normal population, and these values decreased after surgical resection of the tumor.

Aim of the work:

Evaluation of the role of gastrin in colorectal cancer.

REVIEW OF LITERATURE

ANATOMY OF THE COLON

The right colon has been generally designated as consisting of the cecum, the ascending colon, the hepatic flexure and the proximal transverse colon. The left colon is comprized of the distal transverse colon, the splenic flexure, the descending colon, the sigmoid colon, and the recto sigmoid. The greatest diameter of the colon exists in the cecum with the calibre of the lumen decreasing progressively from the cecum to the sigmoid. Two major arterial systems supply the colon. The right colon is predominently supplied by the superior mesentric artery which originates from the abdominal aorta. The major branches of this artery that perfuse the right colon include the ileocolic branch which supplies the ileocecal junction, the right colic which supplies the ascending colon, and the middle colic artery which supplies the hepatic flexure and the transverse colon to its midpoint. The left colon is predominently supplied by the inferior mesentric artery which derives its origin from the abdominal aorta. The distal transverse colon and the descending colon obtain their blood supply from the left colic branch of the inferior mesentric artery, while the sigmoid colon obtains its blood supply from sigmoidal branches. All along the colon, the colic arteries bifurcate and form vascular arcades so that the resultant marginal Drummond artery forms an anastomosis between

the superior mesentric artery and the inferior mesentric artery. Accompanying the arteries perfusing the colon are corresponding veins. The veins draining the right colon enter a major confluent vein known as the superior msentric vein,while those draining the left colon form the inferior mesentric vein. Both these veins empty into the portal vein which in turn drains into the liver. Lymphatic plexuses in both the submucosal and subserosal layers of the bowel drain into major lymphatic vessels and lymph nodes that accompany the veins and arteries.

Similar to the small intestine, the colonic wall contains four layers, these include mucosa, submucosa, muscularis, and serosa. Similar to other regions of the gut, two groups of nerve plexuses exist within the wall of the colon. The submucosal nerve plexus (Meissner's plexus) is located between the muscularis mucosa and the circular muscle layer of the muscularis propria. Sandwiched between the circular muscle and the outer longitudinal muscle is the Myenteric plexus which appears to be involved with colonic motility. The plexus is composed of ganglia and clusters of nerve cell bodies that are linked together by bundles of nerve processes.

Colonic Epithelium

The mucosal surface of the colon consists of columnar epithelium, like that of the small intestine, but because the colon dose not possess a physiologically important absorptive role, villi are absent and the mucosa is generally flat. All along the mucosal surface, the lieberkuhen crypts open into the colonic lumen. The epithelium of the lower portion of the crypts consists of undifferentiated mucus secreting goblet cells, scattered endocrine cells, and columnar cells. The upper parts of the crypts are composed of differentiated columnar cells, goblet cells and fewer endocrine cells. The mucosa between the crypts is columnar in type.

Muscular Structure of the Colonic Wall

The musculature of the colon is smooth muscle and is arranged in three general layers. The innermost layer comprises the muscularis mucosa that resides below the epithelium as one moves from the intestinal lumen to the outer serosal lining. The muscularis mucosa has both an inner circular and an outer longitudinal layer whose bundles are tightly interwoven. Surrounding the musclaris mucosa is a thick layer of circular smooth muscle that subtends the entire

circumference of the colon. An outer longitudinal muscle surrounds the circular muscle, (Seymour et al., 1994).

Anatomy of the Rectum

The rectal wall consists of mucosa, submucosa and two complete muscular layers; an inner circular and an outer longitudinal. The rectum is approximately 12 to 15 cm in length and extends from the sigmoid colon to the anal canal following the curve of sacrum. The rectum contains three distinct curves, the proximal and distal curves are convex to the right, whereas the middle is convex to the left. These folds project into the lumen as the valves of Houston. These mucosal infoldings present some difficulty for proctoscopic examination, but they are excellent targets for mucosal biopsy, since they do not contain all layers of muscular rectal wall and the risk of perforation is therefore diminished.

Arterial Supply:

The terminal branch of the inferior mesentric artery becomes the superior rectal artery as it crosses the left common iliac artery. It's right and left branches supply the upper and middle rectum. The middle and inferior rectal arteries supply the lower two thirds of the rectum. The middle sacral artery arises just proximal to the aortic bifurcation and

provides very little blood supply to the rectum.

Venous Drainage:

The venous drainage of the rectum parallels the arterial blood supply and empties into both the portal and the systemic (caval) systems. The upper and middle rectum are drained by the superior rectal vein which enters the portal system via the inferior mesentric vein. The lower rectum and anal canal are drained by the middle rectal veins which empty into the internal iliac vein and then into the caval system. There are three submucosal internal hemorrhoidal complexes: left lateral, right posterolateral, and right anterolateral located above the dentate line and drain into the superior rectal vein. The external hemorrhoidal veins drain into the pudendal veins. There is communication between internal and external plexi.

Lymphatic drainage :

The rectal lymphatic flow is segmental and circumferential and follows the same distribution as the arterial blood supply. Lymph from the upper and middle rectum drains in to the inferior mesentric nodes. The lower rectum is primarily drained by lymphatics that follow the superior rectal artery and enter the inferior mesentric nodes. Lymph from the lower rectum can also flow laterally along the middle and inferior

COLORECTAL CANCER

Epidemiology :

Worldwide, colorectal carcinoma ties breast cancer as the third most frequent cancer after gastric and lung cancers. (Parkin et al., 1988).

An important feature of colorectal cancer is its broad geographic variation in incidence, which can range as high as 30-fold when comparing different population groups. (Silverberg et al.,1990). These differences appear not to be solely due to genetic factors, since populations migrating from low-to high-incidence regions experience an increase in the rate of colorectal cancer. (Haenszel and Kurihara, 1968).

Colorectal cancer is predominantly a disease of industrialized Western countries (North America, Australia, New Zealand and Intermediate areas of Europe) (Thomas, 1993), and its incidence is low in regions of Asia, South America and especially sub-Saharan Africa (Boyle et al., 1990).

Such data provide indirect evidence that environmental factors are involved in the pathogenesis of colorectal cancer (Chang, 1993). Diet has been implicated as the major environmental determinant of risk (Willet, 1989), and this suggests that the incidence of this disease may be responsive to