Egyptian Journal of Anatomy, Jan. - July 2010; 33(1-2):45-54

Original Article

Histological and Ultrastructural Study of the Stomach Mucosa of Adult Male Albino Rats after Horizontal Gastroplasty and Cimetidine Administration

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ABSTRACT

Background: The severity of mucosal damage after horizontal gastroplasty is closely related to the high PH of the pouch. Cimetidine proved to promote healing of acute gastric erosions.

Aim of the Work: This research was carried out to investigate the effect of horizontal gastroplasty on the stomach mucosa and protective effect of cimetidine.

Materials and Methods: A total of 15 male adult rats were divided into three equal groups. The first one considered as control. The second group was exposed to horizontal gastroplasty. The third group was exposed to horizontal gastroplasty with immediate injection of Cimetidine in a dose of 200 mg/kg/ daily for one month. The rats were sacrificed after the last dose of the drug and the stomach was removed and different sections were prepared for light and electron microscopic investigation.

Results: Examination of the gastric mucosa in the control group revealed the traditional mucosal architecture.

In the second group using L/M examination, the different types of cells of gastric glands were distorted with condensation of their nuclei and disruption of the epithelium of gastric glands. There was a focal area of inflammation with marked increase of inflammatory cells and areas of congestion. The lumens of gastric glands were markedly dilated and the connective tissue between the glands was increased. By E/M examination, some nuclei appeared small and condensed .The cell membrane surrounded the cells disappeared, the Golgi apparatus was dilated, the mitochondria were swelled with distortion of their cristae and the rER were distended with shedding of their ribosomes. The microvilli disappeared and secretory granules were scanty with small clear and irregular vacuoles.

In the third group, L/M and E/M examinations revealed that most affections appeared in the second group have vanished.

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Key Words: Gastroplasty, horizontal, gastric mucosa, cimetidine administration, rats.

INTRODUCTION

The stomach is a distensible organ which receives food from the oesophagus and retains it for two hours or more during which time it undergoes mechanical and chemical breakdown to form chyme. Solid foods are broken up by a strong muscular churning action whilst chemical breakdown is produced by gastric juices secreted by the glands of the stomach mucosa *(Owen, 1986; Barbara & John, 2000)*. There is a little absorption of most food products from the stomach, except for water, alcohol and some drugs. Once chyme formation is completed, the pyloric sphincter relaxes and allows the liquid chyme to be squirted into the duodenum. The stomach mucosa in non-distended state is thrown into prominent longitudinal folds called rugae, which permit great distension after eating *(Junqueira & Carneiro, 2002)*.

The gastric restrictive surgery was used over the past decade as the treatment of choice for morbid obesity. There are two types of gastric

restrictive surgery: the first is vertical banded gastroplasty and the second is horizontal banded gastroplasty *(Kuwano et al., 1988; Suter et al., 1999)*. In horizontal gastroplasty the histology of the proximal pouch of the stomach showed various degrees of mucosal damage with close relationship between its severity and high PH of the pouch.The vertical banded gastroplasty caused deterioration of the gastric histology and this was of minor degree *(Flejou et al., 1988; Kuwano et al., 1988; Suter et al., 2000)*.

The cimetidine is H_2 receptor antagonist and is effective in preventing development of gastric and duodenal ulcers in experimental animals *(Hentschel et al., 1983; Brailski & Dimitrov, 1987)*. Also, the drug promotes healing of acute gastric erosions induced in trapped rats. Cimetidine strongly inhibits gastric acid secretion evoked by a variety of stimulants and its antisecretory activity contributes to its anti-ulcer effect *(Bruley des Varannes et al., 1998)*.

The present study was performed to investigate the effect of horizontal gastroplasty on the glandular portion of the stomach mucosa of rats and the protective effect of cimetidine.

MATERIALS AND METHODS

Surgical procedure (horizontal gastroplasty operation):

The rats were anaesthetized with ether under complete aseptic conditions and a midline abdominal incision was done .The upper part of the stomach was encircled using bands made of synthetic materials. This creates an upper pouch that empties into the lower part of the stomach through a narrow non-stretchable stoma. The incision was closed in layers with 4/0 silk sutures and the animals were allowed to recover and return to the animal-holding facilities where they were observed throughout the experiment (Fig. 1-a) *(Fisher, 1994)*.

Cimetidine: This drug is available as tablets 200,300,400 and 800mg, liquid: 300mg/5ml and injection 2ml ampoules 150mg/ml. The drug was given daily intramuscular in a dose of 200 mg/kg for one month *(Searcy et al., 1982)*.

Animals used:

Fifteen adult male albino rats (200-250gm each) were used and were caged in a well-ventilated room and fed with well-balanced diet at room temperature .The animals were divided into three groups (five rats each).

Group I: were used as control and exposed to an abdominal incision and gastric manipulation.

Group II: In which the rats were subjected to horizontal gastroplasty operation then sacrificed after one month of the operation.

Group III: In which the rats were subjected to horizontal gastroplasty operation with immediate intramuscular injection of cimetidine in a dose of 200mg/kg daily for one month then they were sacrificed after the last dose.

After sacrifice the stomach was removed and small pieces from the proximal part were fixed in 10% formol saline. Paraffin sections were stained with Haematoxylin and Eosin (H &E) stains for light microscopic examination *(Carleton, 1980)*. Furthermore, small pieces 1mm3 were fixed in 2% buffered gluteraldehyde, then washed in phosphate buffer and postfixed in 1% osmium tetra-oxide and then dehydrated and embedded in epoxy resins. Ultrathin sections (40-50um) were cut with glass knife, then stained with uranyl acetate and lead citrate and examined by electron microscope JEOL100s E/M *(Hayat, 1989)*.

RESULTS

Group I: Examination of the stomach by light microscope (L/M) revealed that the fundic glands extended from the gastric pit at the lumen of the stomach to the muscularis mucosae and consisted of three regions (isthmus, neck and base) (Figs. 1, 2).Three types of cells in the gastric gland were recognized. The first type consisted of columnar cells with basally-located nuclei that covered the luminal surface of the stomach, and lined the gastric pits. The cells of the second type were distributed along the length of the glands but were numerous in the middle portion (isthmus and neck) and occasionally present in

the bases of the glands. They had an acidophilic cytoplasm and centrally-located nuclei. The cells of the third type were located in the bases of gastric glands and were recognized by their condensed basally- located nuclei and strongly basophilic cytoplasm. There was little connective tissue in between the gastric glands (Fig. 3).

Ultrastructurly, the first type of cells had short microvilli on their surface, basally-located nuclei with finely granular chromatin and clear nucleoli. They had Golgi apparatus, rough endoplasmic reticulum (rER) and mitochondria which were located mostly in the basal region of the cells. The apical cytoplasm was filled with secretory granules. The cells were separated from each others by clear cell membrane (Fig. 4).The second type had abundant mitochondria that surrounded a centrally -located nucleus. The rER and the Golgi apparatus were scanty (Fig. 5). The third type had extensive rER and a Golgi apparatus, but the mitochondria were scanty. There were membrane-bound secretory vesicles in the apical cytoplasm containing glandular secretion pushing the nuclei to the base of the cells (Fig. 6).

Group II: By L/M, the surface epithelium of gastric glands showed a focal area of disruption with distortion and shrinkage of the cells of gastric mucosa. In the lamina propria, there were areas of marked congestion at the base of gastric glands (Figs. 7, 8).There was a focal area of inflammation with marked increase of inflammatory cells. The lumen of the gastric glands was markedly dilated especially the basal parts. The connective tissue between and at the base of the glands was increased with marked cellular infiltration (Figs. 9, 10).

Ultrastructurly, The cells of the gastric glands showed condensed small size nuclei (pyknotic nuclei) associated with hyperchromatosis. The cell membrane surrounded the cells disappeared, the Golgi apparatus was dilated, the mitochondria were swelled with distortion of their cristae and rER were distended with shedding of their ribosomes (Figs. 11, 12).Also; the microvilli vanished and the secretory granules were scanty with small clear, irregular vacuoles (Fig. 13).

Group III: By L/M, the surface epithelium of the gastric mucosa was nearly intact. The gastric glands were nearly normal in their appearance in the three regions (isthmus, neck and base) with slight dilatation of their lumens and their cells retained their normal shape. The surface cells appeared columnar with basally-located nuclei, the cells of middle portion (isthmus and neck) showed acidophilic cytoplasm with centrally-located nuclei and the cells of the base contained basophilic cytoplasm and basally-located nuclei. There was a decrease in the connective tissue between the gastric glands, in the areas of congestion and cellular infiltration as compared with the group II (Figs. 14, 15, 16).

Ultrastructurly, most cells of the gastric glands appeared with normal nuclei, Golgi apparatus, mitochondria and rER. Their apical cytoplasm was filled with secretory granules. Also; the cells were surrounded by normal cell membrane (Fig. 17).Some cytoplasmic organelles in some cells changed in the form of dilatation of Golgi apparatus, distention of rER and swollen mitochondria (Fig. 18).

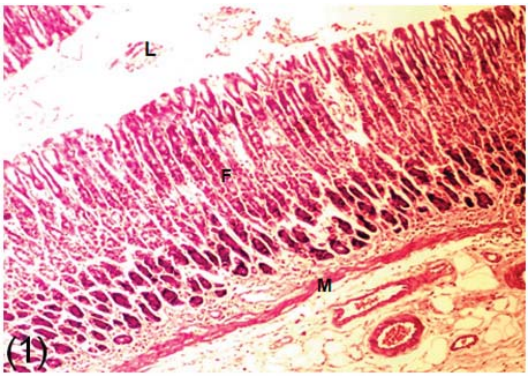

Fig. 1: A photomicrograph of a longitudinal section of the gastric mucosa of group I showing the fundic glands (F) extending from the lumen of the stomach(L) to the muscularis mucosa(M). Hx.&E.; X100

Fig. 1A: A photograph of male albino rat after opening its anterior abdominal wall showing horizontal gastroplasty operation (arrow).

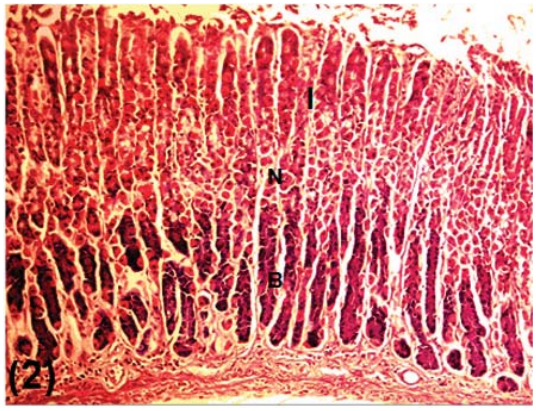

Fig. 2: A photomicrograph of a longitudinal section of the gastric mucosa of group I showing the fundic glands divided into three regions, isthmus(I),neck(N) and base(B). Hx.&E.; X200

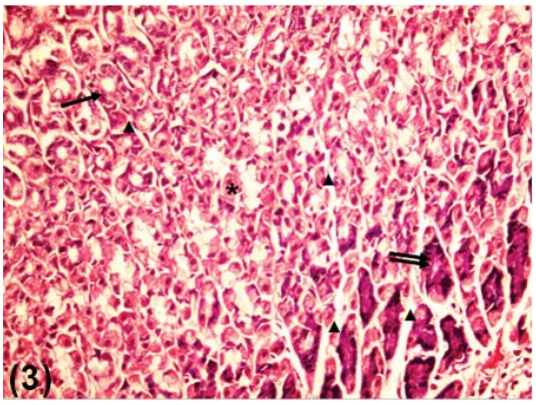

Fig. 3: A photomicrograph of a transverse section of gastric mucosa of group I showing surface columnar cells with basally-located nuclei (single arrow),acidophilic cells with centrally-located nuclei (*) and basophilic cells with basally-located nuclei (double arrows).Notice the little connective tissue between the gastric glands (arrowheads). Hx.&E.; X200

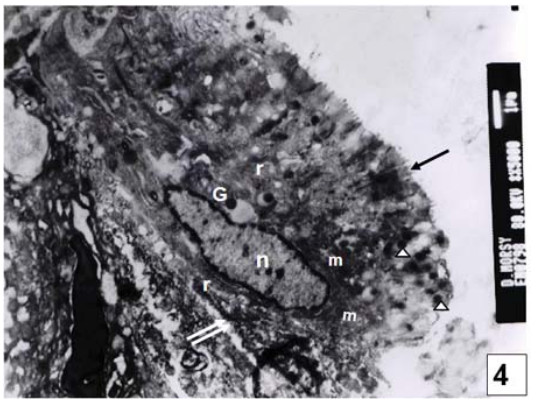

Fig. 4: An electron micrograph of a section in the first type of gastric cell of group I showing basally-located nucleus with fine granular chromatin and clear nucleoli (n), short epithelial microvilli (arrow) and multiple secretory granules(arrowheads).Notice the mitochondria (m), rER(r),Golgi apparatus(G) and the cell membrane (arrows). Uranyl acetate &Lead citrate; X5,000

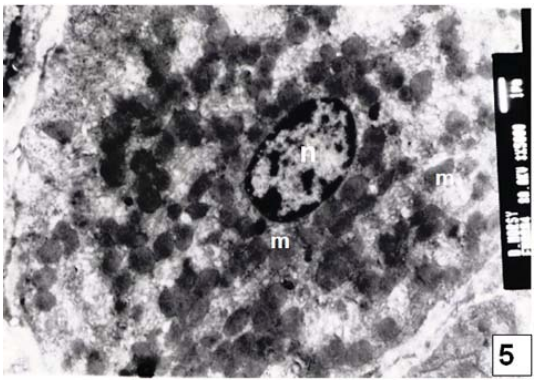

Fig. 5: An electron micrograph of a section in the second type of gastric cell of group I showing centrally-located nucleus (n) surrounded with numerous mitochondria (m). Uranyl acetate &Lead citrate; X5,000

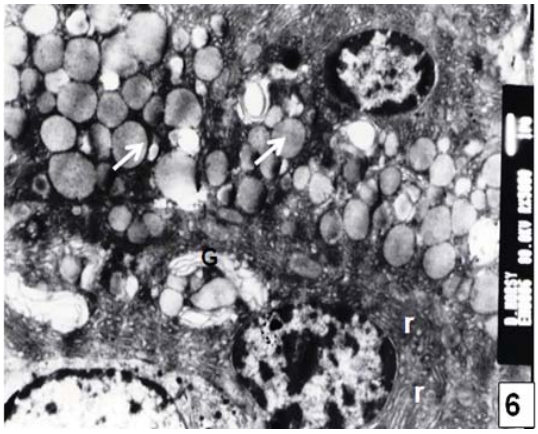

Fig. 6: An electron micrograph of a section in the third type of gastric cells of group I showing extensive rER (r) and Golgi apparatus (G).Notice the secretory vesicles(arrows) in the apical cytoplasm. Uranyl acetate & Lead citrate; X5,000

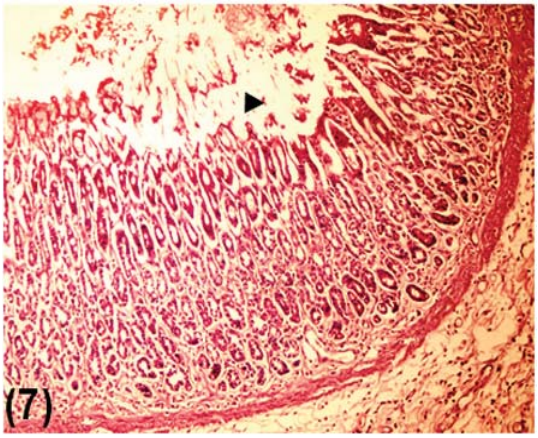

Fig. 7: A photomicrograph of a longitudinal section of the gastric mucosa of group II showing area of disruption in the surface epithelium of the gastric mucosa (arrowhead). Hx.&E.; X100

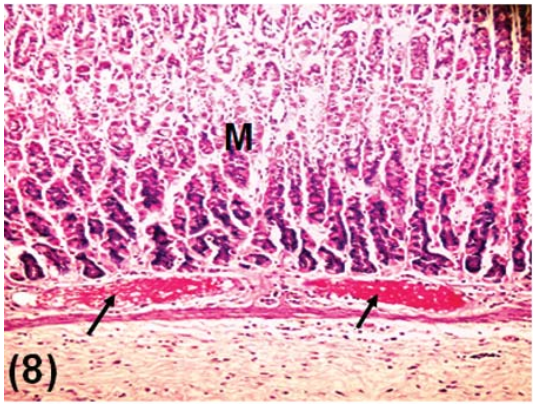

Fig. 8: A photomicrograph of a longitudinal section of the gastric mucosa of group II showing distortion and shrinkage of the cells of the gastric mucosa (M) with areas of congestion (arrows). Hx.&E.; X200

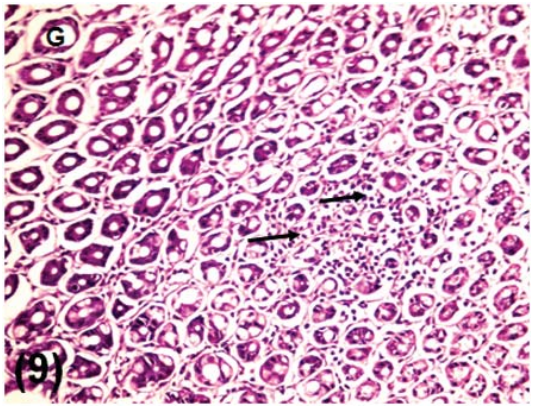

Fig. 9: A photomicrograph of a transverse section of the gastric mucosa of group II showing dilatation of the lumen of gastric glands(G) with a focal area of inflammation (arrows). Hx.&E.; X200

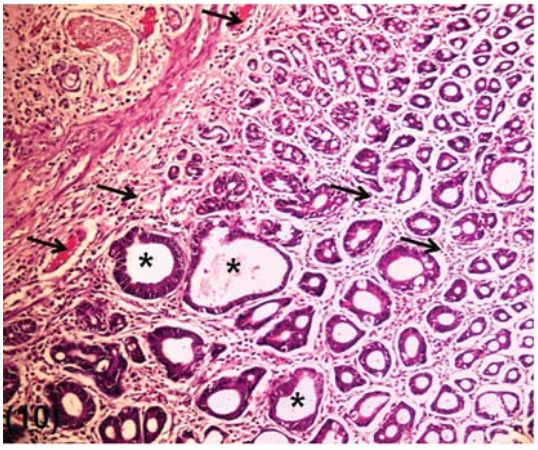

Fig. 10: A photomicrograph of a transverse section of the gastric mucosa of group II showing marked dilatation of the basal part of gastric glands(*). Marked increase of the connective tissue fibers between and at the base of gastric glands with areas of congestion (arrows). Hx.&E.; X200

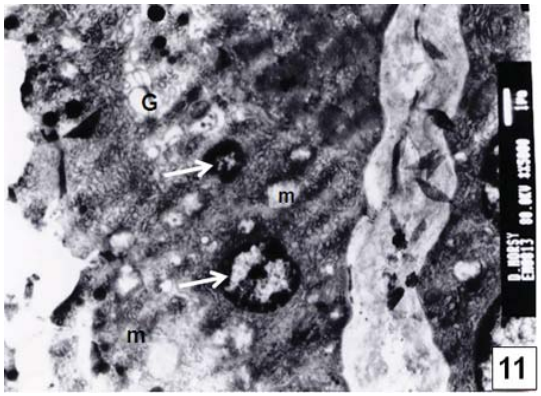

Fig. 11: An electron micrograph of a section in the gastric cells of group II showing condensed and small size nuclei (pyknotic nuclei) (arrows),dilatation of Golgi apparatus(G) and swollen mitochondria with distortion of their cristae (m). Uranyl acetate & Lead citrate; X5,000

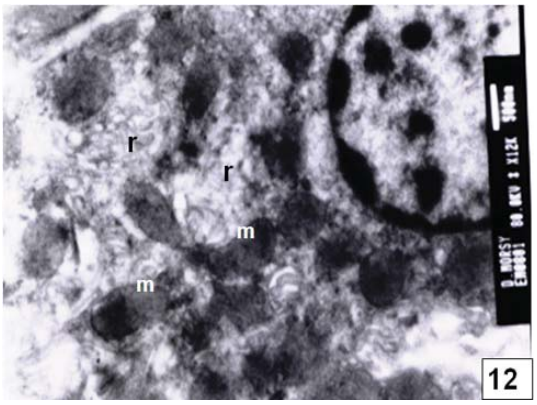

Fig. 12: An electron micrograph of a section in the gastric cells of group II showing condensed and small size nuclei (pyknotic nuclei) (arrows),dilatation of Golgi apparatus(G) and swollen mitochondria with distortion of their cristae (m). Uranyl acetate & Lead citrate; X5,000

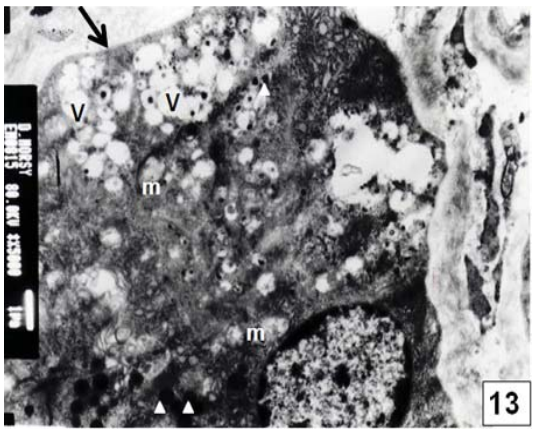

Fig. 13: An electron micrograph of a section in the gastric cell of group II showing loss of epithelial microvilli (arrow) .The secretory granules are scanty (arrowheads) with small clear, irregular vacuoles(v).The mitochondria are swollen with loss of their cristae (m). Uranyl acetate &Lead citrate; X5,000

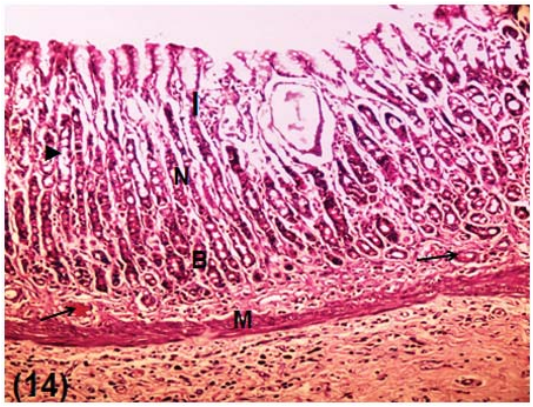

Fig. 14: A photomicrograph of a longitudinal section of the gastric mucosa of group III showing isthmus (I), neck(N) and base(B) of gastric glands. The gastric glands are slightly dilated (arrowhead). Notice the small areas of congestion (arrows). Hx.&E.; X200

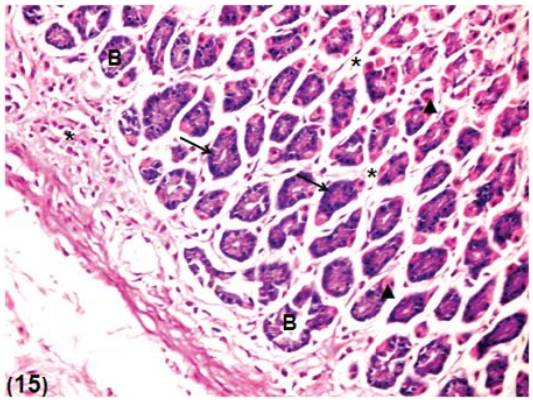

Fig. 15: A photomicrograph of a transverse section of the gastric mucosa of group III showing slight dilatation of the basal part of the gastric glands(B) with normal basophilic cells having basally-located nuclei(arrows).Notice the normal acidophilic cells with centrally-located nuclei(arrowheads). Notice the slight increase of the connective tissue in between the glands (*). Hx.&E.; X200

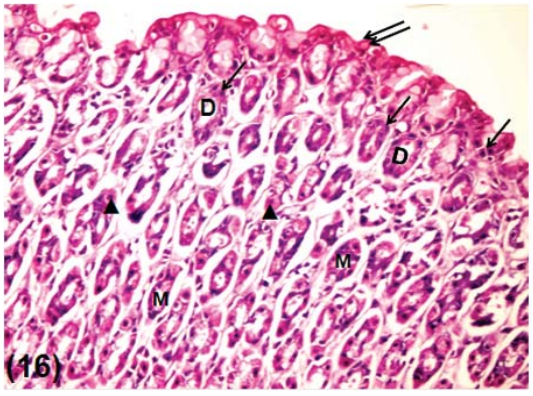

Fig. 16: A photomicrograph of a transverse section of the gastric mucosa of group III showing slight dilatation of the distal (D)and middle (M)parts of gastric glands. Notice the surface columnar cells with basally-located nuclei (single arrow) and acidophilic cells with centrally-located nuclei (arrowheads).The surface epithelium is intact (double arrows). Hx.&E.; X200

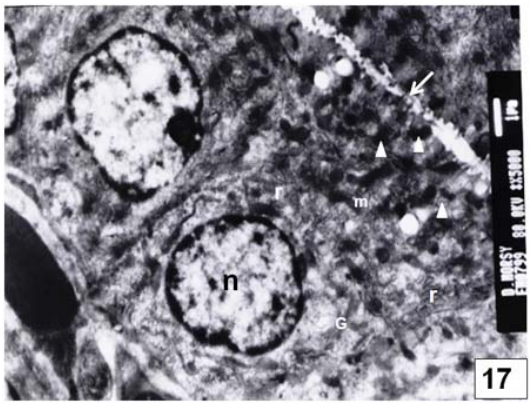

Fig. 17: An electron micrograph of a section in the gastric cells of group III showing normal nucleus (n),normal mitochondria(m),normal Golgi apparatus(G) and normal rER (r).Notice the cell membrane (arrow) and secretory granules(arrowheads). Uranyl acetate & Lead citrate; X5,000

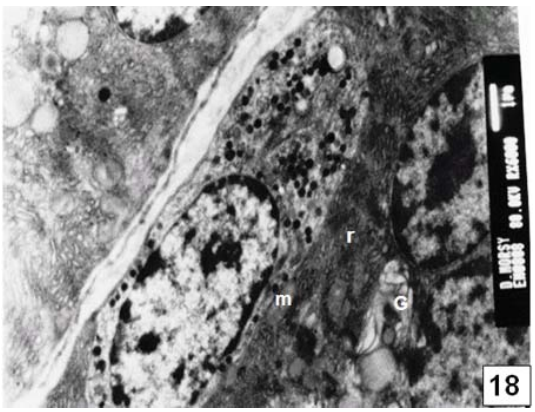

Fig. 18: An An electron micrograph of a section in the gastric cells of group III showing dilatation of Golgi apparatus(G),distention of rER (r) and some swollen mitochondria (m). Uranyl acetate & Lead citrate; X6,000

DISCUSSION

The present study showed that the stomach mucosa had three types of cells in the gastric glands. These findings are in agreement with those described by *Owen (1986)* and *Barbara and John (2000)*. They stated that the gastric glands contained mixed population of cells of three main types(mucous secreting cells cover the luminal surface, acid secreting cells along the length of the glands and pepsin-secreting cells located towards the bases of the gastric glands. *Negri et al.(1995)* reflected the strong basophilic cytoplasm of the pepsin-secreting cells to their large content of ribosomes. The larger parietal cells have eosinophilic cytoplasm due to the numerous mitochondria that are a feature of highly metabolically active cells.

In this work, the gastric mucosal cells showed marked changes after operation. The epithelium of gastric glands was disrupted with hemorrhagic lesions and increased connective tissue (lamina propria). These changes would indicate that the stomach mucosa might be exposed to stress and ischemia from the operation. The present findings are in agreement with *Negri et al. (1995)* and *Kitano et al. (2005)* who stated that the ischemia evoked by gastric mucosal injury affected rat stomach histamine, which resides in entero-chromaffin-like cells and mast cells. Also these results are similar to those obtained by *Flejou et al. (1988)* who mentioned that after gastroplasty there was a marked changes in the gastric cells and secretory granules.

Kuwano et al. (1988) proved that the gastric mucosal damage after horizontal gastroplasty was due to increase gastric acid secretion and decrease of gastric mucous content. *Jain et al. (2003)* stated that cancer was confined to the pouch of the stomach after vertical band gastroplasty. Also, *Koc and Muslu (2007)* observed marked histological changes in the stomach mucosa exposed to hunger and thirst. On the other hand, *Doherty (2001)* indicated that the effects of gastroplasty on the gastric lesions was caused by an alteration in pepsin activity and fluidity of the stomach contents or both and not by a decreased secretion of mucus or increased secretion of acid.

The present study clarified obvious dilatation of the Golgi apparatus, swollen mitochondria, distention of rER, loss of microvilli and pyknotic nuclei of the some cells of gastric glands. These findings are in agreement with *Bernardi, 1996 and Brzozowski et al. (2005)* who stated that the cellular swelling was the first manifestation of almost all forms of injury of the cells. They also stated that reduction in cell ph was the cause of nuclear chromatin clumping and small clear vacuoles seen within the cytoplasm represented distention and pinched off segments of the endoplasmic reticulum.

Bernardi (1996) mentioned that the mitochondria were important targets for virtually all types of injurious stimuli including hypoxia and toxins. They can be damaged by increases of cytosolic ca++, by oxidation stress, by breakdown of phospholipids through phospholipase A2 and sphingomyelin pathways.

In the present work, the administration of cimetidine decreased the injurious effects of gastroplasty on the stomach. This is in accord with *(Lauterbach & Mattes, 1978; Hiroi et al., 1981)* who stated that the cimetidine effectively suppressed development of stress gastric ulcer in intact trapped rats in which ulcer formation might be unrelated to gastric acidity and exogenous given of hydrochloric acid.

Brailski and Dimitrov (1987) and *Khoshbaten et al. (2006)* stated that cimetidine was histamine H2 antagonist. Histamine is a natural chemical that stimulates stomach cells to produce acid. Histamine H2 antagonists inhibit the action of histamine on the acid producing cells of the stomach and reduce stomach acid. In addition, it is postulated that cimetidine favoured the secretion of muco-substances from the gastric glands to constitute a defence factor against peptic ulcer.

Kitano et al. (1997) mentioned that cimetidine possessed a protective effect against acute gastric mucosal injury induced by ischemia-reperfusion not only due to the suppression in gastric acid secretion, but also due to antioxidant action when it is present in a high concentration in the intragastric environment.

Dodi et al. (1978) reported that various types of anti-ulcer drugs prevented the decrease of gastric mucous contents in rats subjected to stress.

Brailski et al. (1979) and *Hentschel et al. (1983)* mentioned that cimetidine protected against the stress- induced decrease in mucus components in the stomach. *Bruley des Varannes et al. (1998)* and *Kitano et al. (2005)* reported that cimetidine strongly inhibited gastric acid secretion evoked by a variety of stimulants and antisecretory activity thus contributed to the anti-ulcer effect.

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دراسة هستولوجية وتركيبية دقيقة للغشاء المخاطي المعدي لذكور الجرذان البيضاء البالغة بعد رأب المعدة العرضي وحقن عقار السيمتيدين

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ملخص البحث

أُجري هذا البحث لفحص تأثير رأب المعدة العرضي علي الغشاء المخاطي المعدي والتأثير الواقي لعقارالسيمتيدين حيث أُستُخدِم في هذة الدراسةِ خمسةَ عشرَ من الجرزان البالغة ، وقد قُسِمَت الجرزان إلي ثلاثِ مجموعاتٍ متساويةٍ: المجموعة الاولي أُعتُبِرَت ضابطة والمجموعة الثانية عُرِّضَت لرأبِ المعدة العرضي أما المجموعة الثالثة فعُرِّضت لرأبِ المعدةِ العرضي وحُقِنَت مباشرةً بعقارالسيمتيدين بجرعة ٢٠٠ مجم /كجم بالحقن العضلي يومياً لمدةِ شهرٍ واحدٍ، وقد تم التضحية بالجرزان بعد آخر جَرَعةٍ من العقار وأُخِذَت المعدةُ وجُهزت منها مقاطعُ مختلفة للفحص بالميكرسكوب الضوئي والإلكتروني.

وقد أظهر فحصُ المجموعةِ الضابطةِ التركيبَ المعتادَ للغشاء المخاطي المعدي ، وبالفحص بالميكرسكوب الضوئي في المجموعة الثانية وُجِد أنَّ مختلفَ أنواع خلايا الغدد المعدية قد تشوهت وتكثفت أنويتها وتمزق النسيج الظَّهَّاريّ لهذة الغدد مع وجود بؤرة إلتهابية ومناطق مُحتقِنة مع زيادةٍ ملحوظةٍ في الخلايا الالتهابية ، وقد لُوحِظ زيادةُ النسيج الضام بين الغدد المعدية واتساع قنواتِها بشكل ملحوظ، وبالفحص بالميكرسكوب الالكتروني وُجِد تكثيفٌ في بعض النوى مع صغر حجمها واختفاء الغشاء الخلوي وتمدد في أجهزة جولجى وانتفاخ في الحبيبات الخيطية وتمزُّق في صهاريجها. وقد أنتفخت الشبكة الاندوبلازمية الخشنة وفقدت جُسيماتها الريبوسية واختفت الزغيبات ونقصت الحبيبات الإفرازية مع وجود فجوات صغيرة واضحة وغير منتظمة.

وبالفحص بالميكرسكوب الضوئى والإلكتروني في المجموعة الثالثة ظهرأن معظم التأثيرات التي وُجِدَت في المجموعة الثانية قد تلاشت.