DISCUSSION
This study was carried out using different gastric and duodenal ulcer models, each of which produces ulcers, by a distinct mechanism. The pylorus ligation model developed by Shay et al\textsuperscript{355} is one of the oldest and most widely used method for the evaluation of effect of different agents on gastric acid secretion and gastric ulcers. The gastric ulcer produced by this method depends on the gastric acid secretion, gastric pepsin secretion and gastric cytoprotection\textsuperscript{372}. Gastric acid is known to catalyse the cleavage of inactive pepsinogen to active pepsin and also provide the low pH for pepsin activity\textsuperscript{39}.

The other commonly used gastric ulcer models include those employed to study the effect on gastric cytoprotection. The two most widely used models to study gastric cytoprotective effect are NSAID (aspirin/indomethacin) induced gastric ulcers and ethanol induced gastric ulcers\textsuperscript{366}. In the present study, NSAID used for induction of ulcer was indomethacin, since this produces gastric ulcer solely due to inhibition of prostaglandin synthesis without any gastric damage due to its physical properties, which is usually seen with aspirin because of the shape of its crystals. The gastric ulcer produced by indomethacin is reduced by agents, which can increase prostaglandin levels, and by certain gastric antisecretory agents\textsuperscript{367}. Ethanol produces gastric damage by direct necrotic action and it is an acid independent injury. Both NSAID and ethanol induced gastric ulcers are reduced by agents which increase gastric mucus secretion making the stomach less prone for damage by exogenous necrotic agents and gastric acid. Some of the agents increase the gastric mucus secretion by their local actions\textsuperscript{368}, while others increase gastric mucus secretion by central mechanisms mediated through vagus\textsuperscript{369}. The gastric damage induced by NSAID and ethanol also depends on gastric motility. Increase in gastric motility aggravates the formation of ulcers due to these agents, as maximum damage is produced at the rugal folds of the stomach\textsuperscript{366}.

The other acute gastric ulcer model used in the present study is histamine induced gastric ulcers in the guinea pigs. Many investigators believe that the final mediator of acid secretion is histamine, this model was used in the present study for evaluating protection against histamine induced gastric ulcer.
The effect of PRL and OXT on gastric ulcer healing was studied by using acetic acid induced chronic gastric ulcers. Acetic acid induces gastric damage by direct corrosive action. Traditionally, assessment of ulcer healing is based on visual endoscopic examination or on gross measurements of ulcer size in experimental animals. Using quantitative histology and ultrastructure assessment of subepithelial mucosa reconstruction, Tarnawski et al\(^{170}\) demonstrated that reepithelialized mucosa of grossly 'healed' experimental gastric ulcers had prominent abnormalities: reduced height, marked dilation of gastric glands, poor differentiation and/or degenerative changes in lining cells. Indeed, clinical studies have demonstrated that gastric ulcers tend to recur at the same location. Therefore, the quality of mucosal structure restoration may be a crucial factor in determining future ulcer recurrence and should be paid more attention in evaluation of action of antiulcer agents. In the present study, since gastric healing effect was observed with OXT and not with PRL, the histological study was carried out only in experiments involving administration of OXT. Ulcer index, ulcer area, ulcer score were used to assess the effect of PRL on gastric ulcer aggravation.

Scyle and Szabo\(^{371}\) first described an experimental duodenal ulcer in rats induced by cysteamine. The pathogenic mechanism leading to ulceration has not been fully understood, but both protective factors and aggressive factors influencing resistance of the duodenal mucosa seems to be involved. Cysteamine inhibits the alkaline mucus secretion from Brunner's glands in the proximal duodenum and stimulates gastric secretion rate. Gastric emptying is also delayed and serum gastrin levels are increased. Cysteamine induced duodenal ulcer model in the rat is widely used as a model of duodenal ulcer disease. This chemically induced ulcer resembles duodenal ulcer in man to its location, histopathology and some aspects of pathophysiology. The anticholinergic agents, antacids, prostaglandins, and \(H_2\) receptor antagonists inhibit the development of duodenal ulcers in response to cysteamine\(^{372}\).

**Prolactin:** In the present study, the effect of PRL on gastric and duodenal ulcer was studied by either implanting adenopituitaries under the kidney capsule or injecting PRL intracerebroventricularly in rats.
The implantation of adenopituitaries to study PRL effect was described by Mena et al.\textsuperscript{353} in 1968. The adenopituitary homografts secrete very high amount of PRL and little, if any, of the other pituitary hormones\textsuperscript{20}. Hence, it is likely that the changes found in the homografted animals with respect to gastric acid secretion, gastric and duodenal ulcer depends on the high level of PRL.

Hyperprolactinemia induced by pituitary homografts under the kidney capsule produced gastric hypersecretion and proulcerogenic effect in pylorus ligated rats. The proulcerogenic effect seems mainly due to gastric hypersecretion, as there was a direct a correlation between the amount of gastric secretion and production of ulcer. This effect could presumably result from the action of PRL in the brain, as earlier reports suggest that PRL does not influence gastric acid secretion by acting at its receptors present in the stomach\textsuperscript{15,16}. Further, there was no significant difference in any parameter between the groups of rats bearing either two or four adenopituitaries suggesting that peripherally released PRL does not show a dose dependent effect on gastric acid secretion in range of 381-764 ng/ml.

Hyperprolactinemia, produced after implantation of either two or four adenopituitaries did not influence the formation of ethanol induced gastric ulcers, but there was reduction in the development of indomethacin induced gastric ulcers in group of rats bearing four adenopituitaries. PRL is known to increase the synthesis of prostaglandins\textsuperscript{373}. The cytoprotective effect was observed in indomethacin induced gastric ulcer model may be due to increased prostaglandin synthesis, but increased prostaglandin synthesis is known to inhibit ethanol induced gastric ulcers\textsuperscript{374} and to reduce the formation of ulcers in pylorus ligated rats mainly due to gastric cytoprotection\textsuperscript{375}. This difference in the cytoprotective action observed with PRL cannot be explained with the present data.

The proulcerogenic effect due to hyperprolactinemia was further confirmed by aggravation of acetic acid induced chronic gastric ulcers. The aggravation of acetic acid induced chronic gastric ulcers suggests that the cytoprotective action produced
presumably due to increased prostaglandin synthesis in the stomach may not be sufficient to prevent the effect of increased acid secretion.

Hyperprolactinemia aggravated the development of cysteamine induced duodenal ulcers. This effect may also be due to increased gastric acid secretion, as there are no reports, on the effect of PRL on gastric emptying.

Hyperprolactinemia did not produce any gastric and duodenal ulcer in normal animals up to 40 days after implantation of either two or four adenopituitaries.

Since, earlier reports suggest that PRL does not influence gastric secretion by acting at its receptors in the stomach, it was decided to study whether the gastric hypersecretory and proulcerogenic effect produced due to hyperprolactinemia is due to central effect of PRL. There are several PRL binding sites in the brain but there are no reports on the effect of PRL on gastric and duodenal ulcer formation, when given centrally, hence it was decided to introduce PRL directly into the CSF through its administration into the lateral ventricles of the brain.

Like hyperprolactinemia, centrally administered PRL also produced increase in gastric acid secretion and aggravated the development of gastric ulcers in pylorus ligated rats. The increase in gastric acid secretion and gastric ulcer formation was more than that produced by hyperprolactinemia. Unlike the hyperprolactinemia, the central effect was dose dependent, as small dose (0.1 μg/kg i.c.v) showed increase only in total acidity, whereas a higher dose (1 μg/kg i.c.v) showed increase in free acidity, total acidity and ulcer index. This difference in effect between peripherally released and centrally administered PRL is in agreement with earlier reports, that transfer of plasma PRL across the blood brain barrier may be limited. These data clearly indicates that the effect of PRL is centrally mediated.

Centrally administered PRL did not show any cytoprotective action in either indomethacin induced or ethanol induced gastric ulcers. This suggests that the reduction
of ulcer index in indomethacin induced gastric ulcer produced due to hyperprolactinemia induced after implantation of four adenopituitaries may be solely due to its peripheral action.

Centrally administered PRL aggravated the acetic acid induced chronic gastric ulcer and cysteamine induced duodenal ulcer, confirming the centrally mediated prolcerogenic effect for PRL.

The effect of hyperprolactinemia and centrally administered PRL on histamine induced gastric ulcers in guinea pigs could not be evaluated in the present study, as implantation of adenopituitaries under the kidney capsule of the guinea pig or implantation of the cannula in the lateral ventricles of the guinea pig was not feasible.

PRL immunoreactivity is found within numerous hypothalamic areas in a variety of mammals. Within the rat hypothalamus, PRL immunoreactivity is detectable in the dorsomedial, supraoptic and paraventricular nuclei. Several approaches have been taken to prove that PRL found in the hypothalamus is synthesized locally, independent of PRL synthesis in the pituitary gland. Moreover, PRL is known to cross the blood brain barrier and PRL may also enter the brain due to retrograde blood flow from the anterior pituitary gland to the hypothalamus. Further, it has been reported that agents which are known to increase the release of pituitary PRL also cause the release of PRL from the hypothalamic areas. However, it is unlikely that implantation of adenopituitaries under the kidney capsule would have caused increase in the synthesis of PRL in the brain. On the contrary it may be suggested that implantation of adenopituitaries might have caused a decrease in the synthesis of brain PRL, as it is well established that implantation of adenopituitaries under the kidney capsule reduces the PRL levels in anterior pituitary gland. Estimation of CSF PRL levels to determine whether implantation of adenopituitaries under the kidney capsule influences PRL level in the CSF is troublesome, in part, because it is difficult to differentiate between the PRL of adenopituitary versus hypothalamic origin in the CNS. One cause of these difficulties is that pituitary PRL from the circulation bypasses the blood brain barrier, as detailed
earlier and enters the CNS through the choroid plexi of the brain ventricles. In the present study, the effect on gastric and duodenal ulcers observed in animals, bearing pituitary homografts may be due to the small amount of the PRL that has crossed the blood brain barrier. This hypothesis is supported by the fact that centrally administered PRL showed a dose dependent increase in gastric acid secretion when compared to the increase in serum PRL levels after implantation of the two or four adenopituitaries where a dose dependent effect was not obtained, probably because transfer of PRL across blood brain barrier may be limited.

Hyperprolactinemia is a common hypothalamic pituitary disorder encountered in clinical endocrinology. The causes of hyperprolactinemia are diverse and many drugs are known to induce hyperprolactinemia. The results of the present study suggests that induction of hyperprolactinemia may aggravate the gastric ulcers and drugs which are known to induce hyperprolactinemia with no gastric antisecretory activity of their own must be used with caution in patients with gastric and duodenal ulcers. Further, PRL is found in very high quantity in hypothalamus and PRL inhibiting factor like dopamine is reported to produce reduction in gastric acid secretion and gastric and duodenal ulcer formation, whereas, thyrotrophin releasing hormone (TRH), a stimulator of PRL secretion is known to increase gastric acid secretion. Hence, it can be suggested that PRL can be one of the mediators in their action. Since, hyperprolactinemia did not produce any gastric or duodenal ulcers in normal animals upto 40 days, it can be concluded that hyperprolactinemia may not lead to the development of gastric or duodenal ulcers in normal animals but can aggravate the already developed gastric or duodenal ulcers.

**Oxytocin:** OXT, a hormone released during lactation and parturition, is physiologically related to PRL. Like PRL, OXT is reported to have anti stress effects and to reduce the development of stress induced gastric ulcers in rats. There are many reports on the effect of OXT on gastric acid secretion in rats as detailed earlier in the introduction.

Like PRL, OXT receptors have been identified in the stomach, where it is known to cause
changes in single cell $K^+$ currents and to produce relaxation of the muscle\textsuperscript{35}. Vasopressin, which is structurally related to OXT is reported to reduce gastric acid secretion by acting at its receptors, the $V_1$ receptors present in the stomach\textsuperscript{36}, however, OXT did not produce any effect on the gastric acid secretion when tested by \textit{in vitro} technique in the same study. Few authors report that there is cross reactivity between OXT and vasopressin receptors, i.e., OXT can act on vasopressin receptors and vice versa and atosiban, a OXT receptor antagonist is known to reverse some of the effects produced by vasopressin\textsuperscript{37}.

About 0.2\% of peripherally released or administered OXT reaches brain. Moreover, OXT is directly released in the brain through parvocellular neurons. The concentration of OXT in CSF is 5-10 fold higher than in the plasma\textsuperscript{33}. The effect of both peripherally administered and centrally administered OXT on gastric acid secretion, gastric and duodenal ulcer formation was studied.

OXT, when administered subcutaneously produced a reduction in the gastric acid secretion and gastric ulcer formation in pylorus ligated rats. The reduction in gastric ulcer production could be directly correlated with reduction in gastric secretion. Atosiban, a OXT antagonist reversed the effect of OXT on gastric acid secretion and gastric ulcer formation, suggesting a direct involvement of OXT receptors in the gastric antisecretory and antiulcer effect.

The possibility of OXT exerting cytoprotective effect to produce its antiulcer effect is not indicated. This is because OXT administration failed to prevent the formation of gastric lesions in the indomethacin induced and ethanol induced ulcer models, on the contrary, it showed a significant increase in the formation of ethanol induced gastric lesions after chronic treatment for 5 days. The reason for the increase in ethanol induced gastric ulcer can not be explained with the present data. OXT did not influence the formation of indomethacin induced gastric ulcers. It is known that OXT increases PGF$_{2\alpha}$ production by acting at its receptors\textsuperscript{379}. Furthermore, OXT is reported to reduce gastric motility in rats\textsuperscript{380}, accordingly a reduction in the development of gastric ulcer was expected in both these models\textsuperscript{366}, such an effect could not be observed in the present study.
OXT antagonized the formation of histamine induced gastric ulcers in guinea pigs, indicating that histaminergic pathways involved in ulcer production is antagonized by systemically administered OXT.

OXT increased the regenerated lining epithelial width, decreased capillary density and produced an increase in collagen content in acetic acid induced chronic gastric ulcers. This indicates that OXT has an ulcer healing effect. Atosiban blocked the effects of OXT, atosiban when given alone aggravated the acetic acid induced gastric ulcers as evident by an increase in ulcer index. The antiulcer effect of OXT was further noticed in cysteamine induced duodenal ulcer model, where OXT significantly reduced the mean ulcer area and ulcer index which may be due to its antisecretory effect.

Atosiban, an OXT antagonist when given intracerebroventricularly prevented the gastric antisecretory and antiulcer effect of subcutaneously administered OXT, suggesting that the effect of OXT may be solely due to its central action.

OXT when given by intracerebroventricular route was more potent in inhibiting gastric acid secretion than when given subcutaneously confirming that the gastric antisecretory and antiulcer effect is due to its central action. An important conclusion drawn from the central administration of OXT was the effect on ethanol induced gastric ulcers, where OXT aggravated the formation of ethanol induced gastric ulcers. This effect may be due to decreased gastric mucosal blood flow. Hence, it can be suggested that peripherally or centrally released OXT decreases the gastric acid secretion and gastric mucosal blood flow by affecting vagal nerve activity. There are several OXT binding sites in the brain as mentioned earlier in the introduction, furthermore, OXT is also known to increase the responsiveness of α2 adrenoceptors in locus coeruleus of the brain381, and recent reports indicate that OXT also increases the α2 adrenoceptors responsiveness in telencephalic and diencephalic regions of the brain382. It is well known that activation of central α2 adrenoceptors reduces gastric acid secretion383. Since, there are reports on the opposite effects of OXT, when injected to different regions of the brain. It is difficult to speculate the site of action of OXT in the brain.
Atosiban, when given alone centrally produced a proucerogenic effect in pylorus ligated rats and in acetic acid induced chronic gastric ulcers indicating that OXT may have a physiological role in the regulation of gastric acid secretion and gastric cytoprotection.

OXT when administered by subcutaneous or intracerebroventricular route may cause a inhibition of the release of endogenous OXT from posterior pituitary and from PVN and SON in the brain by feed back mechanism. Since, subcutaneous administration of OXT produced a decrease in gastric acid secretion and gastric and duodenal ulcers, it may be suggested that peripherally administered OXT enters the brain in sufficient quantities, which may be equal or higher than physiological concentration of OXT in the brain. Unlike, PRL where a dose dependent effect was not observed due to hyperprolactinemia, OXT when given either by s.c or i.c.v routes produced a dose dependent effect indicating the free transfer of OXT from plasma to CSF.

Agents like CCK and lithium chloride are known to increase the plasma OXT levels, both these agents have been reported to reduce the gastric acid secretion. CCK produces satiety, and this effect is reported to be due the release of OXT. On the other hand, lithium chloride prevents the development of stress induced gastric ulcers. From the findings of the present study, it can be suggested that OXT may be one of the mediators, through which these agents produce a reduction in gastric acid secretion.

**Effect of oxytocin on prolactin secretion:** Since, opposite effects for OXT and PRL were obtained in the present study, it was decided to study the effect of OXT on PRL secretion. In the present study, OXT did not produce any significant change in serum PRL levels. The issue of whether OXT possesses an ability to release PRL from pituitary gland is both confused and controversial. Some authors observed no stimulation of the release of PRL after single intra-arterial dose of OXT (0.1 mg). However, using a higher dose of OXT (2 mg) few others observed a brief surge of PRL release 5 min following OXT administration in male rats. In contrast, a large dose of OXT (5 mg) used appeared to inhibit PRL release in lactating female rats. All the above
observations were made 5 min after OXT administration. Since, administration of OXT (s.c and i.c.v) did not alter serum PRL levels after 30 min of administration, PRL antagonizing OXT’s effect on gastric and duodenal ulcers is ruled out.

Lactation is associated with increased gastric acid secretion. This increased gastric acid secretion was due to increased vagal activity\textsuperscript{14}. The effect of pregnancy and lactation on gastric and duodenal ulcers has been studied in rats. It is reported that pregnancy reduces the development of gastric ulcers induced by dimaprit in rats\textsuperscript{389}, this effect was seen till 4 days after delivery. But, after this no effect on the development of gastric ulcers was noted. The authors of this report speculated that the antiulcer effect seen during pregnancy may be due to the sex hormones, as estrogen and progesterone are known to have antiulcer effect\textsuperscript{390}. The antiulcer effect seen for 4 days after the parturition may be also due to these sex steroids, however, work carried out after this reports suggested that OXT influences gastric acid secretion, as detailed earlier. Although there are no reports, which directly evaluated the effect of PRL, the effect of PRL inhibiting factor, dopamine on gastric and duodenal ulcers has been studied in detail. These reports indicated that dopamine has gastric antisecretory effect\textsuperscript{362}, furthermore, PRL releasing factor, TRH is known to increase gastric acid secretion\textsuperscript{352}. Evaluation of the effect of lactation on gastric acid secretion and gastric and duodenal ulcer will give a clear idea about the simultaneous action of these hormones on gastric acid secretion and gastric cytoprotection, this study could not be carried out because of the ethical considerations. Exogenous administration of PRL and OXT simultaneously to study their combined effect would not have substituted for effect of lactation on gastric acid secretion and gastric cytoprotection, as lactation is a complex mechanism involving the release of these hormones in phases. Serum OXT concentration is known to increase only during first 5 min of the lactation and later after 30 min of the total 45 min suckling period studied\textsuperscript{391}. in contrast the serum PRL is known to increase throughout the suckling period. However, the findings of the present study can be extrapolated to indicate that the gastric hypersecretion seen during the lactation may be due to PRL, as increase in plasma OXT is seen only for short periods of lesser duration during suckling in the rat.