The mechanisms and control of gastric secretion have been explained physiologically by cephalic, gastric, and intestinal phase, each of which being regarded as an independent neural or humoral regulatory process. The recent progress in the study of gastrointestinal hormones and other related fields seems, however, to be urging one to the reevaluation of the classical explanation and the establishment of the new reasonable theory for the mechanisms and control of gastric secretion. It is clear that newly developing concepts are influencing not only physiological, but also clinical studies. This paper discusses both basic and clinical problems concerning the mechanisms and control of gastric secretion from new points of view.

I. Physiological review of the mechanisms and control of gastric secretion

1. Parameters in gastric juice and gastric secretion

It has been demonstrated in our previous study\(^1\) that the dose response curves for betazole hydrochloride stimulation were different between acid and pepsin in the dog with gastric fistula. On the other hand pepsin is known to be secreted frequently in some cases of achlorhydria associated with various gastric diseases including atrophic gastritis\(^2\). These findings strongly suggest that problems involved in the mechanisms and controls of gastric secretion should be discussed separately among parameters in gastric juice at the level of both physiology and pathophysiology, although many limitations are recognized to exist that prevent this new approach.

2. Acid secretion

1) Neural regulation of acid secretion

The present view concerning neural regulation of acid secretion may be summarized as follows: a) vagal regulation contains both neural and gastrin-mediated humoral mechanisms, b) neural part of vagal regulation contains not only stimulatory, but also inhibitory process\(^3\)\(^4\) which is seen in its hepatoduodenal branch c) neural stimulation of acid secretion via vagus is mediated by vago-vagal cholinergic reflex (long reflex) as well as intramural local cholinergic reflexes such as oxynto-oxynctic, pyloro-pyloric, oxynto-pyloric and pyloro-oxynctic reflexes (short reflex)\(^5\).

2) Humoral regulation of acid secretion

Humoral regulation of acid secretion consists of the gastrin-mediated acid stimulatory process (gastric phase) and the enterogastrone-mediated acid inhibitory process (intestinal phase). Enterogastrone\(^6\) is regarded to represent a group of active substances such as secretin, GIP, VIP etc.. Since the intragastric pH-mediated feedback mechanism on gastrin release has been well established\(^7\), humoral inhibition of acid secretion is equipped with two types of self-control mechanism, namely the intragastric pH-mediated feedback mechanism (short loop) and the enterogastrone-mediated feedback mechanism (long loop). Secretin is released by acid and lowers blood gastrin level, beside its direct inhibitory action on...
Vagus also takes part in these processes\(^{(4,9)}\). On the other hand the fact\(^{(10)}\) that increased synthesis and release of gastric prostaglandin E accompanies vagal stimulation of gastric acid secretion suggests that the enterogastrone-mediated acid inhibitory process may be extended to gastric prostaglandins, thereby the term "intestinal phase" becomes insignificant.

3) Regulation of acid secretion at parietal cell level

It has been suggested that acid secretion of parietal cell may be under the dual influence of two intracellular cyclic nucleotides\(^{(11)}\). Cyclic AMP appears to have an inhibitory control on acid secretion, whereas cyclic GMP apparently mediates stimulation of the secretion. On the other hand, Kasbekar\(^{(12)}\) reported that the secretagogue-induced tachyphylactic gastric mucosa cannot be restimulated by the same secretagogue once it has become refractory, but can be stimulated by other secretagogues under certain rule observed among acetylcholine, gastrin pentapeptide and histamine. On the basis of these findings, he suggested that tachyphylaxis may be the result of depletion of endogenous secretagogues and also of differential inactivation of secretagogue sensitive receptor sites on intracellular adenyl cyclase. However, the details of mechanisms and control of acid secretion at parietal cell level remains to be elucidated.

3. Pepsin secretion

The stimulatory mechanisms of pepsin secretion were summarized tentatively in Fig. 1, but its inhibitory mechanisms are not clear. It is noteworthy that physiological concentration of HCl stimulate pepsin secretion, when placed in contact with gastric mucosa, through intramural local cholinergic reflex\(^{(13)}\), and also with duodenal mucosa, through release of secretin. It should be pointed out that all stimulatory mechanisms require vagal innervation of pepsin-secreting cells for the full display of their stimulatory effect\(^{(14)}\). A lot of studies are needed to clarify the mechanisms and control of pepsin secretion including the study at its isozyme level.

II. Review of clinical problems related to the mechanisms and control of gastric secretion

The disturbance of the mechanisms and control of gastric secretion is known to play an important role in pathogenesis and/or pathophysiology in certain diseases. In this chapter the discussion about these clinical problems will be centered to peptic ulcer and related clinical entities.

1. Peptic ulcer

Difference in the mode of gastric secretion between gastric and duodenal ulcer has been explained partly by the disorder in its regulatory mechanisms. Hypersecretion seen during basal secretion in duodenal ulcer is known to be caused by hyperactivity of vagus nerve\(^{(5)}\). On the contrary no remarkable contribution of gastrin has been found concerning the development of secre-
tery difference between gastric and duodenal ulcer probably due to the feedback mechanism controlling gastrin release through intragastric pH. However, secretin has been shown to be partly responsible for the development of gastric hypersecretion in duodenal ulcer through a disturbance in its release. Therefore, it is clear that both neural and humoral regulatory mechanisms are involved in pathophysiology of peptic ulcer. These findings indicate that anticholinergic drugs are effective in the treatment of duodenal ulcer, and also that secretin may be one of the choices for the same purpose. Fig. 2 illustrates a case of multiple duodenal ulcer in whom the administration of secretin could heal finally the long standing intractable ulcer lesions following 6 months of ordinary treatment.

2. Retained excluded pyloric antrum
Retained pyloric antrum, kept away from the food-passing route surgically, is a typical example of disorder in gastrin mechanism. In this condition intragastric pH is maintained always high in the retained antrum leading to hypersecretion in the remnant of resected stomach, which contains fundic mucosa, and responds to the accelerated gastrin release. Involvement of gastrin synthesized in the retained pyloric antrum in causing hypergastrinemia, is demonstrated by the decrease in blood gastrin level in response to HCl infusion into retained pyloric antrum as shown in Fig. 3. Therefore the surgical removal of retained excluded antrum is the choice of treatment to prevent the future recurrence of peptic ulcer.

3. Zollinger-Ellison syndrome
Zollinger-Ellison syndrome is regarded to represent a special type of disorder in humoral regulatory mechanisms of gastric secretion. In this clinical condition gastrin is synthesized heterotopically in pancreas adenoma in addition to orthotopic synthesis in pyloric antrum. It is self-evident that the feedback mechanism controlling gastrin release through intragastric pH can not be applied to heterotopic gastrin. Thus one of the outstanding pathophysiological features in Zollinger-Ellison syndrome is the coexistence of acid hypersecretion and hypergastrinemia. However, since the paradoxical response of blood gastrin to secretin has been pointed out in this syndrome, it is presumed that an essential pathophysiological difference exists between ordinary peptic ulcer and Zollinger-Ellison syndrome concerning the mechanisms and control of gastric secretion as illustrated in Fig. 4. Namely secretin released from duodenal mucosa into blood circulation usually acts to control acid secretion in three ways: a) lowering blood gastrin level, b) inhibition of acid secretion at parietal cell level, and c) stimulation of alkaline pancreatic secretion. However, in Zollinger-Ellison syndrome secretin elevates blood gastrin level probably through the acceleration of gastrin release from pancreas adenoma and leads to the formation of pathophysiological vicious cycle together.
with gastrin and acid secretion which may lead this syndrome to catastrophe. Therefore, total gastrectomy is regarded to be the reasonable approach to cut this pathophysiological vicious cycle at the safest, easiest and surest site.

III. Summary
In addition to the physiological review, clinical problems related to the mechanisms and control of gastric secretion were discussed focussing on peptic ulcer and related clinical entities. It was stressed that various disorders of the mechanisms and control of gastric secretion, correspond to characteristic clinical features respectively and require the special approach for the treatment.

REFERENCES
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