Gastric Physiology

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Overview

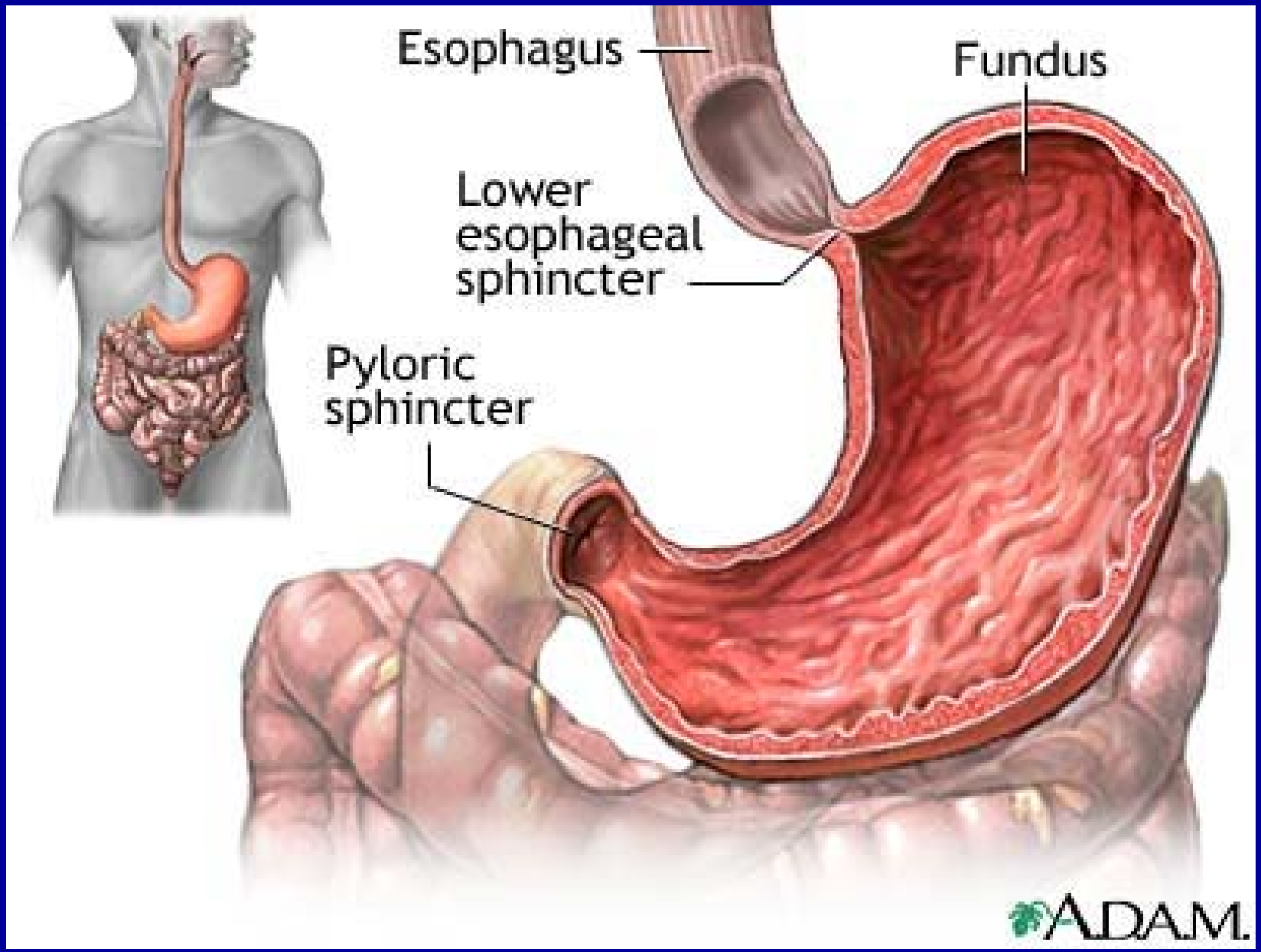
- Gastric Motor Activity
- Gastric Secretory Activity
- Board Questions

Gastric Motor Activity

- Main functions of gastric motility
  - Accommodate and store ingested meal
  - Grind down solid particles (tituration)
  - Empty all constituents of the meal in a carefully controlled and regulated fashion into the duodenum

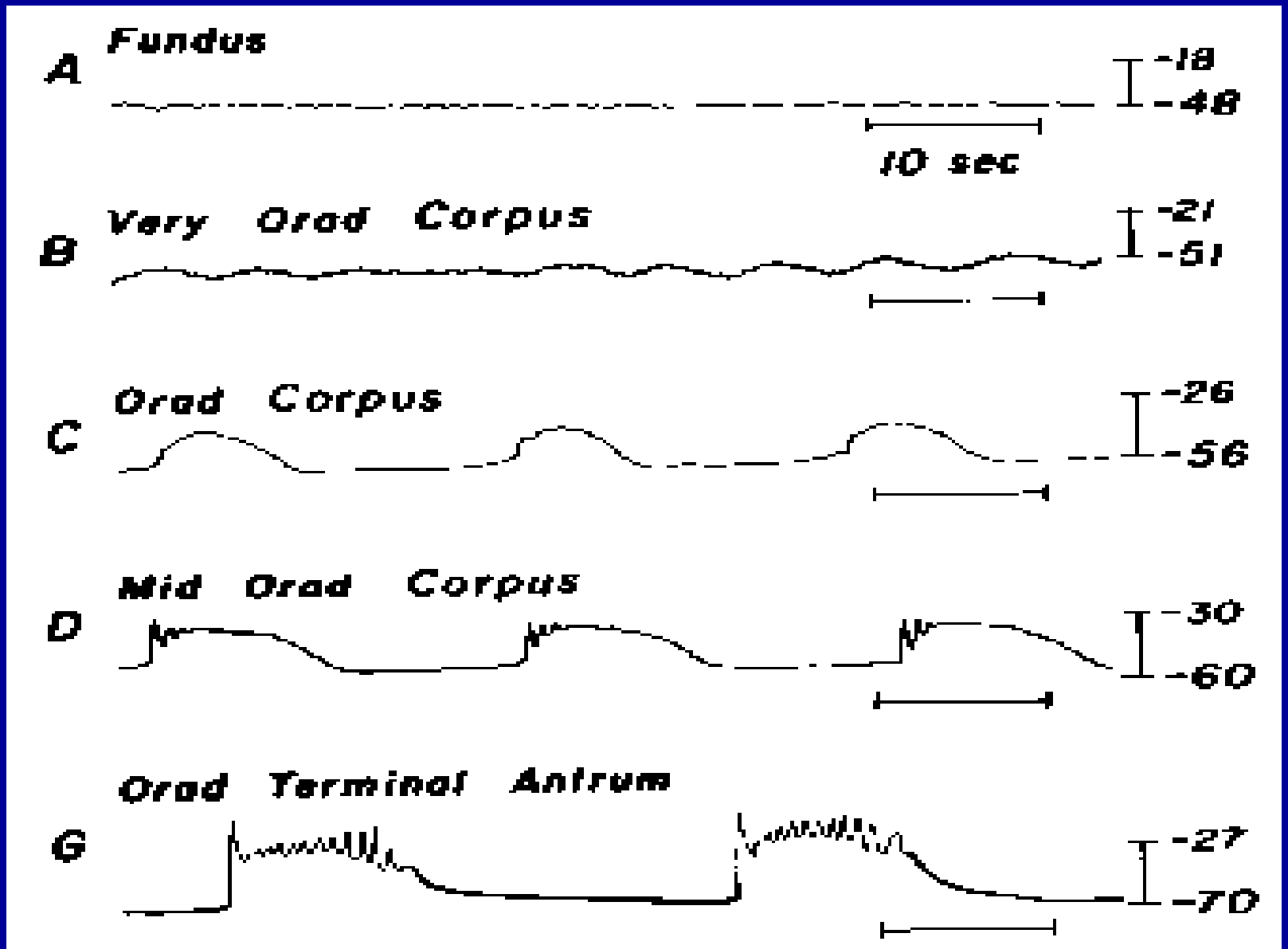
Gastric Anatomy

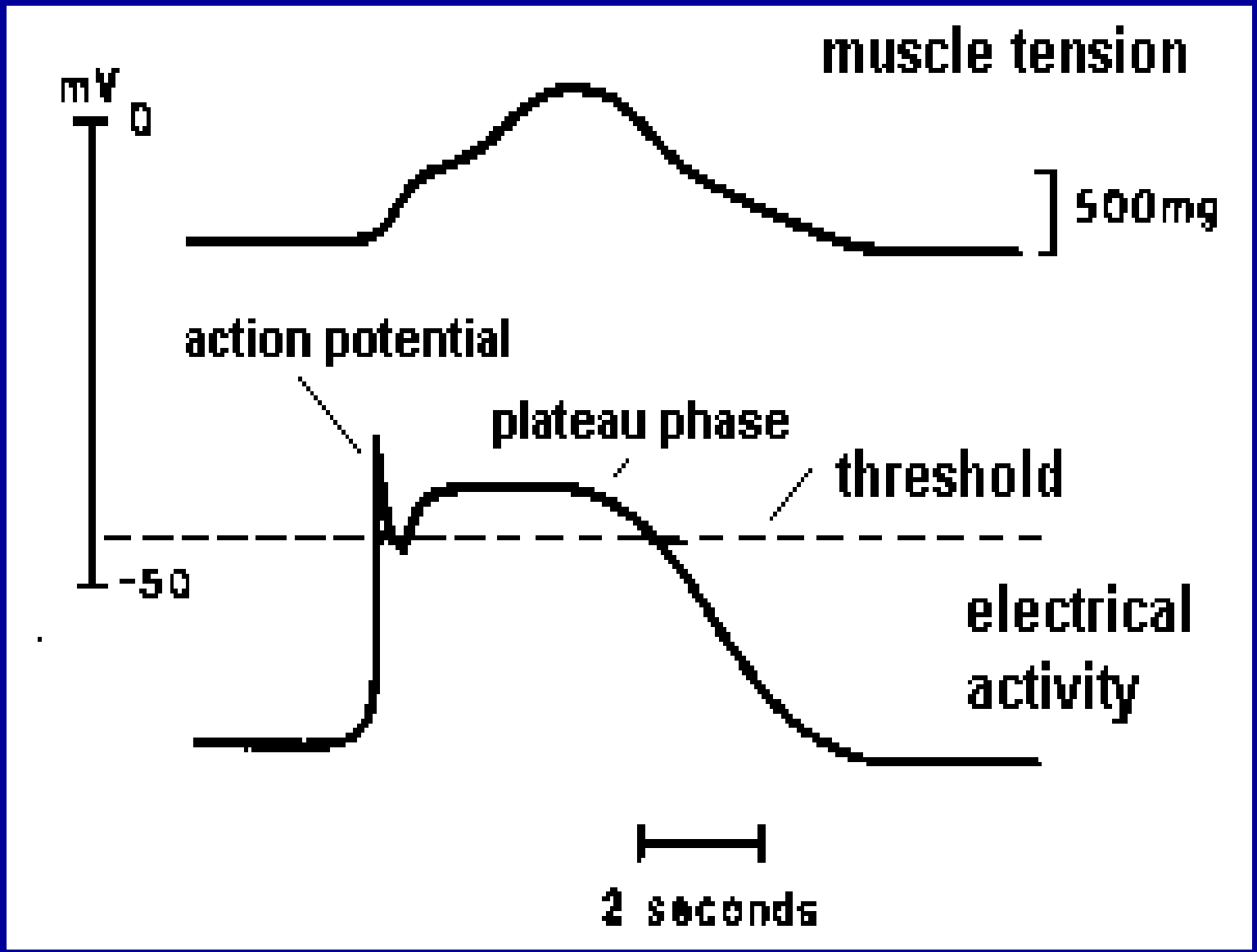
- 3 distinct regions
  - Proximal – cardia, fundus, proximal body
  - Distal – distal body, antrum
  - Pylorus


Esophagus
Fundus
Lower
esophageal
sphincter
Pyloric
sphincter
A.D.A.M.

Electrophysiology

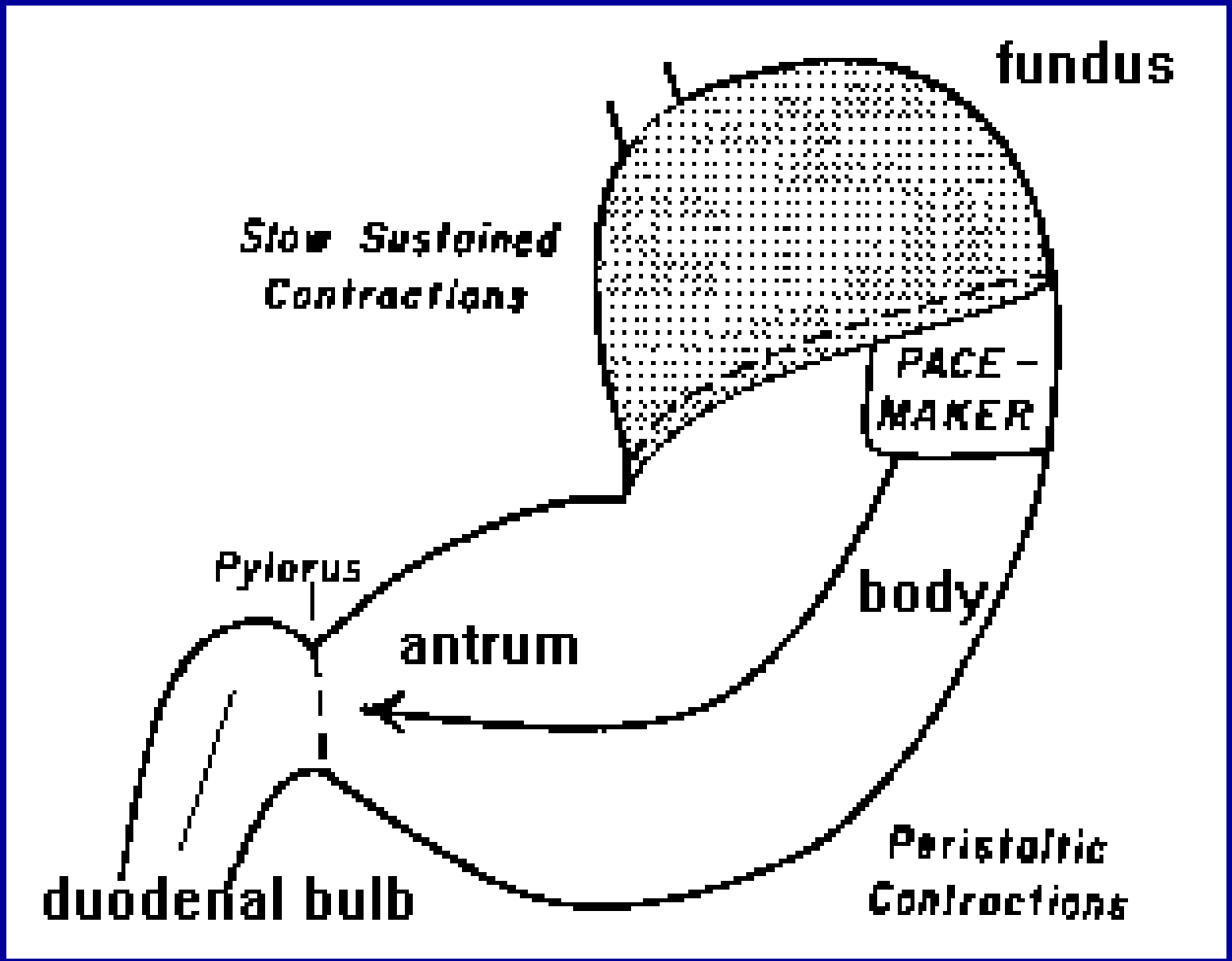
- Slow wave – omnipresent, highly regular and recurring electrical pattern in GI tract
- Does not lead to contractions, but maximal frequency of contractile activity is directly related to slow wave frequency
- Contractions are related to spike potentials
- 3 cycles/min in stomach


A
Fundus
-18
-48
10 sec
B
Very Orad Corpus
-21
-51
C
Orad Corpus
-26
-56
D
Mid Orad Corpus
-30
-60
G
Orad Terminal Antrum
-27
-70


muscle tension
mV
0
500mg
action potential
plateau phase
threshold
-50
electrical
activity
2 seconds

Electrophysiology

- Slow waves thought to originate in “gastric pacemaker” site along the greater curvature in the proximal to middle body
- Migrate in both circumferential and longitudinal directions
- Electrical signals do not traverse the pylorus
- ICC’s (interstitial cells of Cajal) in myenteric plexus generate slow wave activity


fundus
Slow Sustained Contractions
PACE - MAKER
Pylorus
body
antrum
duodenal bulb
Peristaltic Contractions

Electrophysiology

- Fundic smooth muscle cells are electrically silent – resting membrane potential is already above the mechanical threshold
- Generates tone – AP not generated – neural and hormonal input modulates tone rather than generating peristaltic contractions

GI Motor Activity

- Motor activity is highly organized into a distinct and cyclically recurring sequence of events known as MMC (migrating motor complex)
- 3 distinct phases of motor activity
  - I – quiescence
  - II – random and irregular contractions
  - III – burst of uninterrupted phasic contractions
- Patterns of MMC activity commence and end simultaneously at all sites

Fasted Stomach

- Phase III
  - Basal tone in LES in increased and exhibits superimposed phasic contractions
  - Tone increases in proximal stomach
  - One cycle/min high-amplitude waves develop in body
  - Distal antrum 3-5 cycles/min
  - Antropyloroduodenal coordination increases and high-amplitude contractions propagate through the antrum across the pylorus

Fasted Stomach

- Extrinsic nerves (vagus) and hormonal factors (motilin) are involved
  - Phase III – may be induced by motilin released from proximal duodenum
  - Phase II – mediated through vagus

Fed Stomach

- Initiation of swallow – fundus undergoes vagally mediated receptive relaxation
- As meal enters stomach tone and phasic contractions in proximal stomach are inhibited
  - Accommodation – 2-3 fold increase in gastric volume

Fed Stomach

- Fundic tone – balance between cholingeric (excitatory) and nitrergic (inhibitory) input
- Fasting – cholinergic dominates
- Meal – accommodation response triggered by distention-induced stimulation of mechanoreceptors
- Mediated by vasovagal reflex – fundic relaxation may be induced by activation of inhibitory input or the inhibition of excitatory vagal efferents to the fundus

Fed Stomach

- NO is primary inhibitor of fundic tone
- Other factors modulate fundic tone
  - Relaxation
    - Antral distention (gastrogastric reflex)
    - Duodenal acidification
    - Lipid and protein (duodenogastric reflex)
    - Colonic distention (cologastric reflex)

Fed Stomach

- Food ingested results in abolition of cyclical pattern of MMC
- Replaced by random contractions called fed pattern
- May last 2.5-8 hours

Gastric Emptying

- Gastric emptying dependent on the propulsive force generated by tonic contractions of proximal stomach and resistance presented by antrum, pylorus, duodenum
- Fundamental property of stomach – ability to differentiate among different types of meals and the components of individual meals

Liquids

- Liquids rapidly disperse and begin to empty without lag period
- Non-nutrient liquids empty rapidly
- Nutrient containing liquids are retained longer and empty more slowly

Liquids

- Emptying of liquids follows a simple, exponential pattern
- Rate influenced by volume, nutrient content and osmolarity
- Rate of emptying determined by gastric volume and duodenal feedback mechanisms
  - Antroduodenal pressure gradient is primary factor generating liquid emptying

Solids

- 2 phases – initial lag phase followed by a linear emptying phase
- Solid component is first retained in proximal stomach
- As liquid empties, solid moves to antrum and is emptied
- Essential component of normal response is ability of antropyloric region to discriminate solid particles by size and restrict emptying of particles >1mm in diameter

Solids

- Antropyloric mill grinds down (titurates) larger particles to smaller ones
- During tituration, solid emptying does not occur
- Duration of lag phase is directly related to size and consistency of solid component of the meal
  - Typical solid-liquid meal - ~60min

Solids

- Tituration – coordinated high-amplitude waves originate in proximal antrum and are propagated to pylorus
- Pylorus opens and duodenal contractions are inhibited permitting trans-pyloric flow of liquids and suspended or liquefied solid particles
- When liquids and solids reach distal antrum, pylorus closes promoting retropulsion of particles too large to have been exited

Solids

- Pylorus regulates passage of material
  - Relatively narrow and fixed lumen
  - Maintenance of pyloric tone
  - Generation of isolated pyloric pressure waves

Fatty Foods

- Liquid at body temperature
- Float on top of liquid layer but empty more slowly
- Products of fat digestion in duodenum are potent inhibitors of gastric motor events and gastric emptying

Indigestible Solids

- Not emptied in immediate post-prandial period
- Must await MMC activity
- Swept out during phase III

Gastric Secretion

- Stomach secretes water, electrolytes (H^+, K^+, Na^+, Cl^-, HCO_3^-), enzymes with activity at acid pH (pepsin, lipase) and glycoproteins (intrinsic factor, mucins)

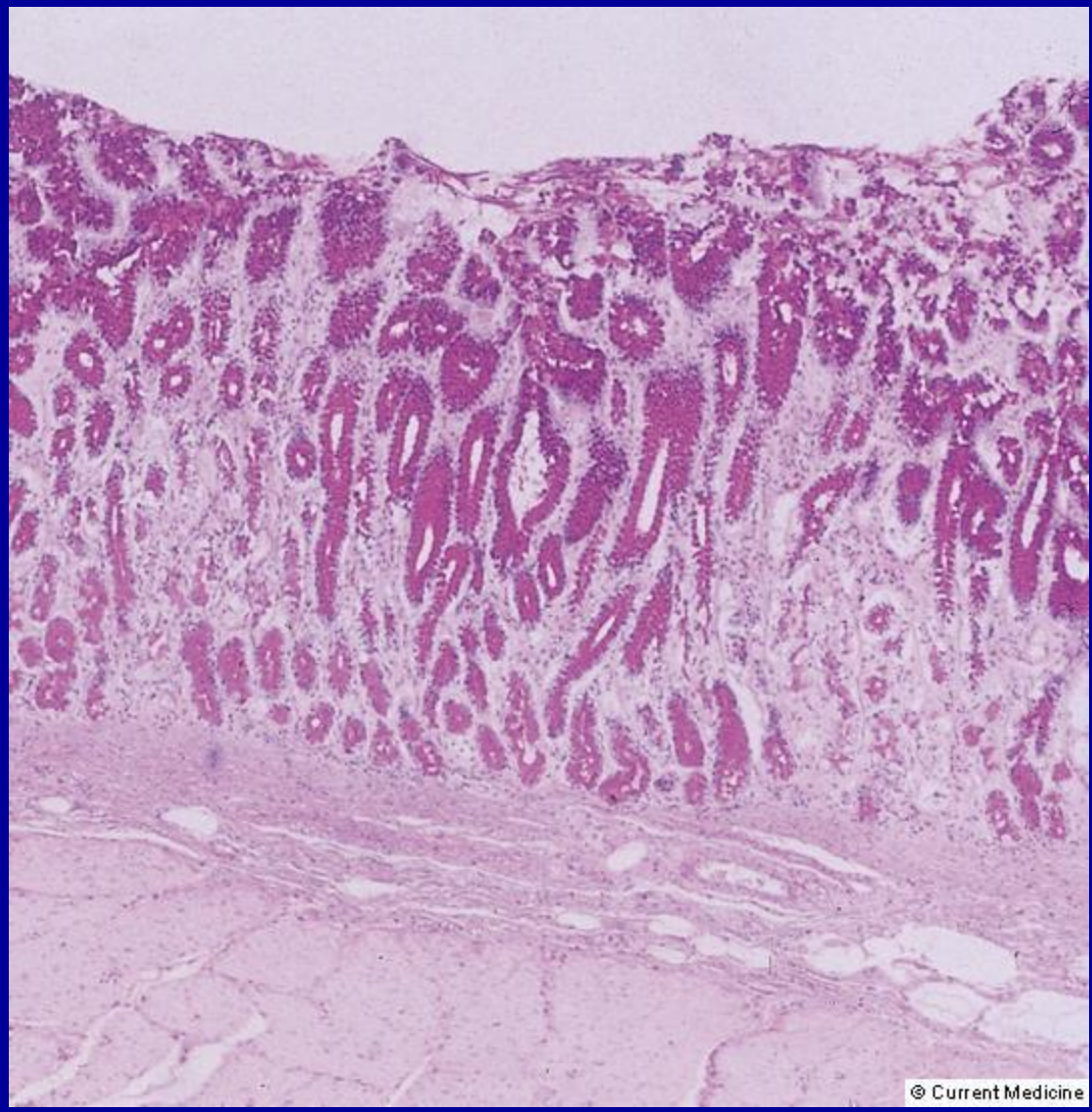
Anatomy

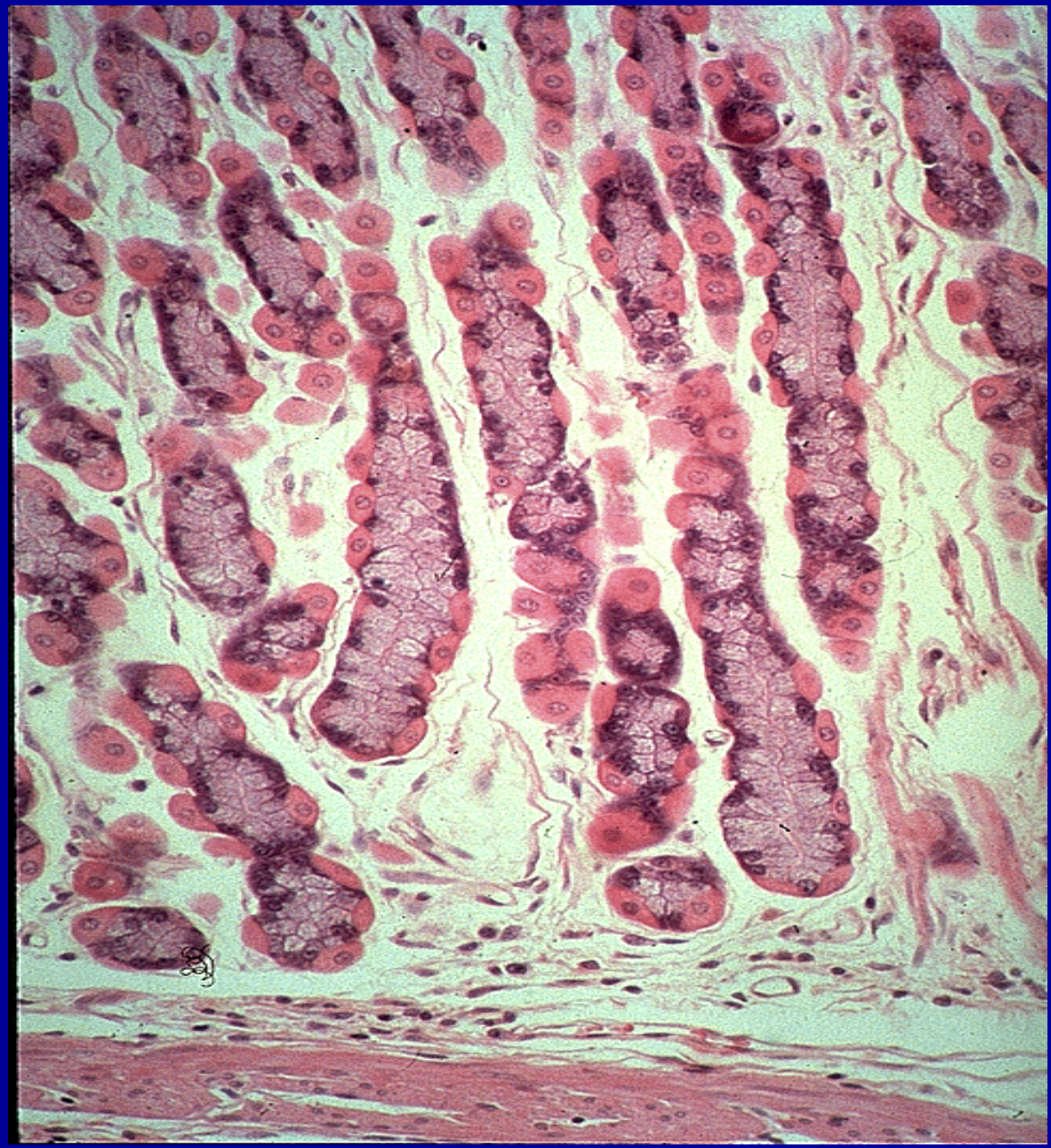
- Mucosal layer composed primarily of simple layer of columnar epithelial cells
- Epithelial lining is invaginated by gastric pits – give gastric glands access to gastric lumen
- Different anatomic regions have different glands

Anatomy

- Cardia – mucus, endocrine and undifferentiated cells
- Fundus & body – oxyntic glands
  - Parietal, chief, endocrine, mucus neck, undifferentiated cells
- Antrum & pylorus – pyloric glands
  - Endocrine, mucus neck, G-cells

Microscopic view of the oxyntic and antral mucosa (C)





Exocrine Epithelial Cells

- Originate from stem cells located in mid-region (neck) of gastric glands
- Columnar cells lining the gastric surface and its pits (surface cells) secrete Na^+ in exchange for H^+, HCO_3^-, mucins, and phospholipids
- Mucus cells secrete mucus and group II pepsinogens (PGII)
- Parietal cells secrete HCl and intrinsic factor (IF)
- Chief cells secrete PGI

Endocrine and Endocrine-like Cells

- Endocrine cells
  - G cells – secrete gastrin
- Paracrine cells
  - D cells – secrete somatostatin
  - Enterochromaffin-like (ECL) cells – secrete histamine

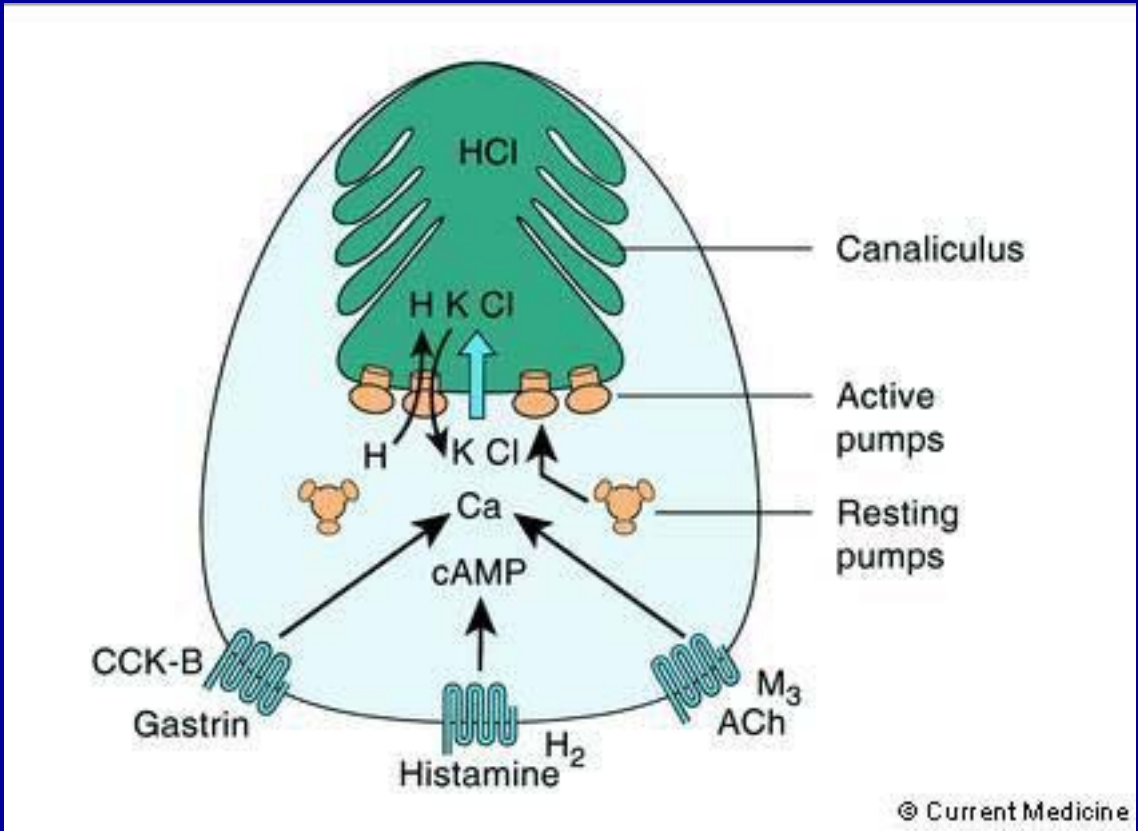
Parietal Cell

- Secretes protons (H^+) or hydronium (H^+O_3) ions through H^+,K^+–ATPase (proton pump)
- Against a concentration gradient
- Active, energy-dependent process
- Contains abundant mitochondria
- ATP provides energy

Parietal Cell

- Stimulated by histamine, gastrin, acetylcholine
- Inhibited by somatosatin, prostaglandins

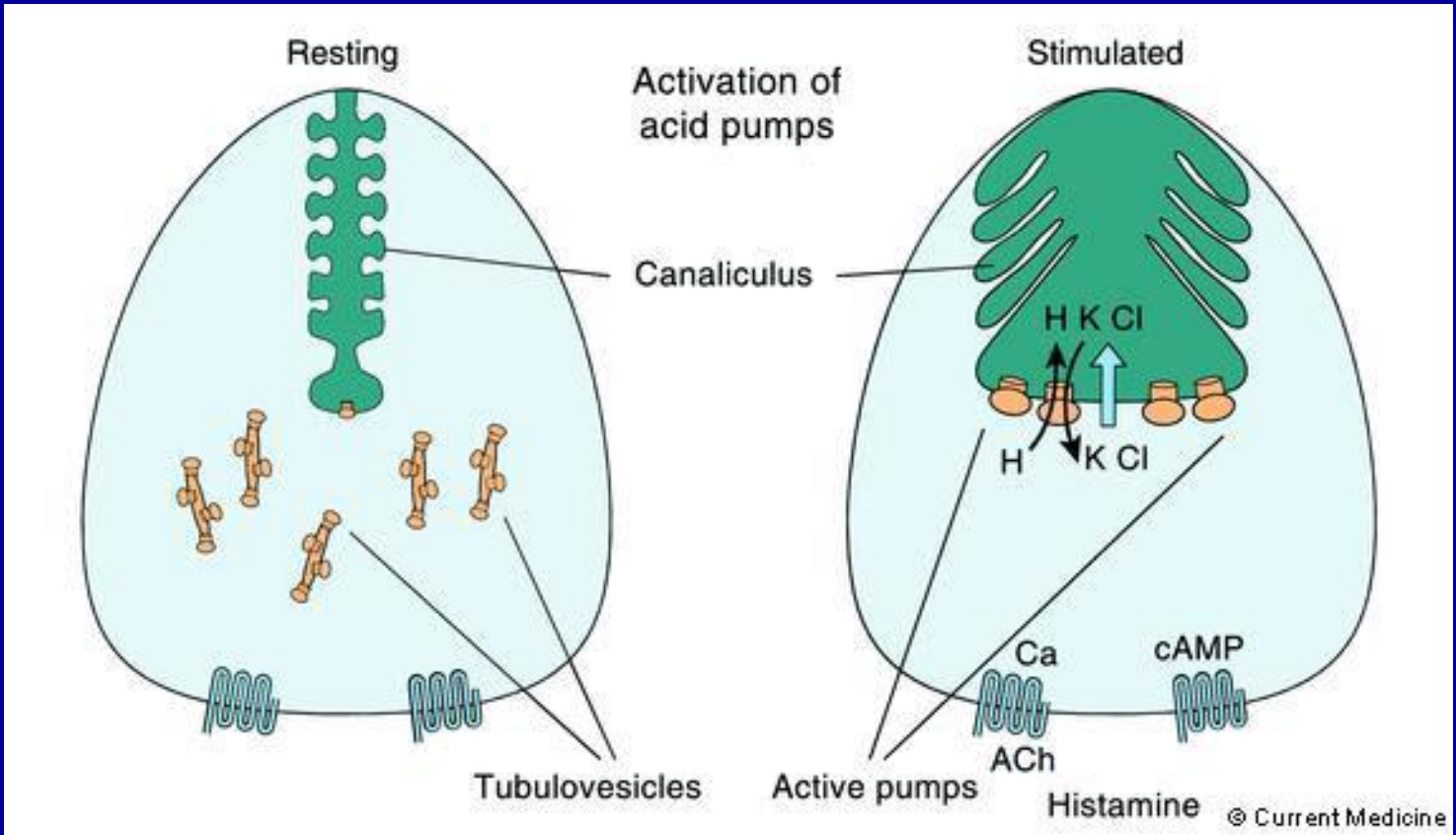
The parietal cell



Parietal Cell

- Acid generated within parietal cell from dissociation of 2 molecules of H_2O to form H_3O^+ and OH^-
- H_3O^+ is secreted by proton pump in exchange for K^+
- OH^- combines in cell with CO_2 to form HCO_3^-
- Intracellular HCO_3^- ions formed during H^+ secretion rapidly exchanged for Cl^- ions at basolateral membrane
- "alkaline tide" – rapid entry of HCO_3^- into blood from parietal cells

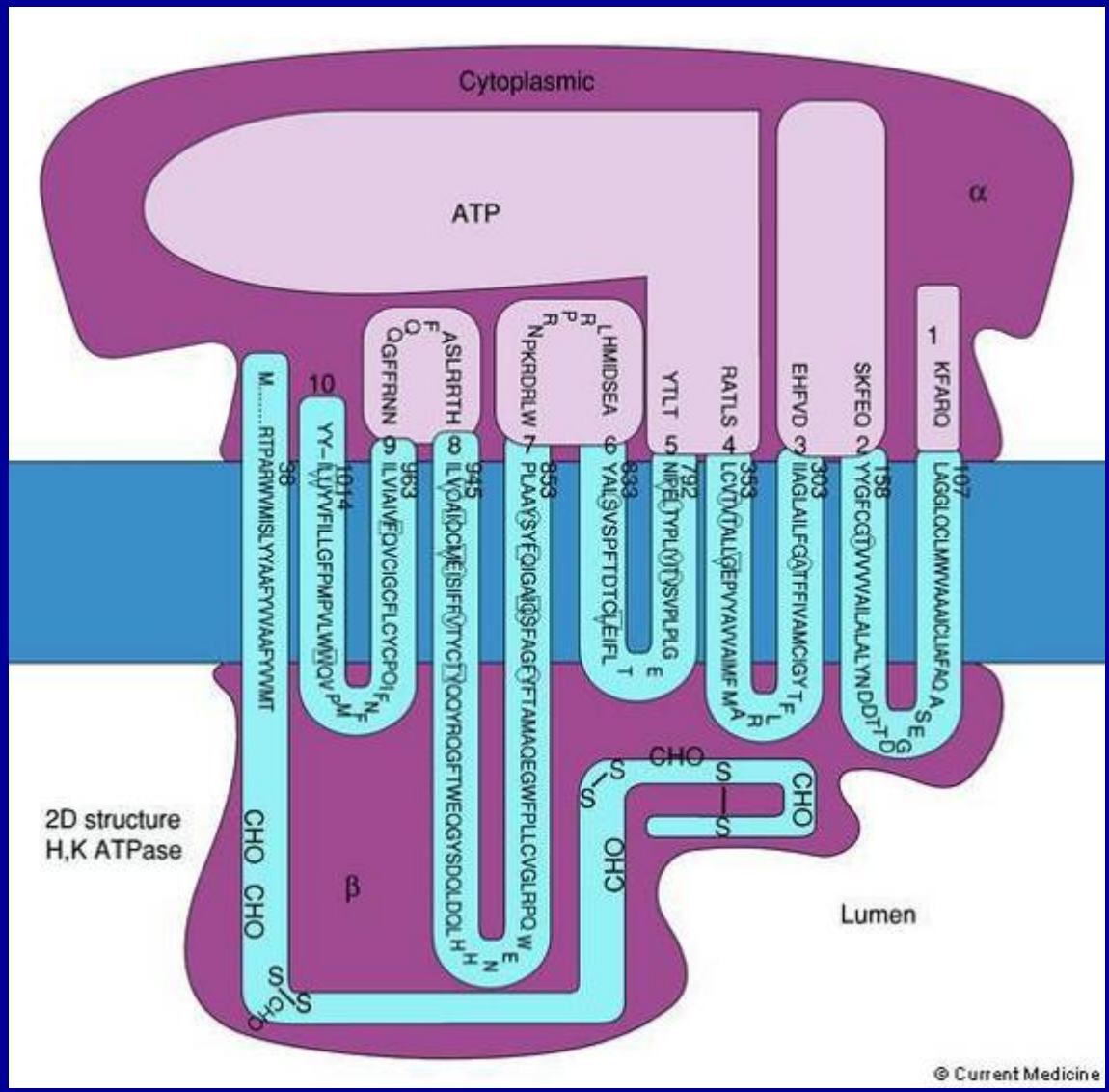
Stimulation of acid secretion



Proton Pump

- Heterodimer composed of 2 polypeptide subunits
- Larger α catalytic subunit that reacts with ATP and a smaller β subunit
- α subunit is inhibited by covalent antagonists – PPIs (substituted benzimidazoles)

Activation of the acid pump



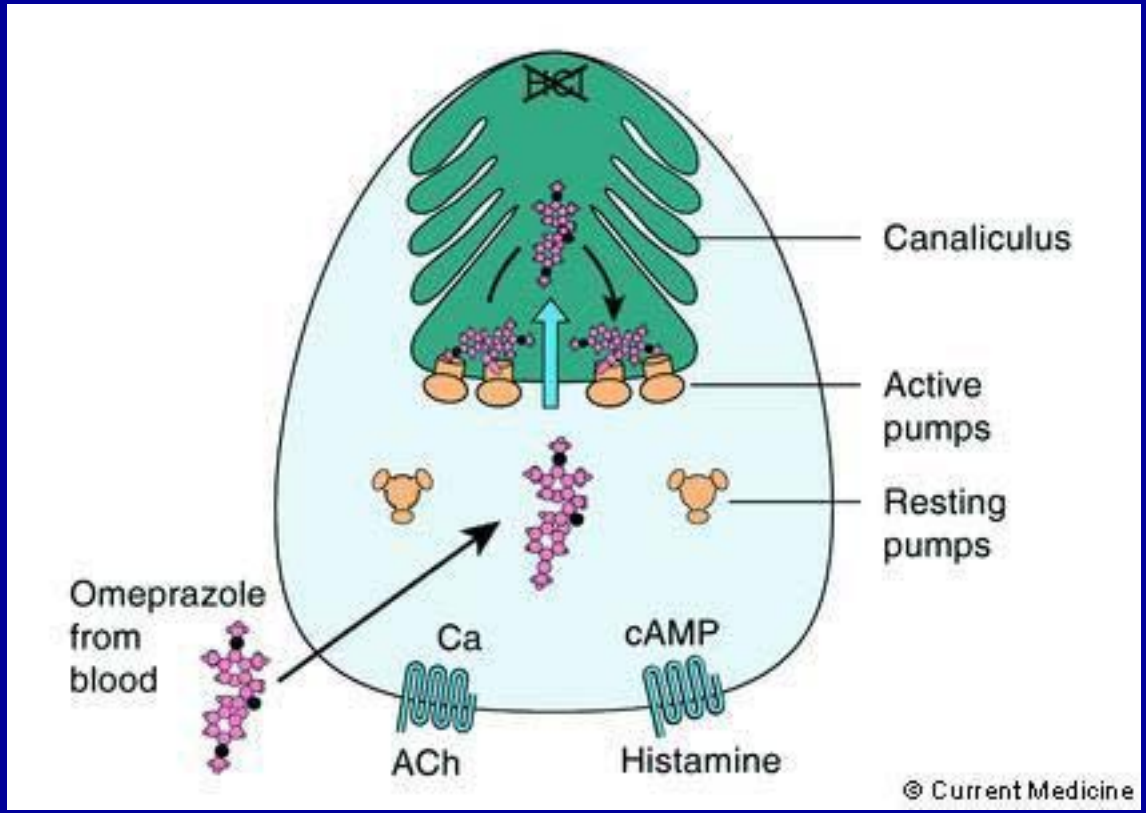
PPIs

- PPIs concentrate in the secretory canaliculi of parietal cells
- Prodrugs are protonated to their “active” ionized forms namely sulfonamides
- Bind covalently with sulfhydryl groups on cystine residues within the luminal (canalicular) domain of the α subunit of H^+,K^+–ATPase
- Cystine residue 813

PPIs

- Ion channels involved in expulsion of $H^+(H_3O^+)$ from cell and retrieval of K^+ are blocked
- Activation of H^+,K^+–ATPase is terminal step in acid secretory process
- Intragastric pH rises which increases serum gastrin

Substituted benzimidazoles (proton pump inhibitors)



PPIs

- Gastrin acts via CCK/gastrin receptors on ECL cells to increase histidine decarboxylase activity – increases histamine production
- Histamine acts on histamine$_2$ (H_2) receptor of parietal cell to increase mRNA for proton pump – attempt to up-regulate acid secretion after PPI administration

Gastrin

- Most potent endogenous stimulant of gastric acid secretion
- Major stimulant is luminal amino acids especially phenylalanine and tyrosine
- AA's decarboxylated to amines -> taken up by G cells
- Major target is fundic ECL cells which produce histamine

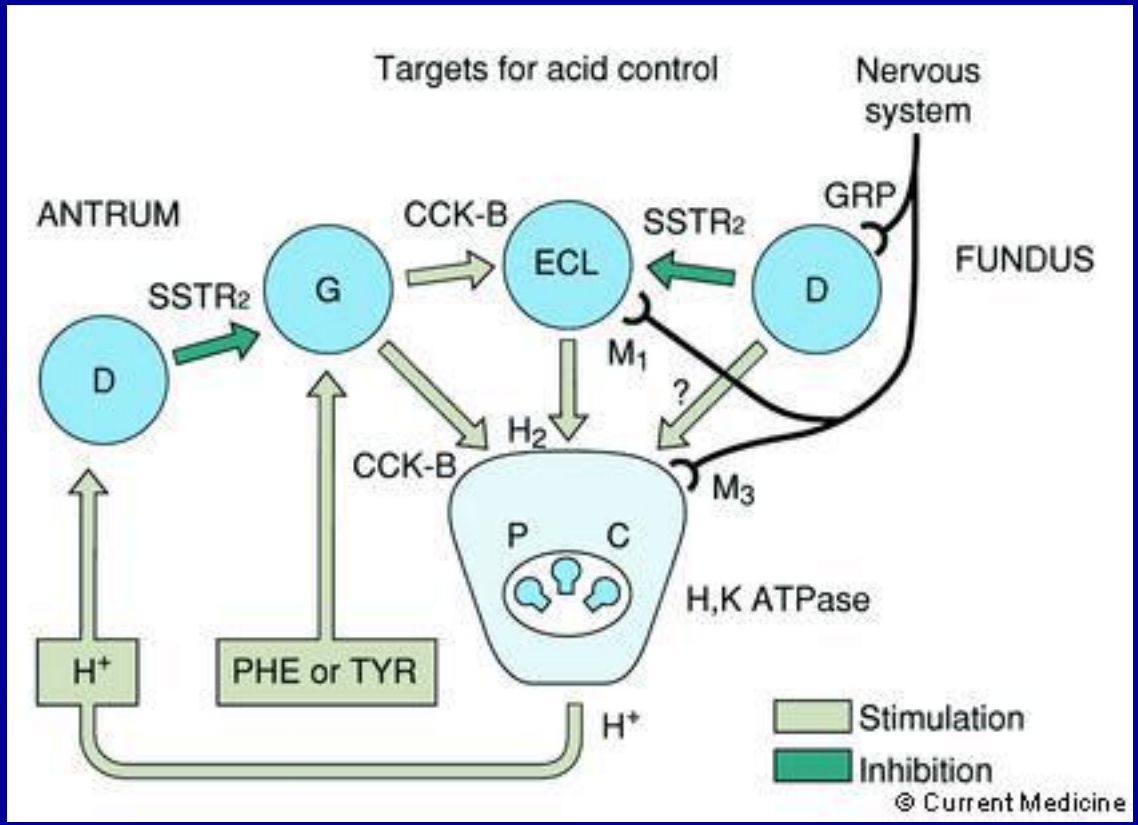
Gastrin

- When pH <3 gastrin release is inhibited by negative feedback
- Luminal H^+ activates sensory nerve endings that enhance somatostatin release from pyloric D cells which suppresses release of gastrin
- Inhibited also by CCK released into circulation by AA's and fatty acids in duodenum

Histamine

- Made by ECL cells (<1% of gastric cells)
- Stimulants – gastrin, CCK, acetylcholine
- Inhibitors – somatostatin from oxyntic D cells, ?histamine
- Hyperplasia of ECL cells occurs with hypergastrinemia

Central nervous system



Somatostatin

- Secreted by D cells
- Stimulated by CCK
- Effects H^+ secretion via inhibitory effects on oxyntic ECL cells and pyloric G cells
- D cell in pylorus stimulated by acid

CCK

- Produced by duodenal endocrine cells in response to dietary fatty acids and amino acids
- In vitro stimulates parietal cells
- In vivo inhibits acid production through D cells

Secretin

- Produced by duodenal S cells in response to H^+
- Inhibits gastric acid secretion, stimulates pancreatic HCO_3^- production

Prostaglandin E_2

- PGE analogs (cytotec) reduce gastric acid secretion to approximately same extent as H_2 blockers
- PGE_2 receptors on parietal cells that have opposite effect as H_2 receptors

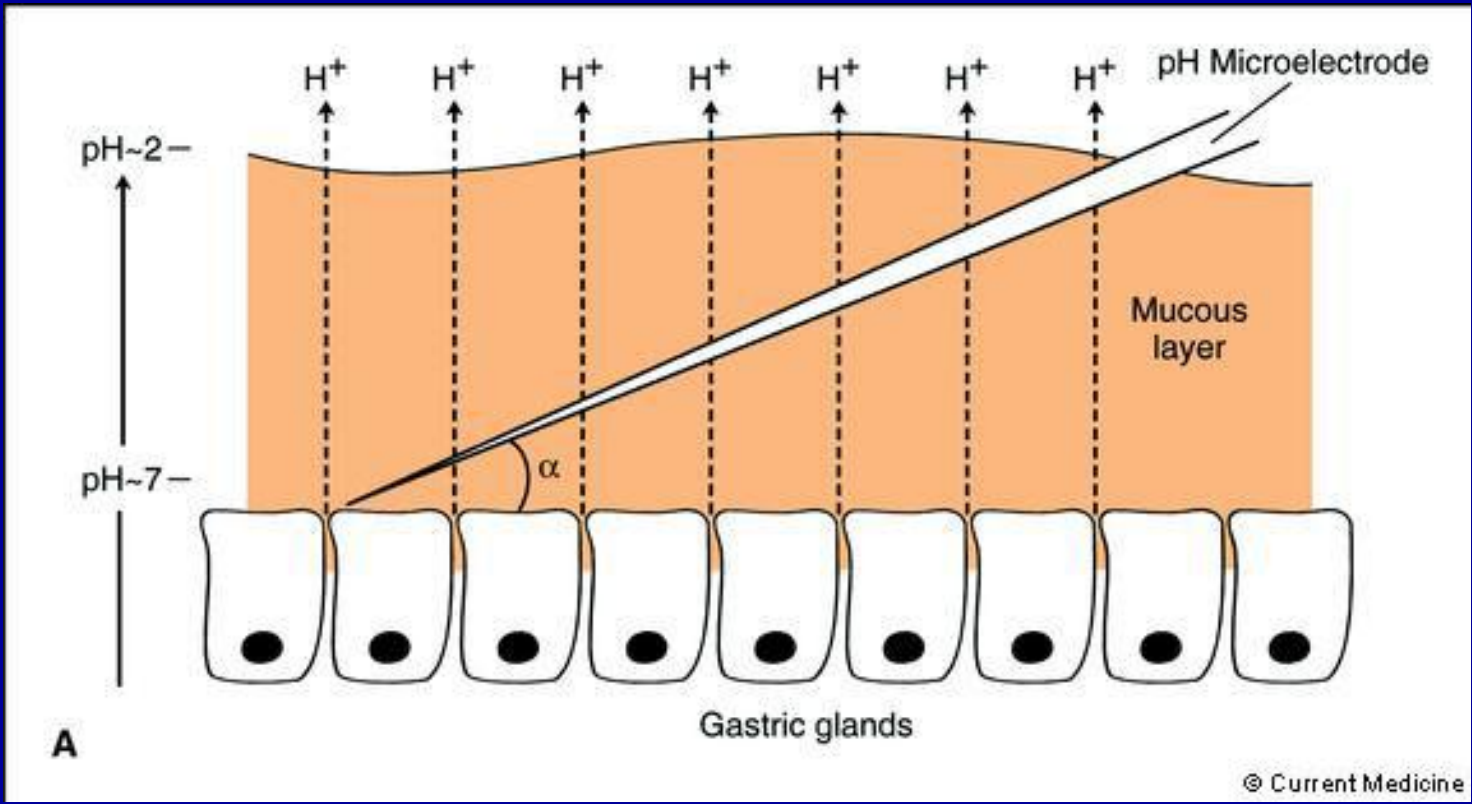
Mucus/Mucins

- Highly viscous gel-like layer of mucus 0.2-0.6mm thick covers the gastric epithelium
- 95% water, 5% mucin glycoprotein
- 2 forms
  - Thin layer adherent to gastroduodenal mucosal surface (adherent)
  - Mucin that mixes with luminal fluid and can be washed off (soluble)

Mucus/Mucins

- Adherent mucus gel is secreted continuously and degraded by pepsin
- Mucin provides lubrication and an unstirred water layer
- Mucus barrier and HCO_3^- protects surface epithelium

Continuous mucus gel adherent to gastric mucosa (A)



Bicarbonate

- Secreted by surface cells rich in carbonic anhydrase II
- Energy dependent and metabolic process
- Vagus stimulation increases HCO_3^- production
- PGE_2 stimulates

Pepsinogens

- Polypeptide proenzymes known as zymogens
- PG's converted to pepsins in gastric lumen by acid
- PGI, PGII
- Pepsin I and II are optimally active at pH 1.8-3.5, reversibly inactivated at pH 5.0, denatured at pH 7-8

Pepsinogens

- Pepsins cleave peptide bonds formed by phenylalanine and tyrosine
- PG secretion stimulated by acetylcholine analogs, histamine, gastrin, secretin
- Inhibited by somatostatin

Gastric Lipase

- Initiates digestion of dietary triglycerides
- Different properties from pancreatic lipase
- pH 4.5-5.5 vs. 6.5-7.5
- Inhibited by bile acid micelles and does not require colipase

Intrinsic Factor

- Secreted by parietal cells
- Binds cobalamin(B_{12}) to facilitate absorption
- 2 cobalamin binding proteins – IF/R
- Initially binds to cobalamin R in acidic stomach then is cleaved in duodenum and binds to IF
- Attaches to ileal mucosa
- B_{12} malabsorption may result from IF deficiency, achlorhydria or hypochlorhydria, bacterial overgrowth, pancreatic insufficiency, ileal receptor defect, ileal disease, ileal resection

Board Questions

- 1.Which one of the following is expected to be associated with a reduction in parietal cell function?

- A.misoprostol
- B.increased intracranial pressure
- C.systemic mastocytosis
- D.increase in acetylcholine
- E.increase in gastrin

Board Questions

- 2.Which one of the following situations would be expected to be associated with a reduction in serum gastrin concentrations?

- A.development of chronic atrophic gastritis
- B.administration of secretin to a patient with Zollinger-Ellison syndrome
- C.administration of secretin to a healthy subject
- D.*H.pylori* infection in a patient with duodenal ulcers
- E.taking a proton pump inhibitor for 6 months

Board Questions

- 3.Which one of the following conditions is most likely to be associated with decreased serum concentrations of vitamin B_{12}?

- A.pancreatic exocrine insufficiency
- B.a 10-day course of oral antibiotics
- C.excess secretion of intrinsic factor
- D.stimulation of parietal cell function
- E.multiple endocrine neoplasia type-1 (MEN-1) syndrome

Board Questions

- 4.An improvement in gastric mucosal defense should be associated with which one of the following?

- A.presence of gastric metaplasia
- B.decrease in gastric mucosal blood flow
- C.decrease in thickness of unstirred layer
- D.decrease in pancreatic secretion
- E.increase in mucosal prostaglandins

Board Questions

- 5.Each of the following conditions may cause elevated serum gastrin concentrations except

- A.MEN-1 syndrome
- B.Zollinger-Ellison syndrome
- C.pernicious anemia
- D.gastric carcinoids
- E.proton pump inhibitors