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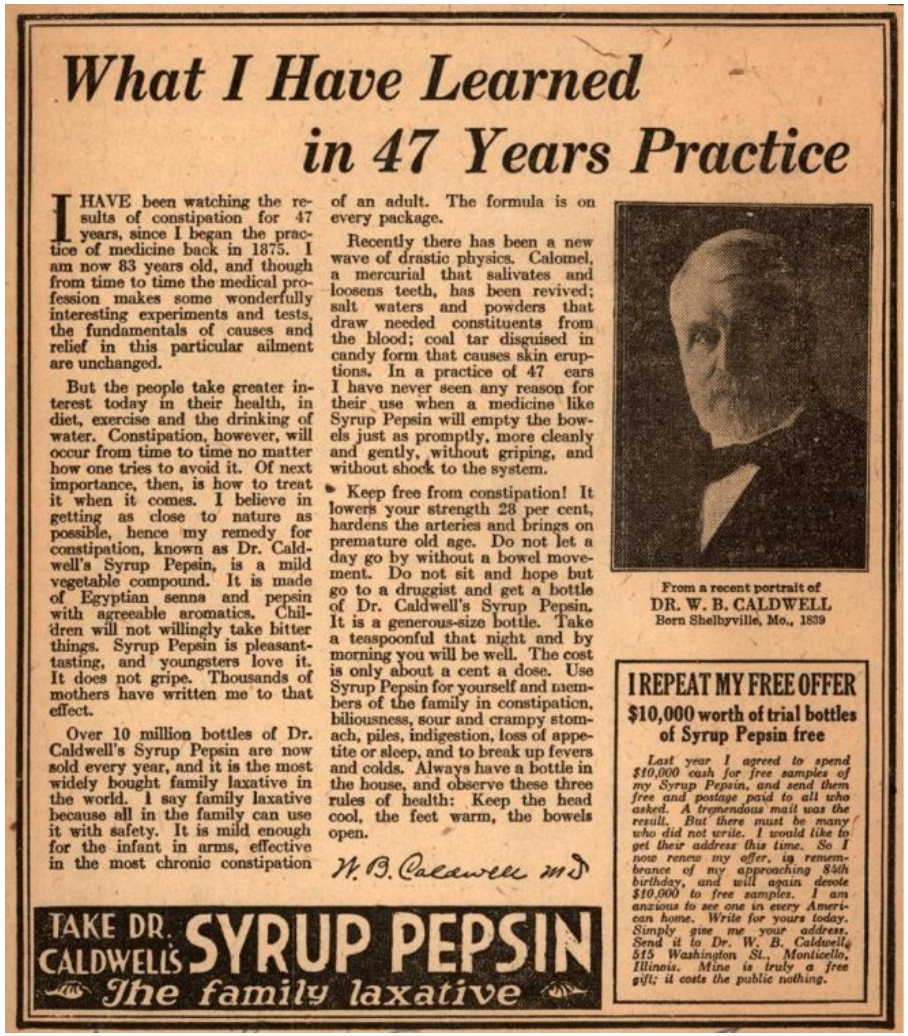

What I Have Learned in 47 Years Practice

I HAVE been watching the results of constipation for 47 years, since I began the practice of medicine back in 1875. I am now 83 years old, and though from time to time the medical profession makes some wonderfully interesting experiments and tests, the fundamentals of causes and relief in this particular ailment are unchanged.

But the people take greater interest today in their health, in diet, exercise and the drinking of water. Constipation, however, will occur from time to time no matter how one tries to avoid it. Of next importance, then, is how to treat it when it comes. I believe in getting as close to nature as possible, hence my remedy for constipation, known as Dr. Caldwell's Syrup Pepsin, is a mild vegetable compound. It is made of Egyptian senna and pepsin with agreeable aromatics. Children will not willingly take bitter things. Syrup Pepsin is pleasant-tasting, and youngsters love it. It does not gripe. Thousands of mothers have written me to that effect.

Over 10 million bottles of Dr. Caldwell's Syrup Pepsin are now sold every year, and it is the most widely bought family laxative in the world. I say family laxative because all in the family can use it with safety. It is mild enough for the infant in arms, effective in the most chronic constipation of an adult. The formula is on every package.

Recently there has been a new wave of drastic physics. Calomel, a mercurial that salivates and loosens teeth, has been revived; salt waters and powders that draw needed constituents from the blood; coal tar disguised in candy form that causes skin eruptions. In a practice of 47 ears I have never seen any reason for their use when a medicine like Syrup Pepsin will empty the bowels just as promptly, more cleanly and gently, without griping, and without shock to the system.

Keep free from constipation! It lowers your strength 28 per cent, hardens the arteries and brings on premature old age. Do not let a day go by without a bowel movement. Do not sit and hope but go to a druggist and get a bottle of Dr. Caldwell's Syrup Pepsin. It is a generous-size bottle. Take a teaspoonful that night and by morning you will be well. The cost is only about a cent a dose. Use Syrup Pepsin for yourself and members of the family in constipation, biliousness, sour and crampy stomach, piles, indigestion, loss of appetite or sleep, and to break up fevers and colds. Always have a bottle in the house, and observe these three rules of health: Keep the head cool, the feet warm, the bowels open.

W. B. Caldwell M.D.

From a recent portrait of
DR. W. B. CALDWELL
Born Shelbyville, Mo., 1839

I REPEAT MY FREE OFFER

$10,000 worth of trial bottles of Syrup Pepsin free

Last year I agreed to spend $10,000 cash for free samples of my Syrup Pepsin, and send them free and postage paid to all who asked. A tremendous mail was the result. But there must be many who did not write. I would like to get their address this time. So I now renew my offer, in remembrance of my approaching 85th birthday, and will again devote $10,000 to free samples. I am anxious to see one in every American home. Write for yours today. Simply give me your address. Send it to Dr. W. B. Caldwell, 515 Washington St., Monticello, Illinois. Mine is truly a free gift; it costs the public nothing.

TAKE DR. CALDWELL'S **SYRUP PEPSIN**
The family laxative

Question 4 LOA: 1 **ANTIEMETICS**	Name some antiemetics used in the Emergency Department.	**Ondansetron (or Granisetron or Tropisetron)** **Metoclopramide** **Prochlorperazine** Diphenhydramine (or other antihistamines). Meclizine. Hyoscine. Benzodiazepines. Chlorpromazine. Droperidol	Bold to pass
	Compare the mechanisms of action of ondansetron and metoclopramide	Act at different receptors: Ondansetron: **Peripheral 5HT3 blockade** (vagal and spinal afferents, Reduces sensory visceral output) + Central 5HT3 blockade (vomiting centre and CTZ) Metoclopramide: **D2 blockade** (CTZ). Increases oesophageal motility. Increases LOS pressure. Increase gastric emptying	Bold to pass
	Describe the potential adverse effects of metoclopramide.	CNS: Restlessness, drowsiness, insomnia, anxiety, agitation – common (20%), esp. elderly Extrapyramidal effects: **acute dystonia**, akathisia, parkinsonian effects, more likely with higher doses Tardive dyskinesia with chronic dosing	Must mention acute dystonia + one other CNS effect

Antiemetics	What clarrrrsses of drug can be used as antiemetics ?	(1) Serotonin 5-HT3 antagonists: the "trons" (2) Phenothiazines: prochlorperazine, promethazine (3) Butyrophenones: haloperidol (4) Substituted benzamides: metoclopramide (5) H1 antihistamines: diphenhydramine (6) Anticholinergics: hyoscine (Benzos, Cannabinoids, Corticosteroids)	Name three groups to pass – if name agents, prompt for group or mechanism of action.
	List and explain the adverse effects of prochlorperazine ?	Acute dystonia (dopamine blockade) Sedation (antihistamine effects) Anticholinergic effects (antimuscarine effects) Allergy	Acute dystonia + one other to pass

Antiemetics	List the major categories of antiemetic agents. (3 of 7) Describe the mechanism of action of three of these. (2 of 3)	**Antihistamines** Diphenhydramine, hydroxyzine - antimuscarinic and sedative effects + H1 blocking effect - effective for nausea and vomiting associated with motion sickness - specific depression of conduction in vestibulocerebellar pathway Anticholinergics (scopolamine) – also useful **Phenothiazines** Prochlorperazine, promethazine - Block dopamine receptors in chemoreceptor trigger zone - use limited by degree of sedation - also cause extrapyramidal symptoms esp.dystonias **Metoclopramide** Dopamine antagonist – enters CNS + 5HT4 agonist action Releases Ach from cholinergic neurons in enteric nervous systems myenteric plexus + may sensitize intestinal sm.muscle cells to action of Ach Not increase gastric or pancreatic secretion Hasten esophageal clearance, raise lower esophageal sphincter pressure, accelerate gastric emptying, shorten sm.bowel transit time **5-HT inhibitors** Odansetron, granisetron and dolasetron – equal efficacy, adverse reactions, Convenience of administration, cost Very effective controlling acute nausea and vomiting assoc. with ordinary dose chemo, leff in delayed emesis and that from high dose cancer chemo new class, neurokinin antagonists under investigations **Marijuana derivatives** – tetrahydrocannabinol (THC) effective in some patients dronabinol – receptors in the chemoreceptor trigger zone **Steroids** = dexamethasone – mechanism unknown **Sedative hypnotics** = benzodiazepines can control anticipatory nausea and vomiting	Rapidly absorbed, peak concentration at 40-120 minutes T ½ 2-4 hours Usual dose 10mg qid with meals, meadtime 1-2mg/kg for cancer chemotherapy Side effects = somnolence, nervousness, dystonic reactions

Question 5: Laxatives	1. Using examples, outline the mechanism of action of the various types of laxative? *Prompt: How does X work for example*	**Irritants or Stimulants** - (act early) castor oil -(act late)cascara, ***senna***, aloes (contain emodin alkaloids which are liberated after absorption from the intestine and excreted in the colon) -(prolonged action by enterohepatic circulation) phenolphthalein & biscodyl **Bulking agents** -hydrophyllic colloids, agar, psyllium seed, ***bran*** **Osmotic** -magnesium citrate and magnesium hydroxide, polyethylene glycol, sorbitol, ***lactulose*** **Stool softeners**: agents that emulsify with the stool and soften it (mineral oil, ***glycerine***, detergents such as docusate (dioctyl sodium sulphosuccinate)	3 out of the 4 mechanisms with at least 1 correct example NB –anything that distends intestine leads to peristaltic activity i.e. bulking and softening agents

TOPIC: Laxatives **NUMBER: 5**

OPENING QUESTION	**What different mechanisms of actions of laxatives do you know? Give examples.**	**COMMENTS**
POINTS REQUIRED	1. **Bulk-forming** Psyllium, methylcellulose Increased bloating and flatus	1-3 to pass
	2. **Stool softening** Permit water and lipids to penetrate. Docusate, glycerine, mineral oil	
	3. Osmotic 1 – nonabsorbable sugars/salts. MgO2 Sorbitol, lactulose	
	4. Osmotic 2 Polyethylene glycol	
	5. Stimulant Senna, aloe, cascara Castor oil	
PROMPTS		
SECOND QUESTION (if needed)	**Polyethylene glycol is used as a prep for endoscopic procedures. What features make it safe for all patients?**	
POINTS REQUIRED	1. Balanced. Osmotically active sugar (PEG) with NaCl, NaHCO3, KCl	
	2. No significant osmotic shifts. Best ingested rapidly for bowel cleansing	.
PROMPTS		

Metoclopramide 2016-2-D

Stem: A 70yo man presents with vomiting and abdominal pain. He is given metoclopramide. We will start with Pharmacology.			
TOPIC	QUESTIONS	KNOWLEDGE **(essential in bold)**	NOTES
Question 1 Metoclopramide / antiemetics **Subject:** Pharmacology LOA: 1	a. Describe the mechanisms of action of metoclopramide	**Dopaminergic** (D2) **antagonist at chemoreceptor trigger zone/CTZ.** Increases oesophageal motility. Increases LOS pressure. Increase gastric emptying	Bold + 1/3 to pass
	b. Describe the potential adverse effects of metoclopramide	CNS: Restlessness, drowsiness, insomnia, anxiety, agitation – common (20%), esp. elderly Extrapyramidal effects: **acute dystonia**, akathisia, parkinsonian effects, more likely with higher doses Tardive dyskinesia with chronic dosing Prolactinemia – galactorrhea	bold + 2

Metoclopramide 2008-2

Question 4: Metoclopramide	1. Describe the mechanism of action of metoclopramide? *Prompt: what receptor does it act on?* *What are the peripheral/central actions?*	**Dopamine antagonist** (D2 receptors) **Central –** via anti - nauseant and anti - emetic effect on the Chemoreceptor Trigger Zone (area postrema) **Peripheral –** blockade of GI dopamine receptors allowing cholinergic smooth muscle stimulation - increases oesophageal peristaltic amplitude - increases lower oesophageal sphincter pressure - enhances gastric emptying	Pass dopamine antagonist, peripheral & central action
	2.. List the adverse effects of metoclopramide?	Relate to central dopamine antagonist action - restlessness, drowsiness, insomnia, anxiety, agitation - **extrapyrimadal effects –** dystonias, akathisia, parkinsonian features. - risk of tardive dyskinesia with chronic use - hyperprolactinemia (galactorrhoea, gynecomastia, impotence, menstrual disorders)	Extrapyramidal + 1

Ondansetron 2017-1-B

Stem: Moving on to Pharmacology. The patient is vomiting.			
Question 2 Antiemetics - Ondansetron **Subject:** Pharmacology LOA: 1	a) List anti-emetics with different mechanisms of action	- Serotonin 5HT3 antagonists (e.g. Ondansetron) - Dopamine antagonist: Phenothiazines (Prochlorperazine) and Butyrophenones (droperidol) . Metoclopramide(has peripheral effects) - H1 antihistamines and anticholinergic (e.g. Hyoscine, Diphenhydramine) - Corticosteroids (i.e dexamethasone) - Benzodiazepines (i.e diazepam, lorazepam) - Cannabinoids - Neurokinin Receptor antagonist (e.g. Aprepitant)	Minimum of 3
	b) How is the effect of ondansetron mediated?	b) Mostly **peripheral 5HT3/Serotonin receptor blockade** on extrinsic intestinal vagal and spinal afferent nerves. Some effect on Central 5HT3 receptor blockade in vomiting centre and chemoreceptor trigger zone. Anti-emetic action mostly restricted to emesis attributable to vagal stimulation (e.g. postop) and chemotherapy. Less effect for other emetic stimuli (e.g. motion sickness).	Bold to pass
	c) What are possible adverse effects of Ondansetron?	c) Headache, dizziness, constipation, diarrhoea Uncommon – small prolongation of QT.	Minimum of one.

Ondansetron 2015-2-D

Stem: Moving onto Pharmacology. He is given Ondansetron for nausea.			
Question 4 Ondansetron **Subject:** Pharm LOA: 1	What is the mechanism of action of Ondansetron? Prompt- Where are these receptors found?	**5-HT$_3$ receptor antagonist**; Effect brought about at peripheral (Gut) > central receptors (chemoreceptor trigger zone and vomiting centre)	**Bold,** plus 1 receptor location
	What are the doses and routes of administration of Ondansetron ?	**4-8mg** SL , PO, IV , SC, IM	**Bold**, plus 3/5
	What are the adverse effects of Ondansetron?	Constipation, headache, dizziness, QT prolongation	**1/4** to pass
	In which disease state would you need to modify the dosing?	**Hepatic failure** Not with renal failure or age	**Bold**
	What are some other classes of antiemetic drugs? (ask for drug class if just name a drug)	Phenothiazines Antihistamines Cannabinoids Benzodiazepines Butyrophenones (Droperidol) Benzamides (eg Metoclopramide) Neurokinin receptor antagonists Corticosteroids	**3/8** to pass

Ondansetron 2009-1

Question 3 Ondansetron	1. What is the mechanism of action of ondansetron?	selective 5-HT_3 receptor antagonists both peripheral in intestinal vagal afferents and central in chemoreceptor trigger zone and vomiting center in lateral medulla	Pass: serotonin
	2. What are the clinical uses of ondansetron?	a) Chemotherapy –induced nausea and vomiting eg 8 mg every 8 -12 hours b) Postoperative and post radiation nausea and vomiting. c) Other indications: acute or chronic medical conditions or gastroenteritis – not well evaluated	2 out of 3
	3. Name some side-effects of ondansetron?	Headache, dizziness and constipation. Small prolongation of QT interval	Pass: 1

Ondansetron 2006-2

3. Ondansetron	**How does ondansetron work as an anti-emetic?** **What are the routes of administration and dose of ondansetron?**	**5-HT3 antagonism (gut and brain / central)** **Similar doses 4-8 mg oral – tablet/wafer, IV**	

Proton Pump Inhibitors 2014-2-A

Stem: Initial treatment included commencement of a Pantoprazole infusion			
Question 2 Proton Pump Inhibitors (pp 1085-1089) **Subject:** Pharm LOA: 2	1. Describe the MOA of PPIs	**Irreversibly inactivates H^+K^+ATPase**, blocking the proton pump-inhibiting >90% acid secretion, for up to 24 hrs (time taken for synthesis new enzymes).	Bold to pass.
	2. Why is an IV infusion preferred to a single bolus dose?	**Only inactivates actively secreting acid pumps** (<10% in fasting patients). Hence single dose only decreases acid secretion for a few hours.	Bold to pass.
	3. Regarding oral formulations of proton pump inhibitors, please describe strategies used to increase their bioavailability and activity.	Taken as **inactive pro-drugs**, Begin as **acid resistant enteric coated** to prevent gastric elimination. Take on **empty stomach** as food decreases bioavailability. Weak bases so pass into acidified parietal cells, where concentrated 1000x, ecomes activated and binds to H^+K^+ATPase. **Take 1 hour prior to meal** so peak dose drug occurs when most pumps are active.	2 concepts.