

Laxatives

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Laxatives

- **Definition:**

Laxatives promote and facilitate bowel evacuation

- **Mechanism of action:**

Evacuation by laxatives is promoted by acting locally to stimulate intestinal peristalsis, to soften bowel contents, or both.

- **Classification according to the mechanism of action:**

1. Bulk laxatives.
2. Irritant laxatives (purgatives) or (stimulants of the gut)
3. Lubricant laxatives (stool softeners). E.g Liquid paraffin

Laxatives

- **Side effects:**

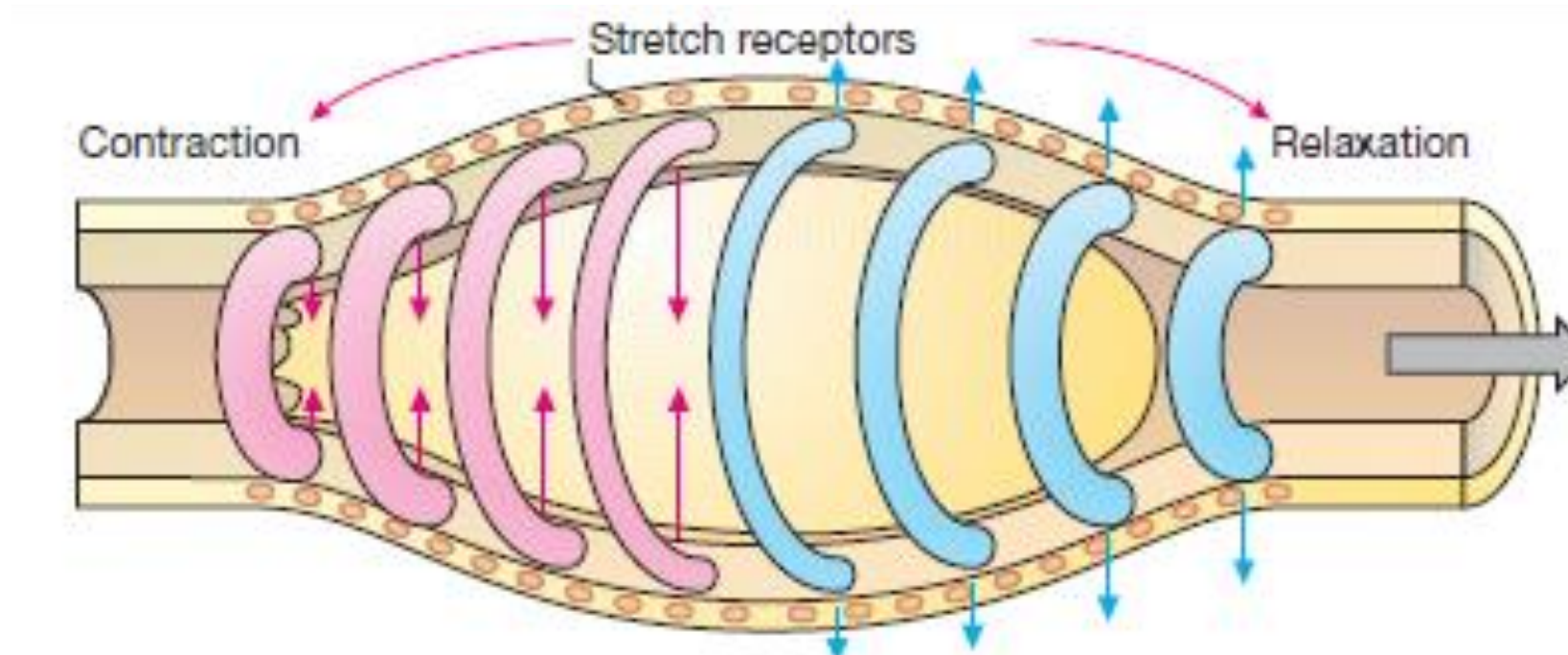
1. Habit forming laxatives
2. Drug-drug interactions due to acceleration of transient time through the intestine which may lead to poorly absorbed drugs. E.g. : Griseofulvine and controlled release drugs
3. Electrolyte embalance

Bulk laxatives

- **Mechanism of action:**
- Distention of the intestinal wall by bowel contents stimulates propulsive movements of the gut musculature (peristalsis).
- Activation of intramural mechanoreceptors induces a neurally mediated ascending reflex contraction and descending relaxation.
- Stimulation of defecation occur centrally in the spinal cord and in the cortex.

Bulk laxatives : Stimulation of peristalsis by intraluminal bolus

- Ascending reflex contraction (red)
- Descending relaxation (blue)
- whereby the intraluminal bolus is moved in the anal direction



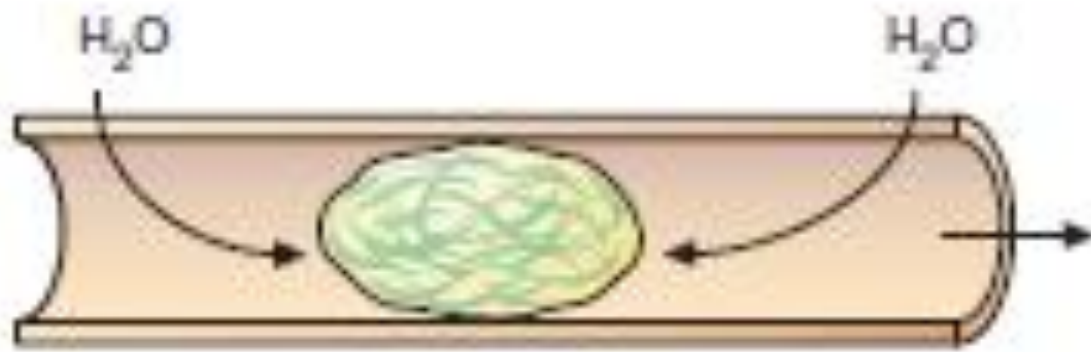
Example on bulk laxative

- **Hydrophilic colloids or bulk gels**
- comprise insoluble and nonabsorbable carbohydrate substances that expand on taking up water in the bowel.
- Vegetable fibers in the diet act in this manner. They consist of the indigestible plant cell walls containing homoglycans that are resistant to digestive enzymes,
- e.g., cellulose (1→4 β -linked glucose molecules vs. 1→4 α glucoside bond in starch).

Example on bulk laxative

- *Bran*, a grain milling waste product, and *linseed* (flaxseed) are both rich in cellulose. Other hydrophilic colloids derive from the seeds of *Plantago* species or *karaya gum*.
- Ingestion of hydrophilic gels (derived from indigestible parts of fruits and vegetables) for the prophylaxis of constipation usually entails a low risk of side effects.
- However, with low fluid intake in combination with a pathological bowel stenosis, mucilaginous viscous material could cause bowel occlusion (ileus).
- Caution: They should be used cautiously in patients who are bed-ridden due to the potential of intestinal obstruction.

Bulk laxatives (Cellulose, Agar, Bran and Linseed)



Cellulose, agar-agar, bran, linseed



Osmotically active laxatives

1. Non absorbable salts: (anions and cations)

- Magnesium citrate
- Magnesium Sulfate
- Sodium phosphate
- Magnesium hydroxide

2. Lactulose: Semisynthetic disaccharide sugar

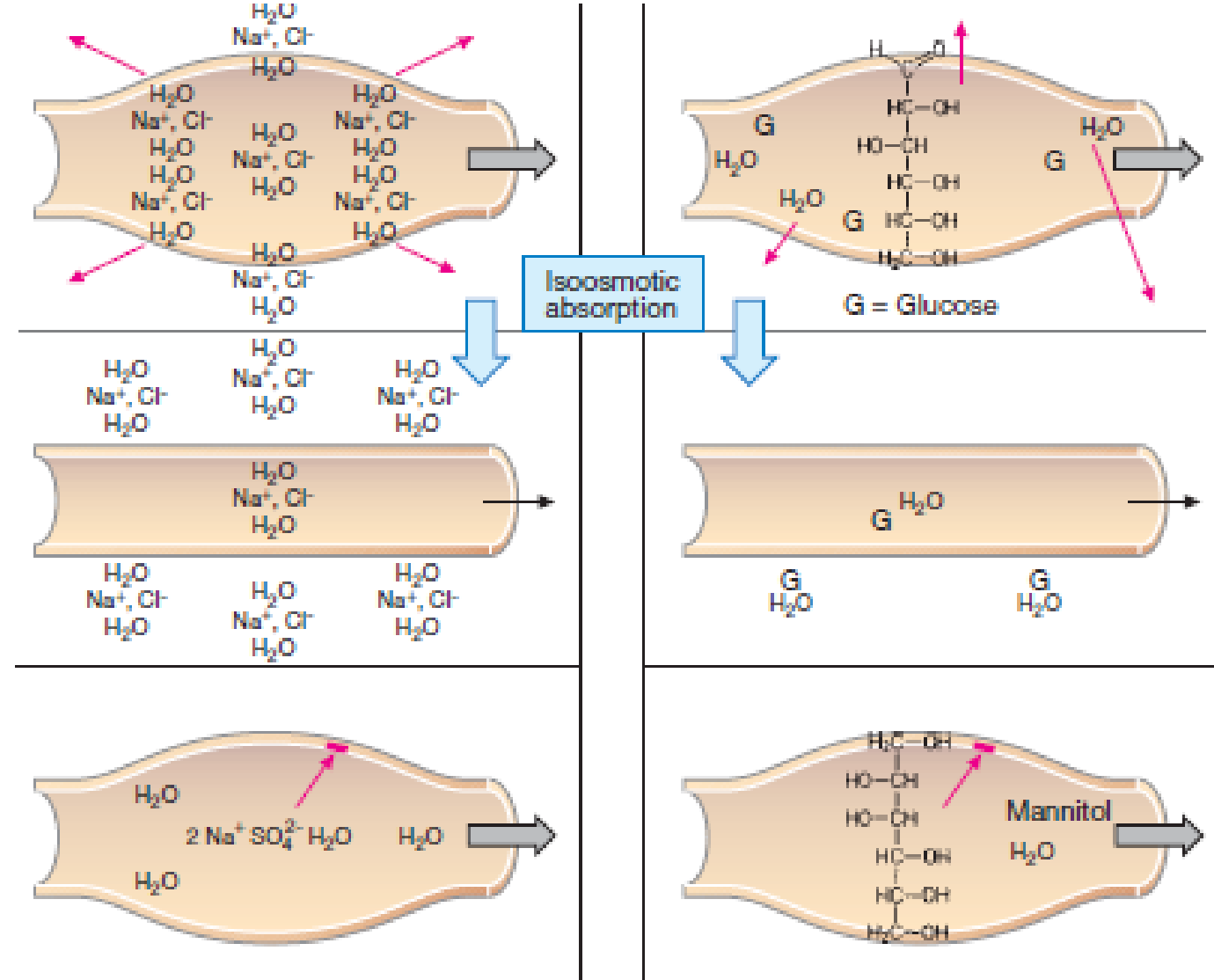
3. Polyhydric alcohol (Mannitol, sorbitol, polyethylene glycol (PEG))

Osmotically active laxatives and saline laxative drugs

- Mechanism of action:
- These are soluble but nonabsorbable particles that retain water in the bowel by virtue of their osmotic action.
- The osmotic pressure (particle concentration) of bowel contents always corresponds to that of the extracellular space.
- The intestinal mucosa is unable to maintain a higher or lower osmotic pressure of the luminal contents.
- Therefore, absorption of molecules (e.g., glucose, NaCl) occurs
- i.e., solute molecules are followed by a corresponding amount of water.
- Conversely, water remains in the bowel when molecules cannot be absorbed.

Osmotically active laxatives

- They are non absorbable salts (anions and cations) that can hold water in the intestinal lumen by osmosis
- This results in distended bowel and stimulates the reflex peristalsis and defecation in few hours



Osmotically active laxatives

- Mechanism of action
- With *Epsom and Glauber's salts* (MgSO_4 and Na_2SO_4 , respectively), the SO_4^{2-} anion is nonabsorbable and retains cations to maintain electroneutrality. Mg^{2+} ions are also believed to promote release from the duodenal mucosa of cholecystokinin/pancreozymin, a polypeptide that also stimulates peristalsis.
- These so-called saline cathartics elicit a watery bowel discharge 1–3 h after administration (preferably in isotonic solution).
- They are used to purge the bowel (e.g., before bowel surgery) or to hasten the elimination of ingested poisons.
- Glauber's salt (high Na^+ content) is contraindicated in hypertension, congestive heart failure, and edema. Epsom salt is contraindicated in renal failure (risk of Mg^{2+} intoxication).

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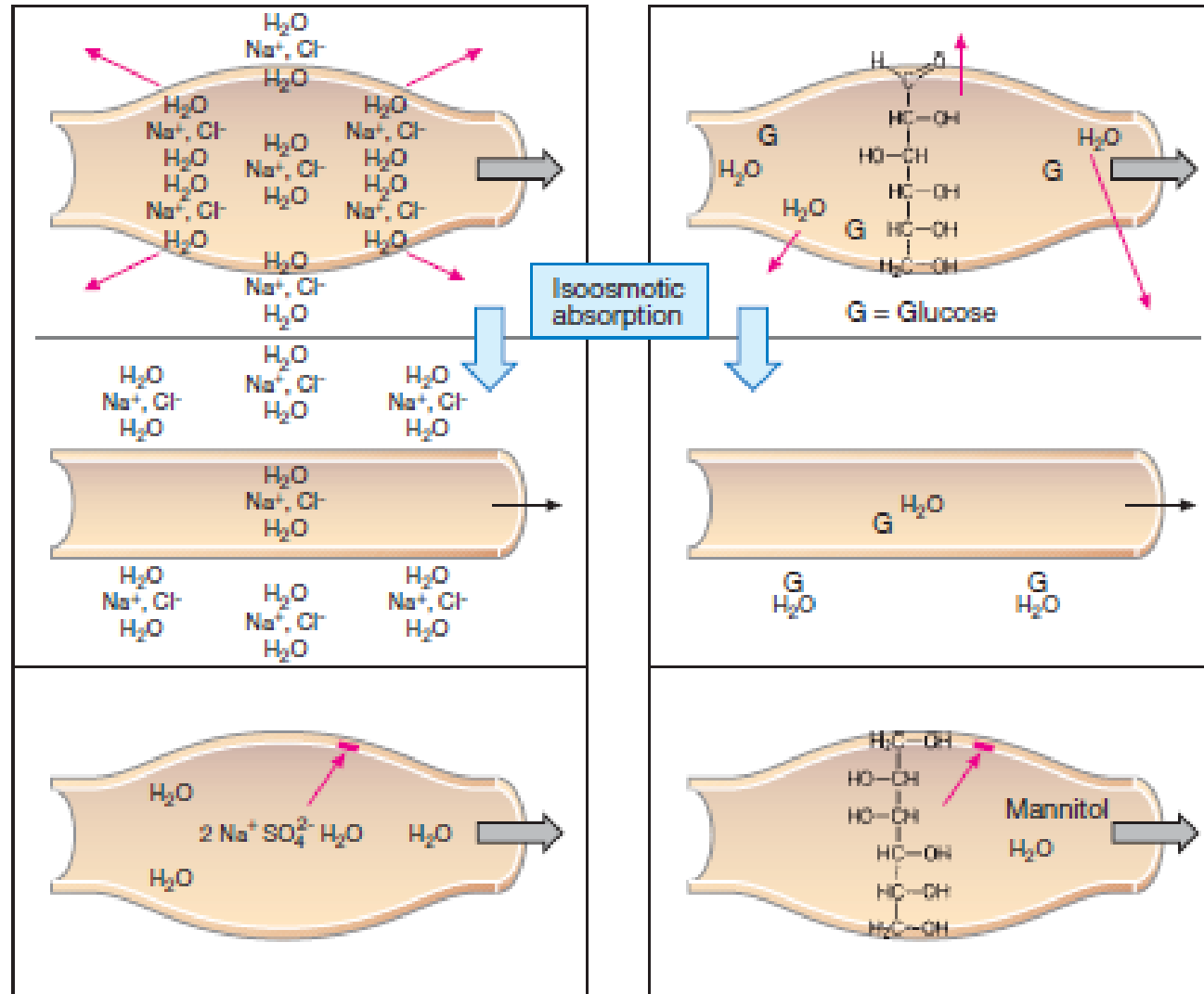
Osmotically active laxatives

- Indications
 - They are used to purge the bowel (e.g., before bowel surgery) or to hasten the elimination of ingested poisons.
- Contraindications
 - Glauber's salt (high Na^+ content) is contraindicated in hypertension, congestive heart failure, and edema. Epsom salt is contraindicated in renal failure (risk of Mg^{2+} intoxication).

Osmotically active laxatives

- Osmotic laxative effects are also produced by the *polyhydric alcohols*, *mannitol* and *sorbitol*, which unlike glucose cannot be transported through the intestinal mucosa,
- as well as by the nonhydrolyzable disaccharide, *lactulose*.
Fermentation of lactulose by colon bacteria results in acidification of bowel contents and microfloral damage.
- Lactulose is used in hepatic failure in order to prevent bacterial production of ammonia and its subsequent absorption (absorbable NH_3 nonabsorbable NH_4^+), so as to forestall hepatic coma.

Osmotically active laxatives



C. Osmotically active laxatives

Irritant laxatives—purgatives cathartics. (stimulant laxatives)

- Laxatives in this group exert an irritant action on the enteric mucosa. Consequently, less fluid is absorbed than is secreted. The increased filling of the bowel promotes peristalsis; excitation of sensory nerve endings elicits enteric hypermotility.
- According to the site of irritation, one distinguishes the small bowel irritant castor oil from the large bowel irritants anthraquinone and diphenolmethane derivatives

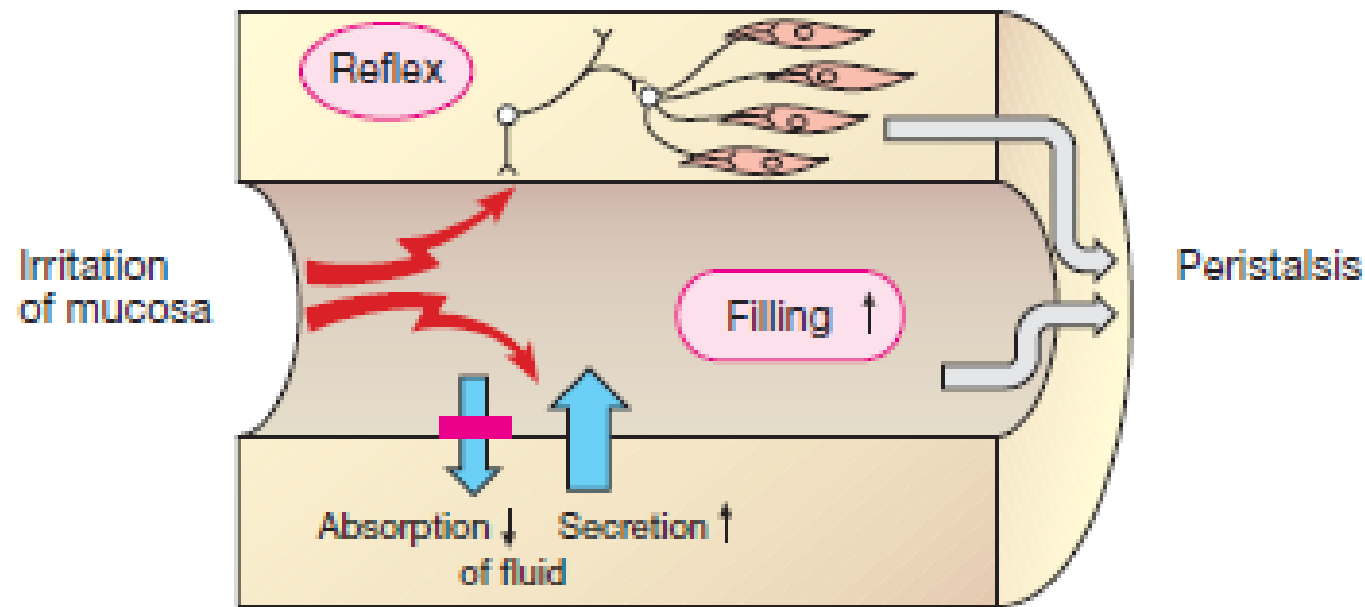
Irritant laxatives—purgatives cathartics. (stimulant laxatives)

A. Castor oil (active principal is Ricinoleic acid) , it irritates the gut and increase the peristalsis which causes defecation

B. Senna (active ingredient is sennoside – anthraquinone glycosides) and it used to treat opioid constipation

C. Bisacodyl (diphenolethane derivative) it causes abdominal cramps and atonic colon (prolonged use)

Stimulation of peristalsis by mucosal irritation



Irritant Purgative,

- **Small Bowel Irritant Purgative,**
- **Large Bowel Irritant Purgatives**

2.a Small Bowel Irritant Purgative,

- **Ricinoleic Acid Castor oil** comes from *Ricinus communis* (castor plants; Fig: sprig, panicle, seed); it is obtained from the first cold pressing of the seed (shown in natural size).
- Oral administration of 10–30 mL of castor oil is followed within 0.5 to 3 h by discharge of a watery stool.
- Ricinoleic acid, but not the oil itself, is active. It arises as a result of the regular processes involved in fat digestion: the duodenal mucosa releases the enterohormone cholecystokinin/pancreozymin into the blood.
- The hormone elicits contraction of the gallbladder and discharge of bile acids via the bile duct, as well as release of lipase from the pancreas (intestinal peristalsis is also stimulated). Because of its massive effect, castor oil is hardly suitable for the treatment of ordinary constipation.

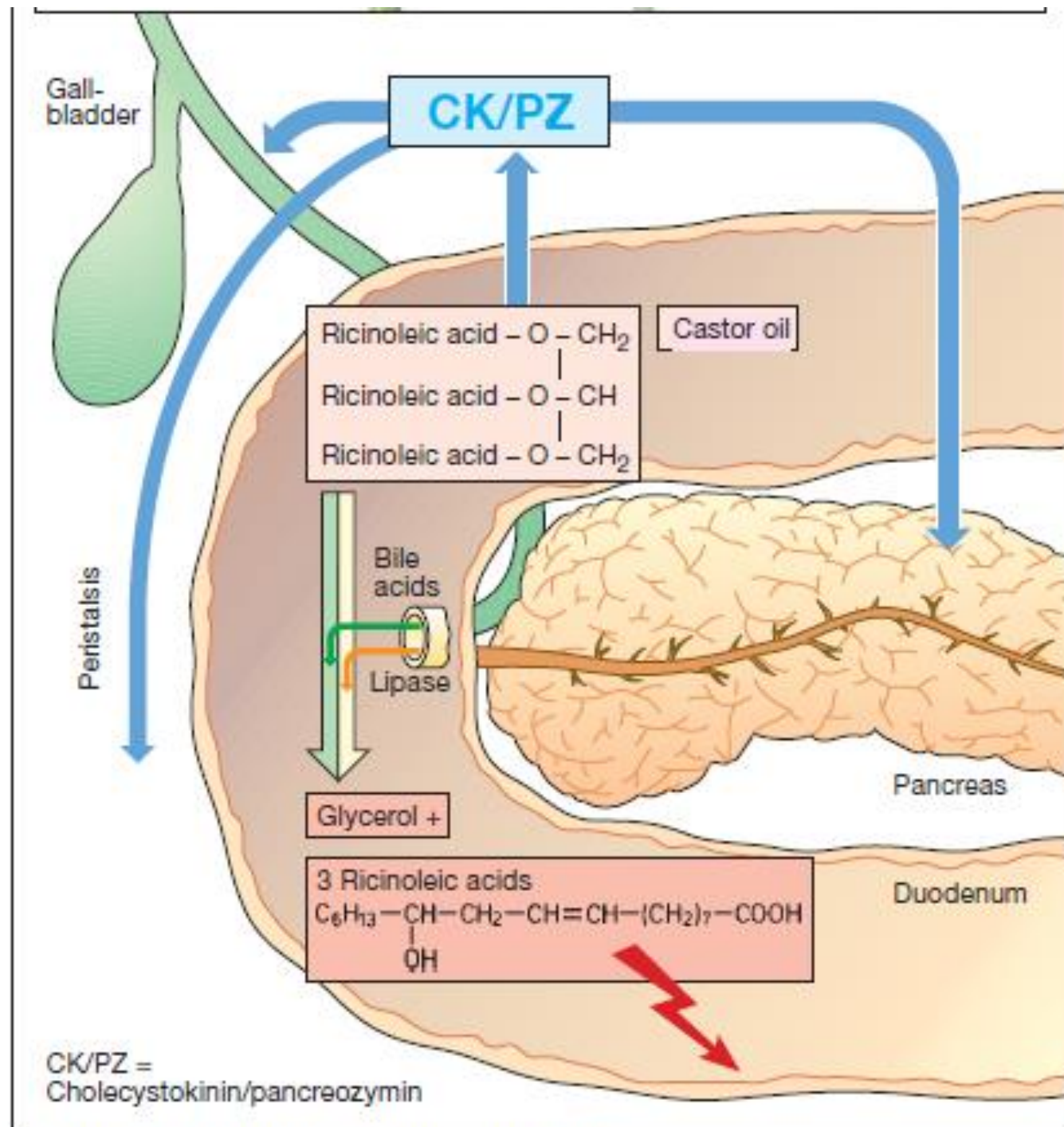
Small Bowel Irritant Purgative,

- **Ricinoleic Acid Castor oil (Cont.)**
- It can be employed after oral ingestion of a toxin in order to hasten elimination and to reduce absorption of toxin from the gut.
- Castor oil is not indicated after the ingestion of lipophilic toxins likely to depend on bile acids for their absorption.



*Ricinus
communis*

Ricinoleic Acid Castor oil (Cont.)



Large Bowel Irritant Purgatives

- **Anthraquinone derivatives** are of plant origin.
- They occur in:
 - the leaves (*folia sennae*)
 - fruits (*fructus sennae*) of the *senna* plant
 - the bark of *Rhamnus frangulae* and *Rh. purshiana*,
 - (*cortex frangulae, cascara sagrada*),
 - the roots of rhubarb (*rhizoma rhei*), or the leaf extract from *Aloe* species

Senna



Frangula



Rhubarb



Aloe



Large Bowel Irritant Purgatives

- structural features of anthraquinone derivatives are illustrated by the prototype structure depicted

2.b Large Bowel Irritant Purgatives

- Among other substituents, the anthraquinone nucleus contains hydroxyl groups, one of which is bound to a sugar (glucose, rhamnose). Following ingestion of galenical preparations or of the anthraquinone glycosides, discharge of soft stool occurs after a latency of 6 to 8h.
- The anthraquinone glycosides themselves are inactive but are converted by colon bacteria to the active free aglycones.

2.b Large Bowel Irritant Purgatives

- **Diphenolmethane derivatives** were developed from *phenolphthalein*, an accidentally discovered laxative, use of which had been noted to result in rare but severe allergic reactions.
- *Bisacodyl* and *sodium picosulfate* are converted by gut bacteria into the active colonirritant principle.
- Given by the enteral route, bisacodyl is subject to hydrolysis of acetyl residues, absorption, conjugation in liver to glucuronic acid (or also to sulfate), and biliary secretion into the duodenum.
- Oral administration is followed after approx. 6 to 8 h by discharge of soft formed stool. When given by suppository, bisacodyl produces its effect within 1 h.

Indications for colon-irritant purgatives

- prevention of straining at stool following surgery,
- myocardial infarction, or stroke;
- provision of relief in painful diseases of the anus, e.g., fissure, hemorrhoids.
- Purgatives must **not** be given in abdominal complaints of unclear origin.

Lubricant laxatives

- . Liquid paraffin (*paraffinum subliquidum*) is almost nonabsorbable and makes feces softer and more easily passed. It interferes with the absorption of fat-soluble vitamins by trapping them.
- The few absorbed paraffin particles may induce formation of foreign-body granulomas in enteric lymph nodes (paraffinomas).
- Aspiration into the bronchial tract can result in lipoid pneumonia. Because of these adverse effects, its use is not advisable.

Misuse of laxatives

- It is a widely held belief that at least one bowel movement per day is essential for health; yet three bowel evacuations per week are quite normal. The desire for frequent bowel emptying probably stems from the time-honored, albeit mistaken, notion that absorption of colon contents is harmful.
- Thus, purging has long been part of standard therapeutic practice. Nowadays, it is known that intoxication from intestinal substances is impossible as long as the liver functions normally.
- Nonetheless, purgatives continue to be sold as remedies to “cleanse the blood” or to rid the body of “corrupt humors.”

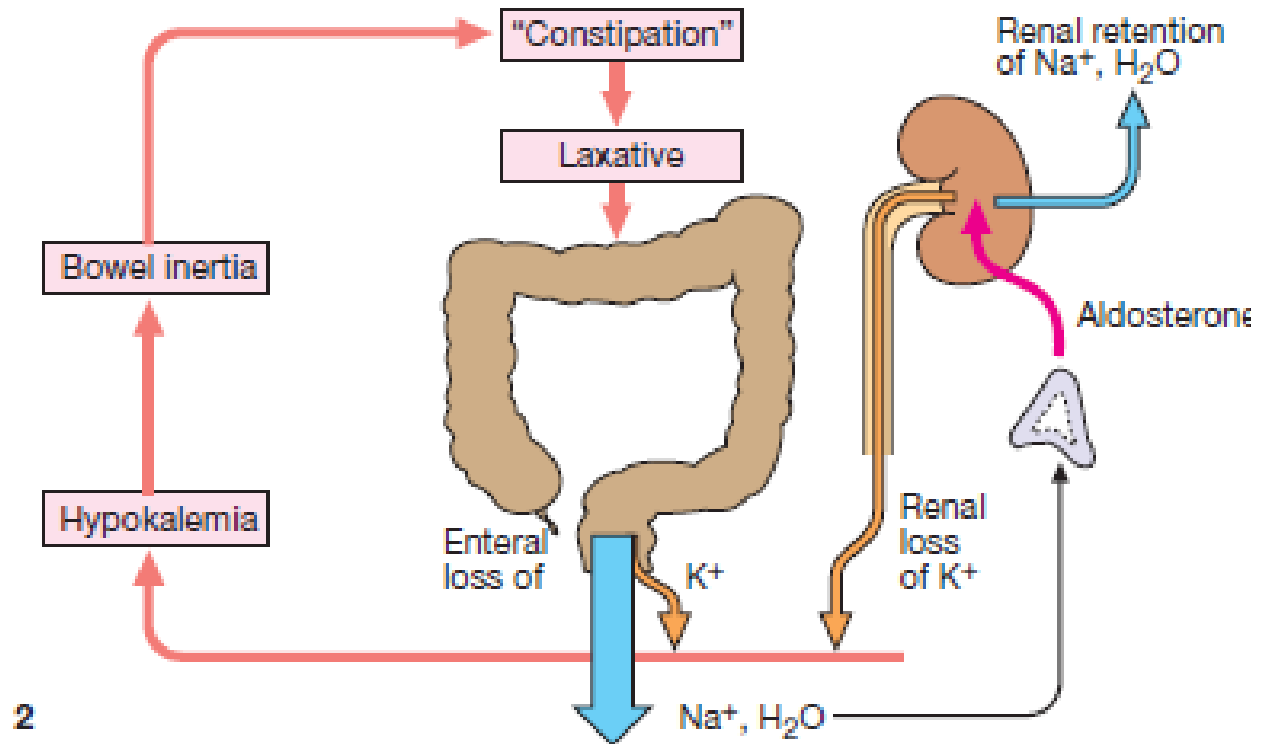
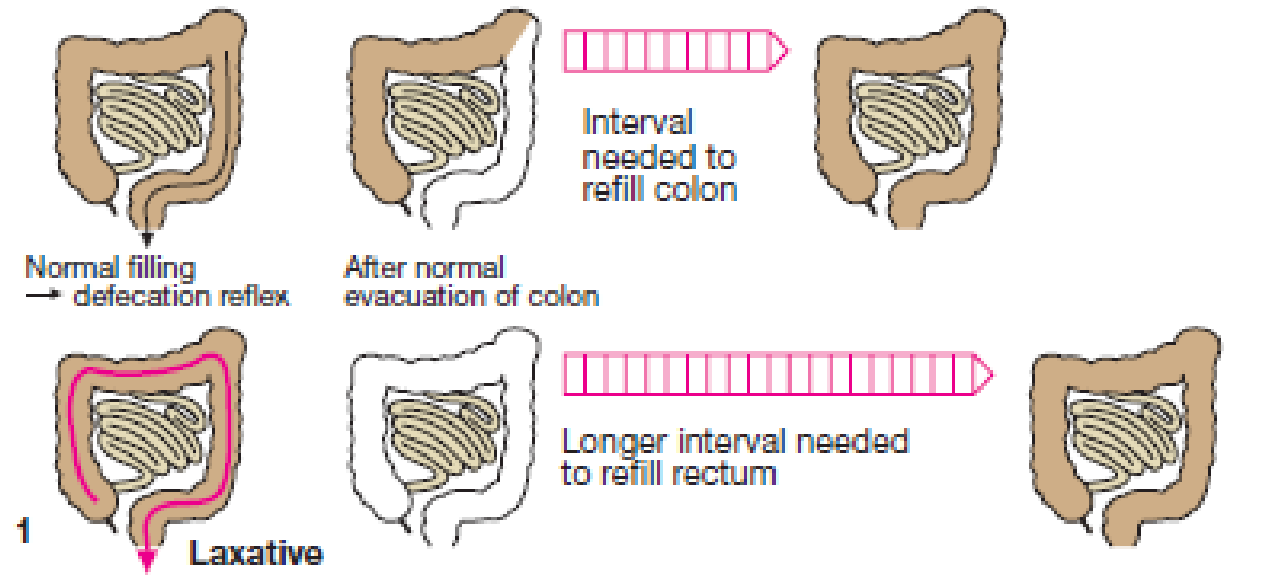
Misuse of laxatives

- There can be no objection to the ingestion of bulk substances for the purpose of supplementing low-residue “modern diets.” However, use of irritant purgatives or cathartics is not without hazards. Specifically, there is a risk of laxative dependence, i.e., the inability to do without them.
- Chronic intake of irritant purgatives disrupts the water and electrolyte balance of the body and can thus cause symptoms of illness (e.g., cardiac arrhythmias secondary to hypokalemia).

Causes of purgative dependence

- The defecation reflex is triggered when the sigmoid colon and rectum are filled. A natural defecation empties the large bowel up to and including the descending colon. The interval between natural stool evacuations depends on the speed with which these colon segments are refilled.
- A large bowel irritant purgative clears out the entire colon. Accordingly, a longer period is needed until the next natural defecation can occur. Fearing constipation, the user becomes impatient and again resorts to the laxative, which then produces the desired effect as a result of emptying out the upper colonic segments.
- Therefore, a “compensatory pause” following cessation of laxative use must not give cause for concern.

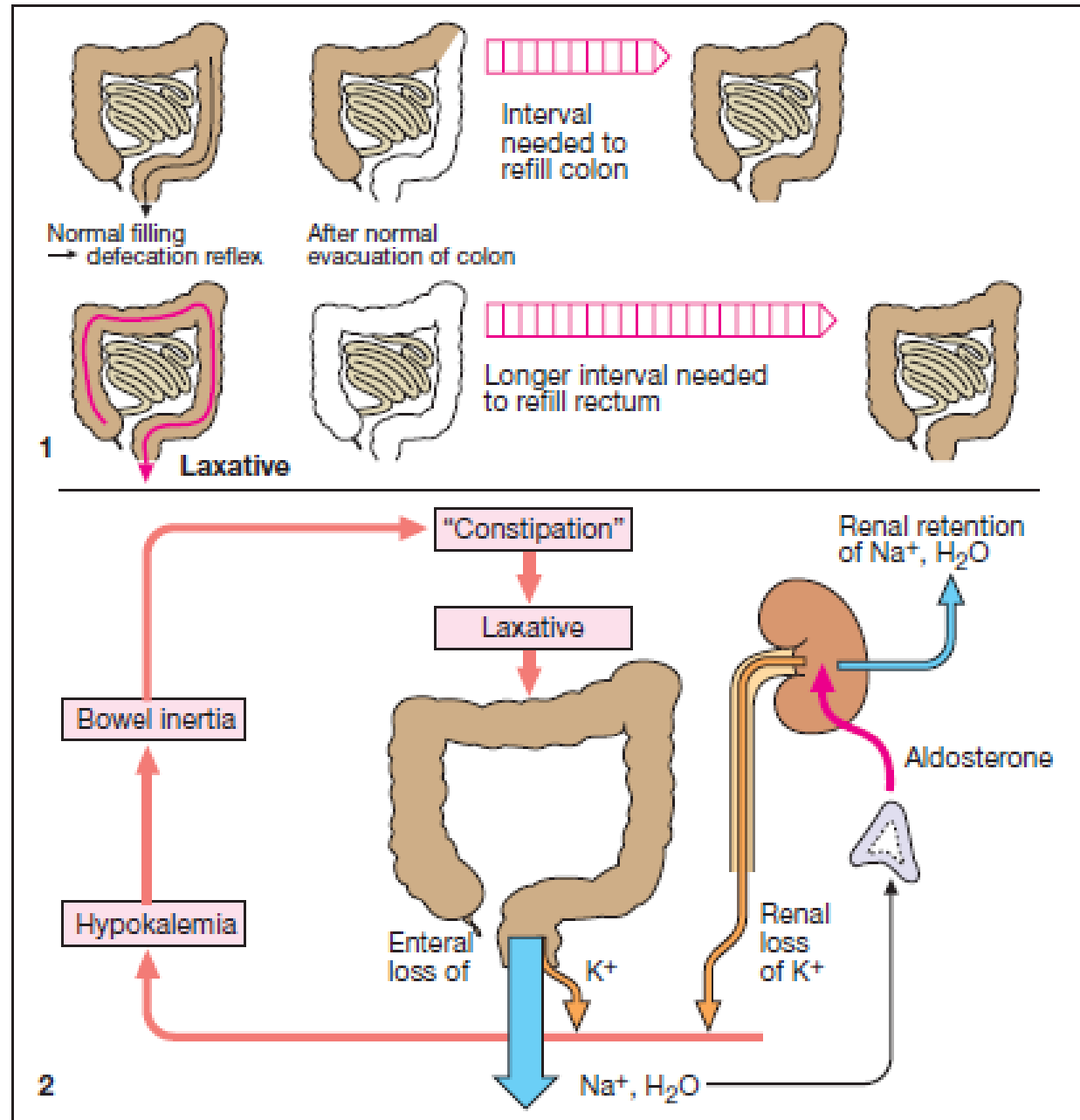
Causes of laxative habituation



Causes of purgative dependence

- In the colon, semifluid material entering from the small bowel is thickened
- by absorption of water and salts (from about 1000 to 150 mL/d). If, due to the action of an irritant purgative, the colon empties prematurely, an enteral loss of NaCl, KCl and water will be incurred.
- To forestall depletion of NaCl and water, the body responds with an increased release of aldosterone which stimulates their reabsorption
- in the kidney. The action of aldosterone is, however, associated with increased renal excretion of KCl. The enteral and renal K⁺ loss add up to a K⁺ depletion of the body, evidenced by a fall in serum K⁺ concentration (hypokalemia).
- This condition is accompanied by a reduction in intestinal peristalsis (bowel atonia). The affected individual infers “constipation,” again partakes of the purgative, and the vicious circle is closed (2).

Causes of laxative habituation



- *Chologenic diarrhea* results when bile acids fail to be absorbed in the ileum (e.g., after ileal resection) and enter the colon, where they cause enhanced secretion of electrolytes and water, leading to the discharge of fluid stools.

