Gastrointestinal Tract Toxicology

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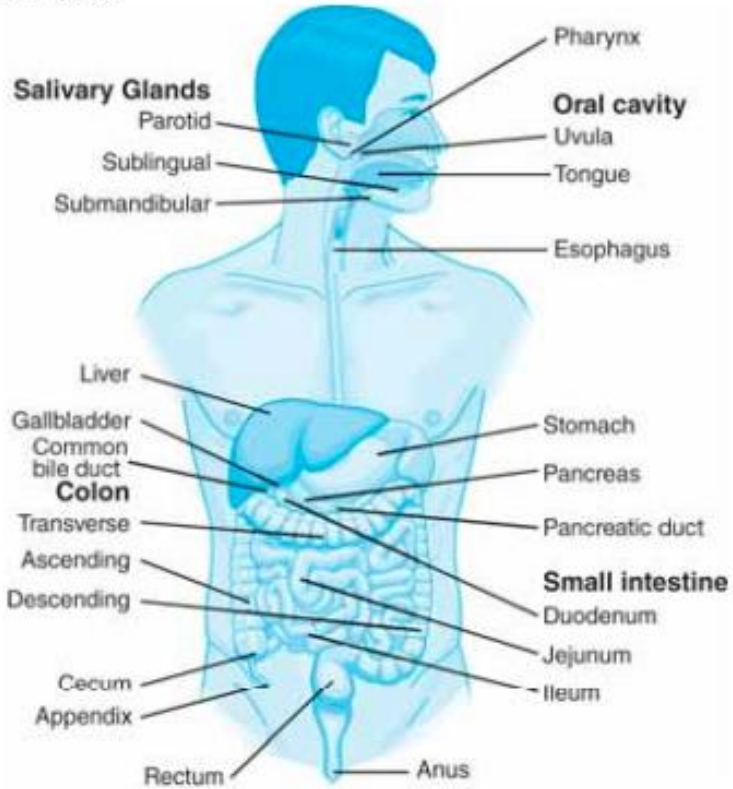
Introduction

- Also known as the *alimentary system* is an open-ended tubular organ that courses from the oral cavity to the anus. "Open-ended"
- GIT Functions include ingestion, propulsion, digestion, absorption, secretion, storage, and elimination of excreta.
- Proper digestion and assimilation of nutrients is critically important for health and requires carefully coordinated muscular, secretory, absorptive, neurologic, and endocrinologic events.
- Importantly, a healthy alimentary system requires maintenance of barrier function.

I. Gastrointestinal (GI) system



A. Most likely accidental poisoning of animals, infant humans, and route of contaminated food or suicidal ingestions

B. Damage to GI structures (proximal → distal)—see Table 16-1

1. Mouth

a. Teeth—stain with food products (coffee, tea), tetracycline, chlorhexidine (in prescription mouthwash), fluoride; TCDD arrests molar development (AhR stimulation → apoptosis) and formation of enamel; cleft palate caused by cell cycle progression and proliferation disruption (TCDD, mycotoxin, glucocorticoids, secalonic acid, retinoic acid)

CONCEPTUALIZING TOXICOLOGY 16-1

- Contents considered exterior to the body until absorbed.
- Salivary glands, liver, and the pancreas are accessory glands of the GI tract as ducts secrete enzymes and other substances.
- Foreign substances to enter the body, pass through the GI mucosa, several membranes before entering the bloodstream.
- Substances must be absorbed from the GIT tract in order to exert a toxic effect throughout the whole body,

- Glands are the first line of defense against ingested foreign substances and pathogens of all types.
- Then, the anatomic, biochemical, physical, secretory, and endocrinologic properties of the alimentary epithelium.
- Additionally, resident and blood-borne effector cells, microbiota, genetic polymorphisms, and gut-associated lymphoid tissue (GALT) (comprising one-quarter of the body's total)
- Physically or functionally altered GIT results in a dysfunction/clinical/toxic effects such as ptyalism (hypersalivation), regurgitation, emesis (vomiting), abdominal pain, gas production, and/or diarrhea to occur.

- Local GI damage occur from direct exposures to toxicants.
- Absorption can occur at anywhere along the entire GI tract. However, the degree of absorption depends on the site.

factors affecting absorption within the various sites of the tract: include

- Type of cells at the specific site.
- Duration that the substance remains at the site.
- pH of stomach or intestinal contents

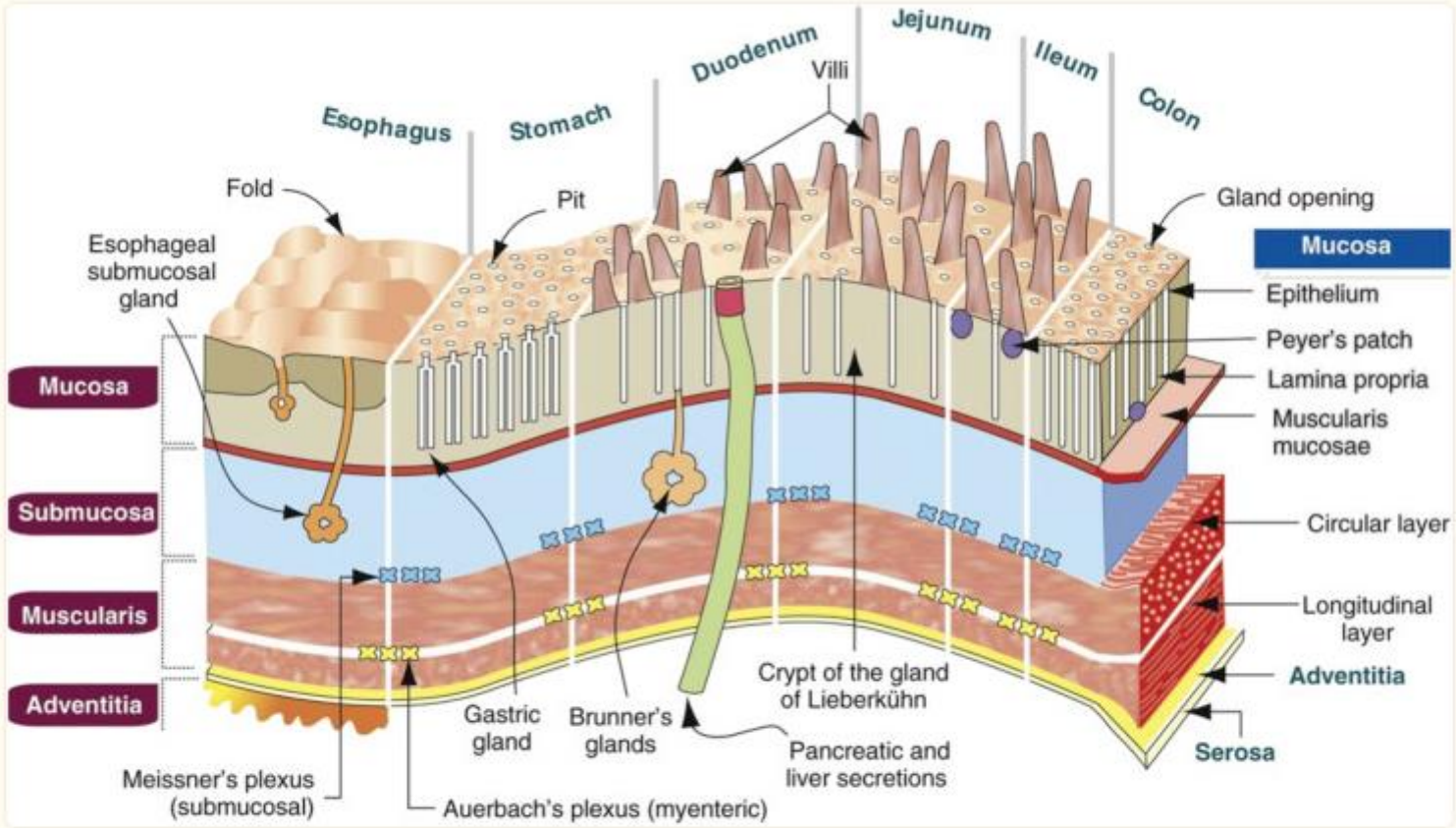


Fig. 1

Schematic diagram of the anatomic and histologic organization of the digestive tube.

Mouth and Esophagus

- Under normal conditions, xenobiotics are poorly absorbed within the **mouth** and **esophagus**
- due mainly to the very short time that a substance resides within these portions of the gastrointestinal tract.
- There are some notable exceptions. For example: Nicotine readily penetrates the mouth mucosa.
- Nitroglycerin is placed under the tongue (sublingual) for immediate absorption and treatment of heart conditions.
- The sublingual mucosa under the tongue and in some areas of the mouth is thin and highly vascularized and allows some substances to be rapidly absorbed.

Stomach

- The stomach, with its high acidity (pH 1-3), is a significant site for the absorption of weak organic acids, which exist in a diffusible, nonionized and lipid-soluble form.
- In contrast, weak bases will be highly ionized and therefore poorly absorbed.
- The acidic stomach may chemically break down some substances. For this reason, those substances must be administered in gelatin capsules or enteric coated tablets,

Stomach

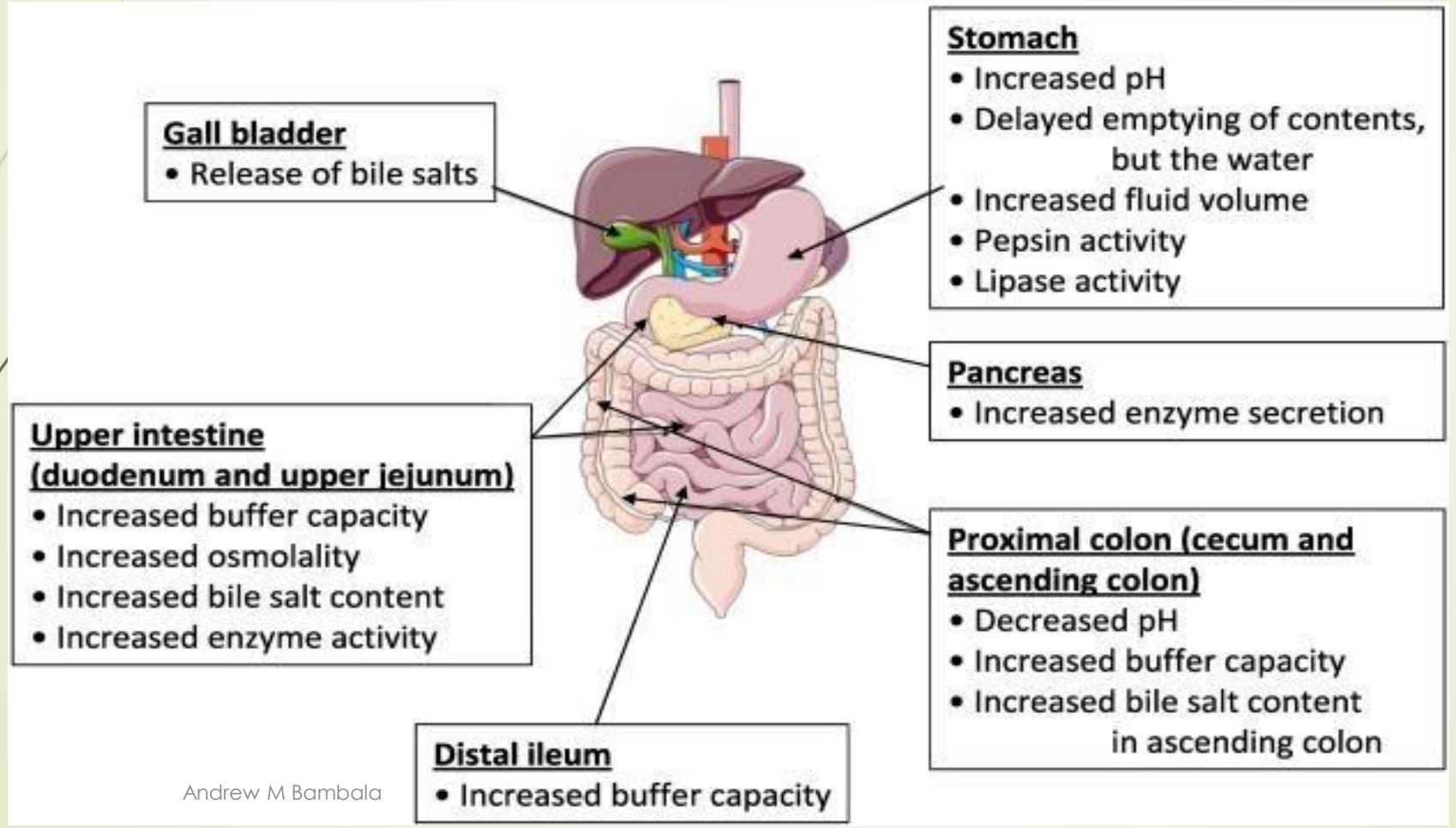
- Food/Chemicals that can pass through the stomach into the intestine before can they dissolve and release their contents for absorption
- Another determinant that affects the amount of a substance that will be absorbed in the stomach is the presence of food in the stomach which affects the gastric emptying rate
- Food ingested at the same time as the xenobiotic may result in a considerable difference in absorption of the xenobiotic.

Factors that affect absorption (Bioavailability)

Foods/Toxicants may influence the bioavailability of drugs by:

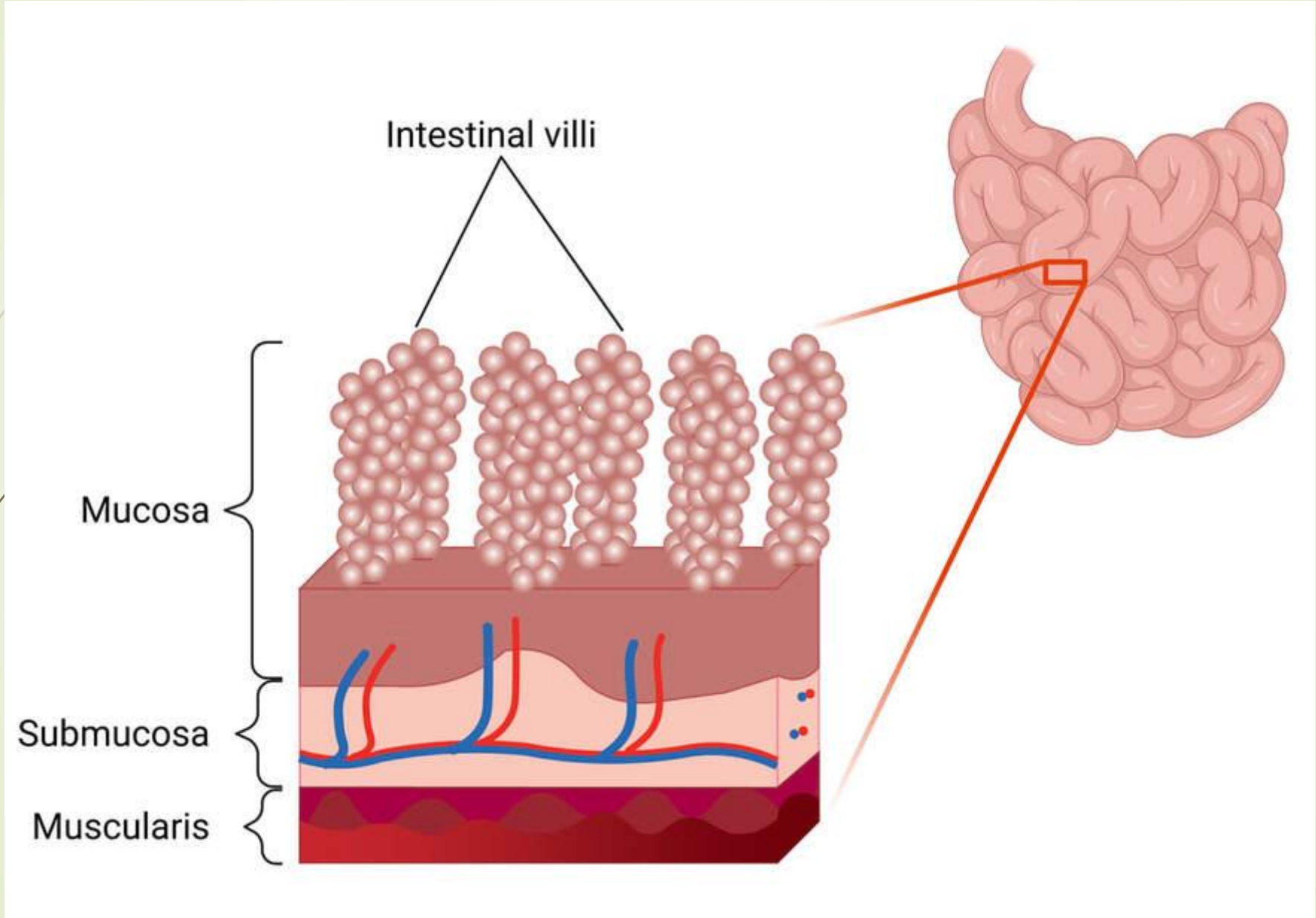
- altering luminal pH
- direct binding of drugs to substances in the food
- gastric emptying
- intestinal transit time
- mucosal absorption
- chemical interactions
- hepatic blood flow

Factors affecting absorption at the different sites of the GIT



Intestine

- The greatest absorption of chemicals, as with nutrients, takes place in the intestine, particularly in the small intestine.
- The intestine has a large surface area consisting of outward projections of the thin (one-cell thick) mucosa into the lumen of the intestine (the villi)
- This large surface area facilitates diffusion of substances across the cell membranes of the intestinal mucosa.
- Since the pH is near neutral (pH 5-8), both weak bases and weak acids are nonionized and are usually readily absorbed by passive diffusion.
- Lipid soluble, small molecules effectively enter the body from the intestine by passive diffusion.


Intestinal villi
Mucosa
Submucosa
Muscularis

Intestine

- In addition to passive diffusion, facilitated and active transport mechanisms move certain substances across the intestinal cells into the body, including essential nutrients such as glucose, amino acids, and calcium.
- These mechanisms also transport strong acids, strong bases, large molecules, and metals, including some important toxins.
- For example, lead, thallium, and paraquat (herbicide) are toxins that active transport systems move across the intestinal wall.

Intestine

- The slow movement of ingested substances through the intestinal tract can influence their absorption.
- This slow passage increases the length of time that a compound is available for absorption at the intestinal membrane barrier.
- Intestinal microflora and gastrointestinal enzymes can affect the toxicity of ingested substances.
- Some ingested substances may be only poorly absorbed but they may be biotransformed within the gastrointestinal tract. In some cases, their biotransformed products may be absorbed and be more toxic than the ingested substance.
- An important example is the formation of carcinogenic nitrosamines from non-carcinogenic amines by intestinal flora.

Colon and Rectum

- Very little absorption takes place in the colon and rectum.
- As a rule, if a xenobiotic has not been absorbed after passing through the stomach or small intestine, very little further absorption will occur.
- However, there are some exceptions, as some medicines may be administered as rectal suppositories with significant absorption.
- An example is Anusol (hydrocortisone preparation) used for the treatment of local inflammation which is partially absorbed (about 25%).

"Humans and other animals swallow a great variety and often large amounts of chemicals as nutrients, incidental food additives and contaminants, drugs, and microbes of all sorts exposing the alimentary system to many potentially toxic substances .

It is estimated that there are > 10,000 food additives and residues totaling 1.5 kg year− 1 capita− 1 in the typical human diet (Gad, 2007). Concern about these chemicals has led to a surge of the natural/organic/unprocessed food industry."

Pathophysiological mechanisms of gastrointestinal toxicity

Mechanisms	Examples
Direct effects on cell membrane	Plant lectins, alcohol, NSAIDs, bile acids, sodium chloride
Stimulation of mucosal proliferation	Dioxins, aromatic hydrocarbons, pancreatic enzyme preparations, alcohol
Inhibition of mucosal proliferation	Anticancer drugs
Nerve damage	Surfactants, capsaicin
Reduced blood flow	NSAIDs, alcohol
Activation of emetic pathways	Anticancer agents, 5-HT, dopamine
Disruption of intracellular signal transduction	Cholera toxin
Release of regulatory substances	Antigens, endotoxins, inflammation. NSAIDs
Generation of oxygen free radicals	NSAIDs, laxatives, lipid hydroperoxides, inflammatory responses
Chemotaxis and activation of granulocytes	Endotoxins, antigens
Release of enzymes	Endotoxins, antigens, cytokines
Activation of enzymes	Cholera toxin, nitric oxide
Inhibition of enzymes	NSAIDs, AChEI pesticides
Increase susceptibility to H^+	NSAIDs
Intracellular toxicity	Heavy metals

Toxic clinical effects

- Nausea, emesis, diarrhea, and/or pain.
- Enzyme insufficiency (lactase, lipase),
- inflammation, polyps, neoplasms,
- functional disturbances such as excess mucus production, delayed gastric emptying, or structural damage such as ulcers are more subtle.
- Over three-fourths of documented poisoning cases result from ingestion of xenobiotics (Bronstein et al., 2008).
- GIT disturbances are second only to the neurologic effects of toxins (Olson et al., 2000).
- The use of animal models in preclinical studies is effective in predicting gastrointestinal system damage over 80% of the time (Betton, 2013).

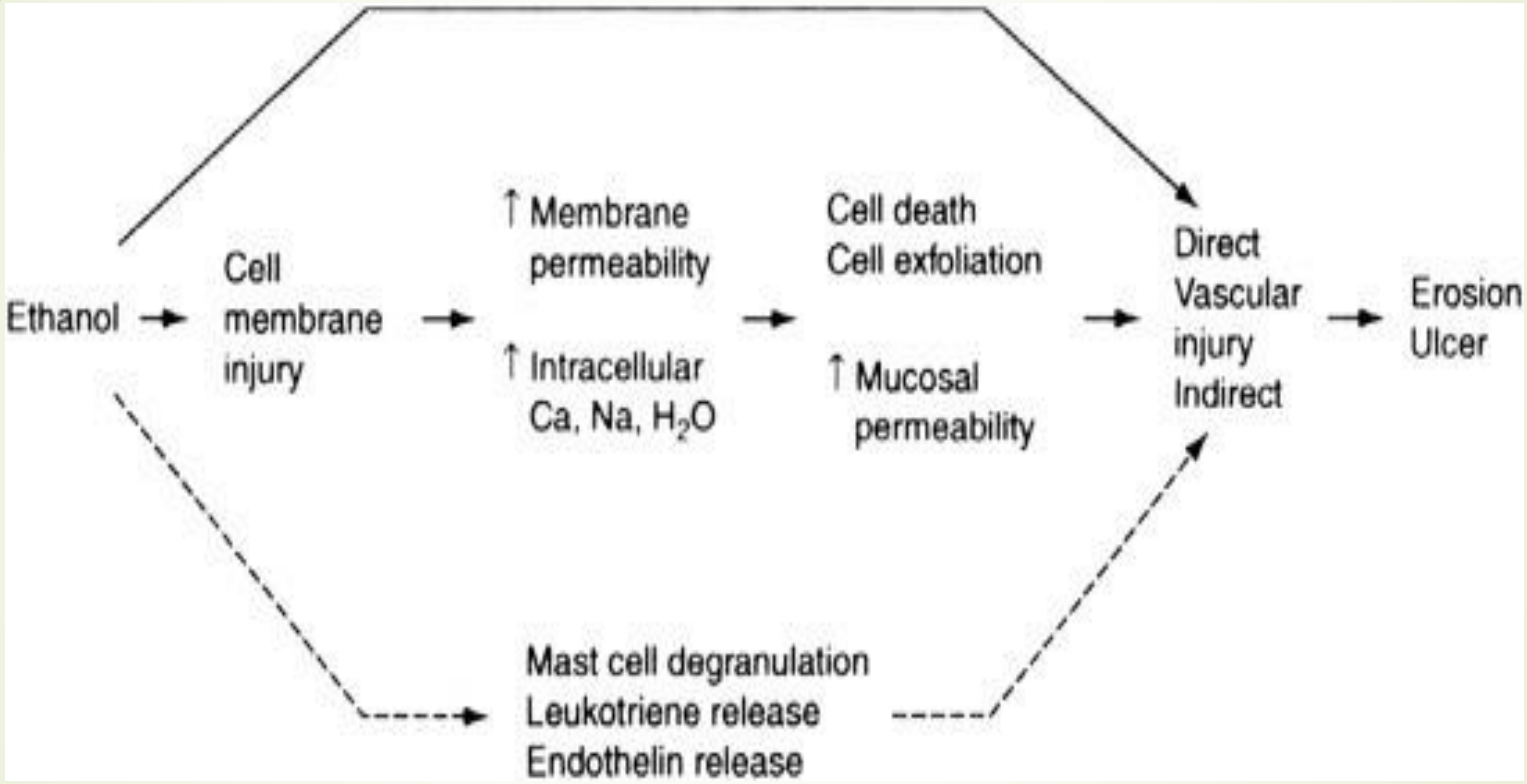
Toxic clinical effects

Direct Effects on Cell Membranes

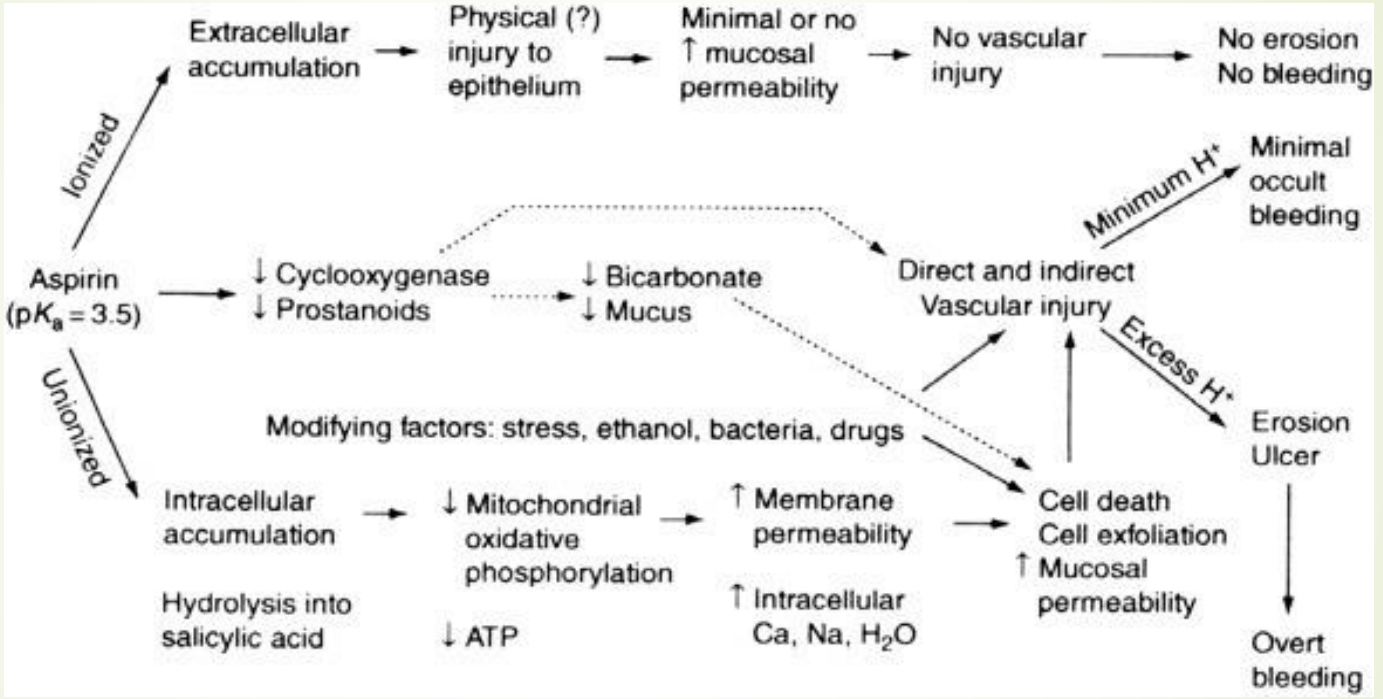
- Ingested substances can induce toxic effects by direct actions on gastrointestinal epithelial cell membranes. Examples include alcohol and *other organic solvents, aspirin-like drugs bile acids, sodium chloride, and certain constituents of edible plants*.
- High concentrations of ethyl alcohol (> 40%) can cause direct damage to esophageal and gastric epithelial cell membranes.

Toxic clinical effects

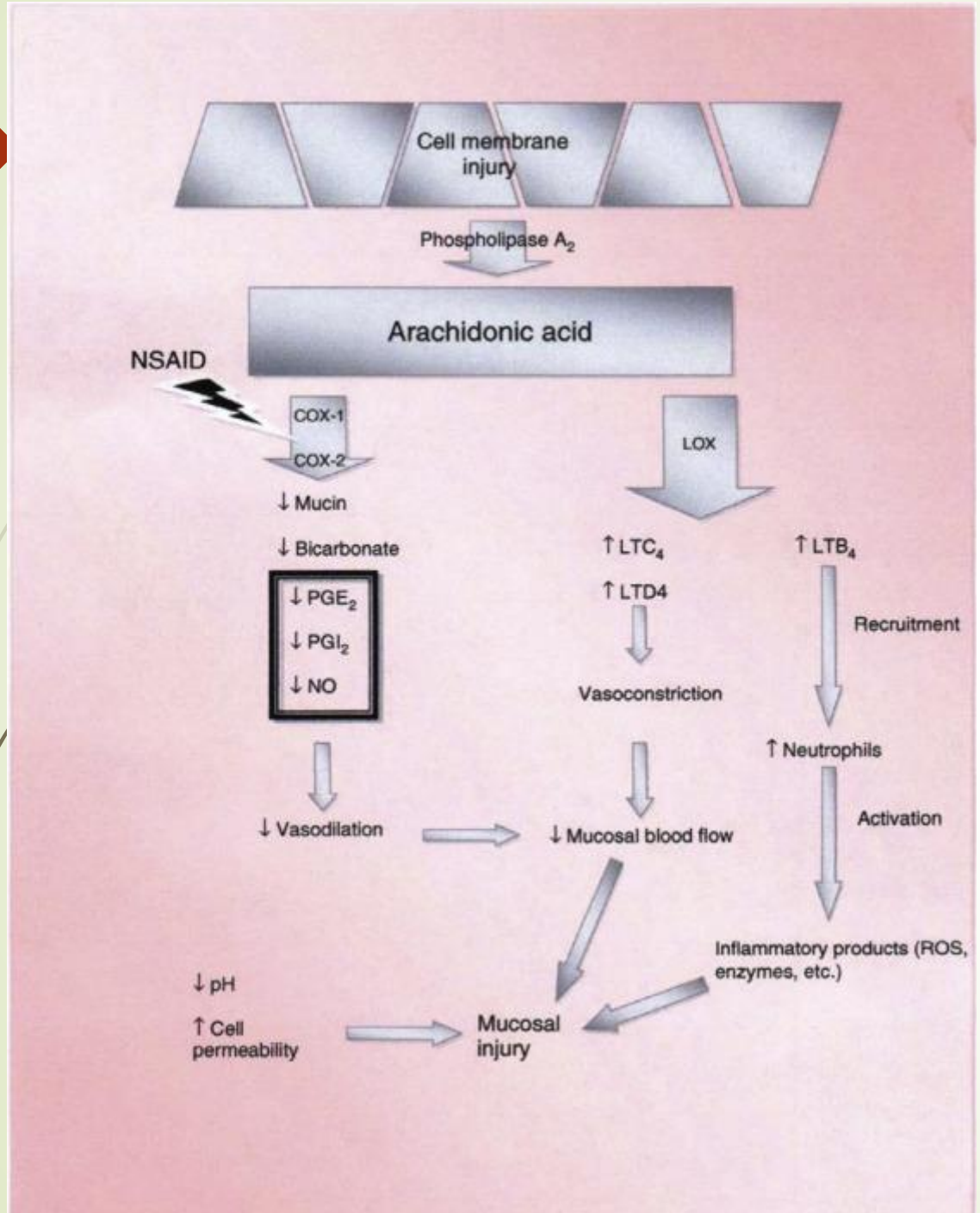
- Bile acids, aspirin, and salicylate exhibit similar effects (Black et al., 1973, Kasbekar, 1973). Aspirin and salicylate can alter production of prostanoids, products of the cyclooxygenase pathway of arachidonic acid metabolism.
- Exposure of the gastric mucosa to a high concentration of alcohol is associated with increased synthesis of prostaglandins and prostacyclin (Smith et al., 1991).



Pathogenesis of alcohol-related gastric injury.



The pathophysiology of aspirin toxicity.



Mechanism of nonsteroidal antiinflammatory drug (NSAID)-induced gastrointestinal erosion and ulceration. Inhibition of cyclooxygenase (COX) by NSAIDs results in decreased production of mucin, bicarbonate, prostaglandins (PGE2, PGI2), and nitric oxide (NO). Decreases of the latter three compounds result in decreased vasodilation within the gastric mucosa, predisposing it to injury. With the COX pathway inhibited, the lipoxygenase (LOX) pathway is favored, increasing production of leukotrienes (LTC4, LTD4) that promote vasoconstriction; coupled with decreased vasodilation, there is decreased gastrointestinal mucosal blood flow. Increases in LTB4 trigger attraction and activation of neutrophils and release of reactive oxygen species (ROS) and enzymes, which promote mucosal injury.

Conclusions

- Foreign and endogenous chemicals can produce gastrointestinal toxicity by a number of mechanisms that result in alterations in normal function.
- It is likely that the toxicities are often unrecognized because the changes in function may be minor or may be compensated by the complex regulatory apparatus that protects vital gastrointestinal functions.
- The gastrointestinal system has a number of structures and functions that are in a delicate balance to effect digestion.
- Because the alimentary route delivers most xenobiotics, it is exposed to high local concentrations of these agents or their biotransformed metabolites directly or after uptake and biliary excretion.

Conclusions

- The GI system is quite plastic in adapting to dietary or altered metabolic demand.
- Crypt cells are highly responsive to stimulation and are affected by pharmaceuticals, microbes, and DNA damaging agents.
- Significant interspecies and target organ differences exist in both the predisposition to toxicants and carcinogens, making the choice of an appropriate animal model critical.
- A greater mechanistic appreciation and understanding of toxic gastroenteropathy is needed to facilitate effective treatment

Reading List

- Rang, Dale, Ritter (2007).Rang&Dale's Pharmacology,6thed.,Ch.9–11.
- Brantonetal (2008).Goodman & Gilman : Manual of Pharmacology & Therapeutics. Ch.6–10.
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- Klaassen CD, Casarett LJ, Doull J. Casarett and Doull's toxicology : the basic science of poisons. 8th ed. ed. New York: New York : McGraw-Hill; 2013.
- Gelberg H. Pathophysiological Mechanisms of Gastrointestinal Toxicity. Comprehensive Toxicology. 2018;139-178. doi:10.1016/B978-0-12-801238-3.10923-7