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M2 GI Sequence

Malabsorption of Nutrients

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University of Michigan
Medical School

Learning Objectives

- At the end of this lecture on malabsorption, students should be able to:
- 1. Identify the major pathophysiological mechanisms responsible for generalized malabsorption and malabsorption of specific nutrients.
- 2. Construct a differential diagnosis for a patient with suspected malabsorption with items listed in the order of relative likelihood.
- 3. Identify the most appropriate tests to identify malabsorption of specific nutrients.

Gastrointestinal Tract

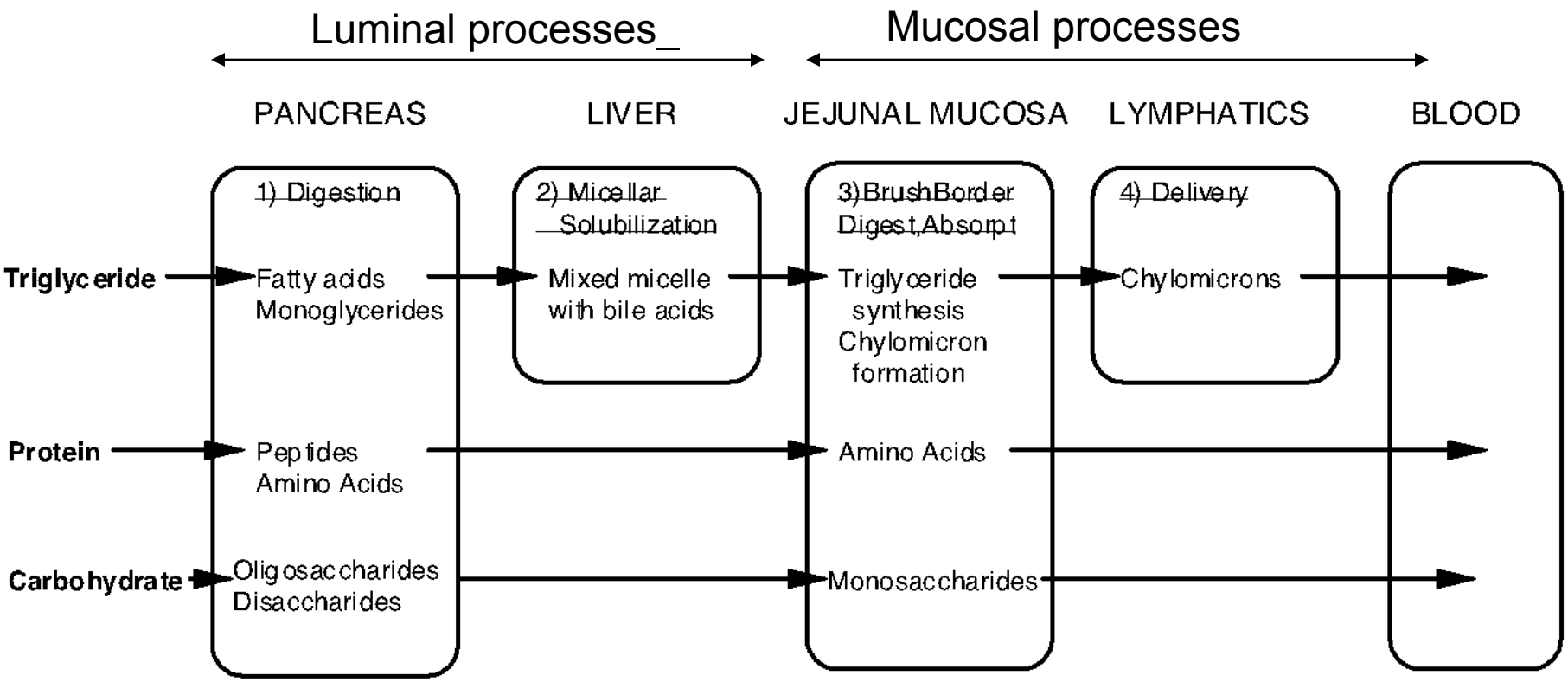
A series of organs connected in series to the outside world whose function is:

1. Efficient uptake from a mixed intake of sufficient amounts of fuel (hexoses, amino acids, fatty acids) and essential chemicals (I.e., those that cannot be synthesized).

2. Exclusion other, potentially harmful, organic and inorganic compounds and infectious agents.

This process is not normally perfect, however malabsorption is the clinical state in which digestion/absorption are impaired sufficiently to lead to clinical symptoms.

Normal Digestion and Absorption



These phases of digestion are reviewed and defined in the textbook.

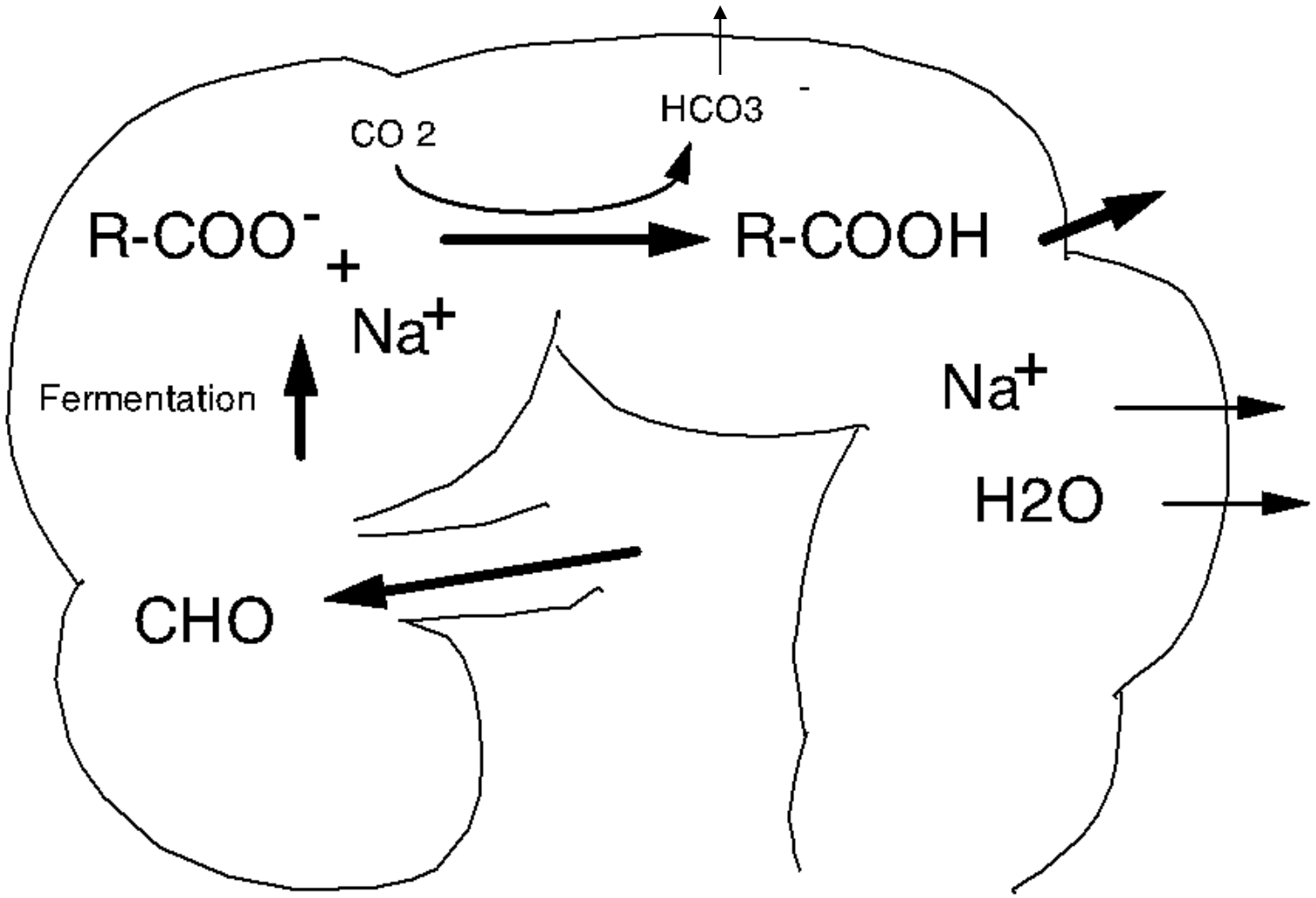
Efficiency of Small Bowel Absorption: not perfect

- Nutrients
  - Fat — 93-95% of triglyceride
  - Starch — 80-95% depending on type
  - Disaccharides — 96-98%
  - Protein — 95-99%
- Minerals
  - Iron — 6-20% depending on body iron status

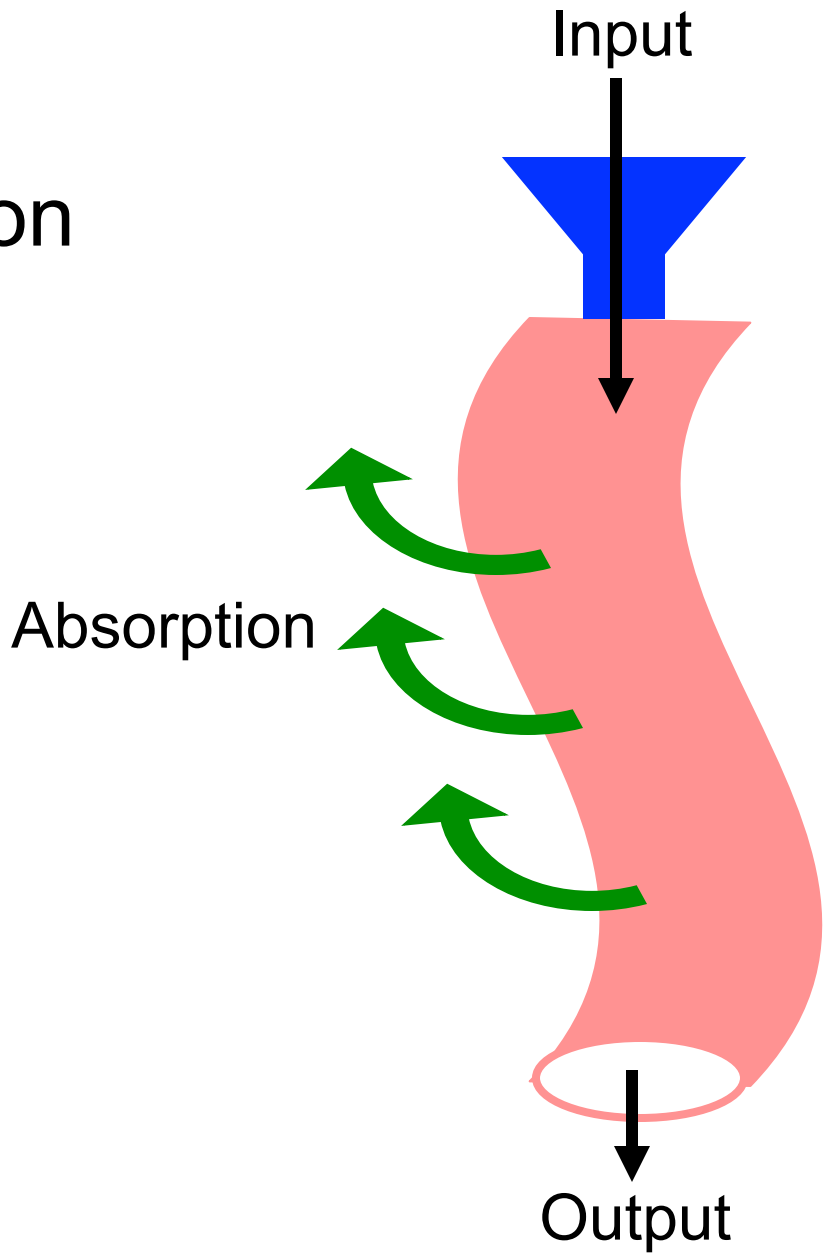
Intestinal Reserve: excessive capacity is built-in

- Several processes/enzymes are present for some digestive processes
  - Pancreatic and brush-border oligosaccharidases and proteinases
- Pancreas secretes an excess of enzymes
- Surface area for absorption is in excess
- Colon scavenges malabsorbed carbohydrates as short chain fatty acids, products of bacterial fermentation

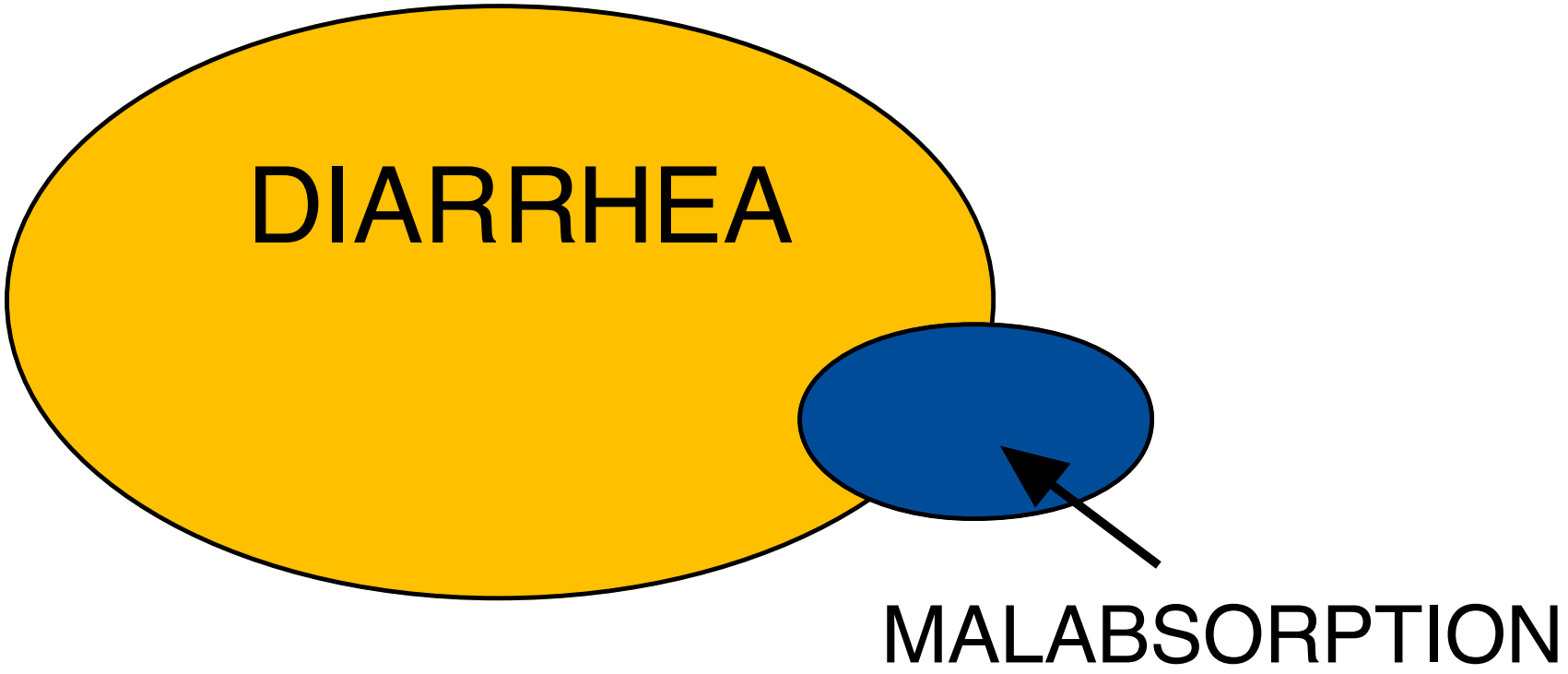
Colon Salvage of Malabsorbed Carbohydrate



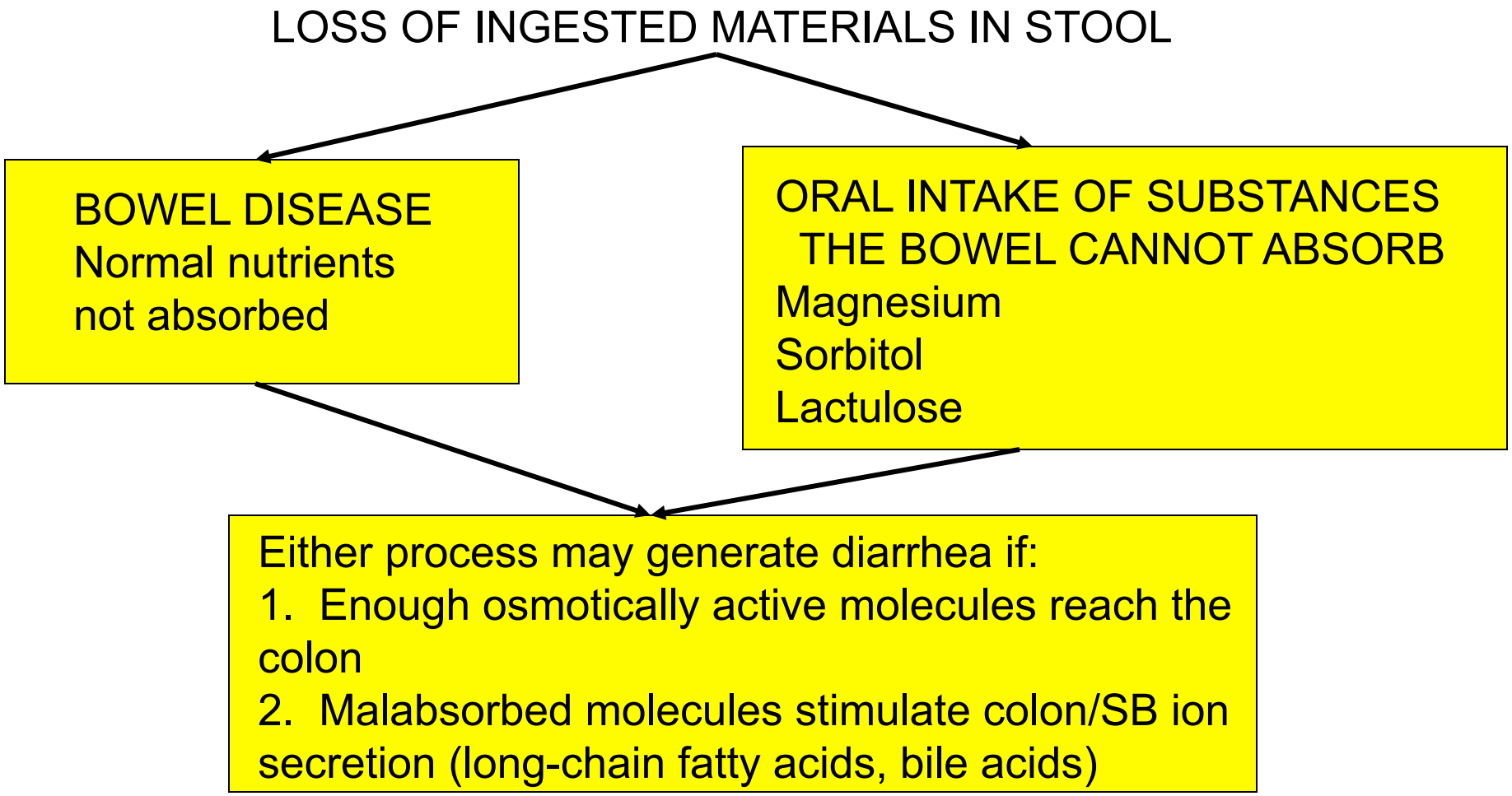
Malabsorption
= input – absorption



Relationship between Diarrhea and Malabsorption



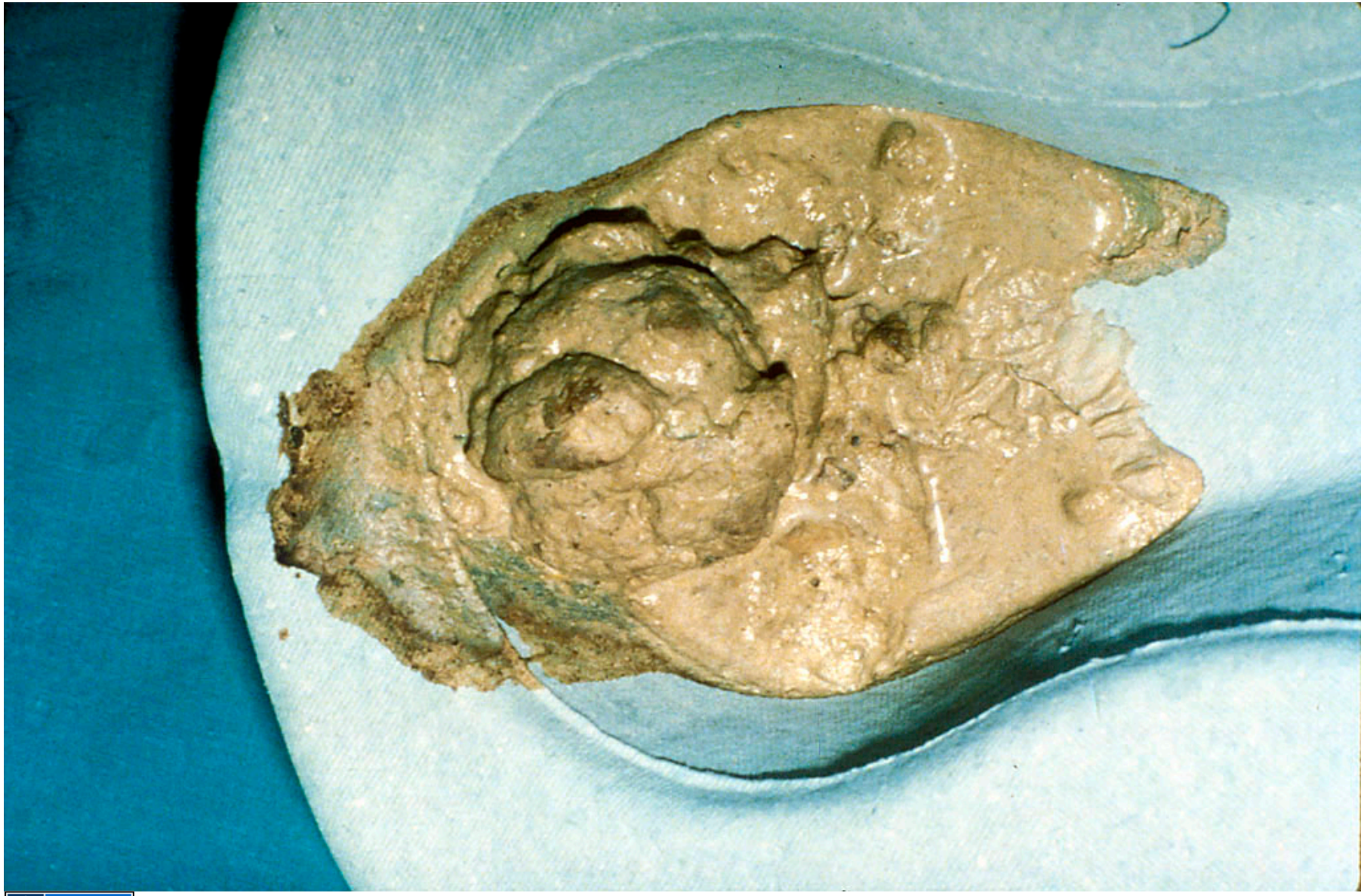
Malabsorption: Relationship to Diarrhea



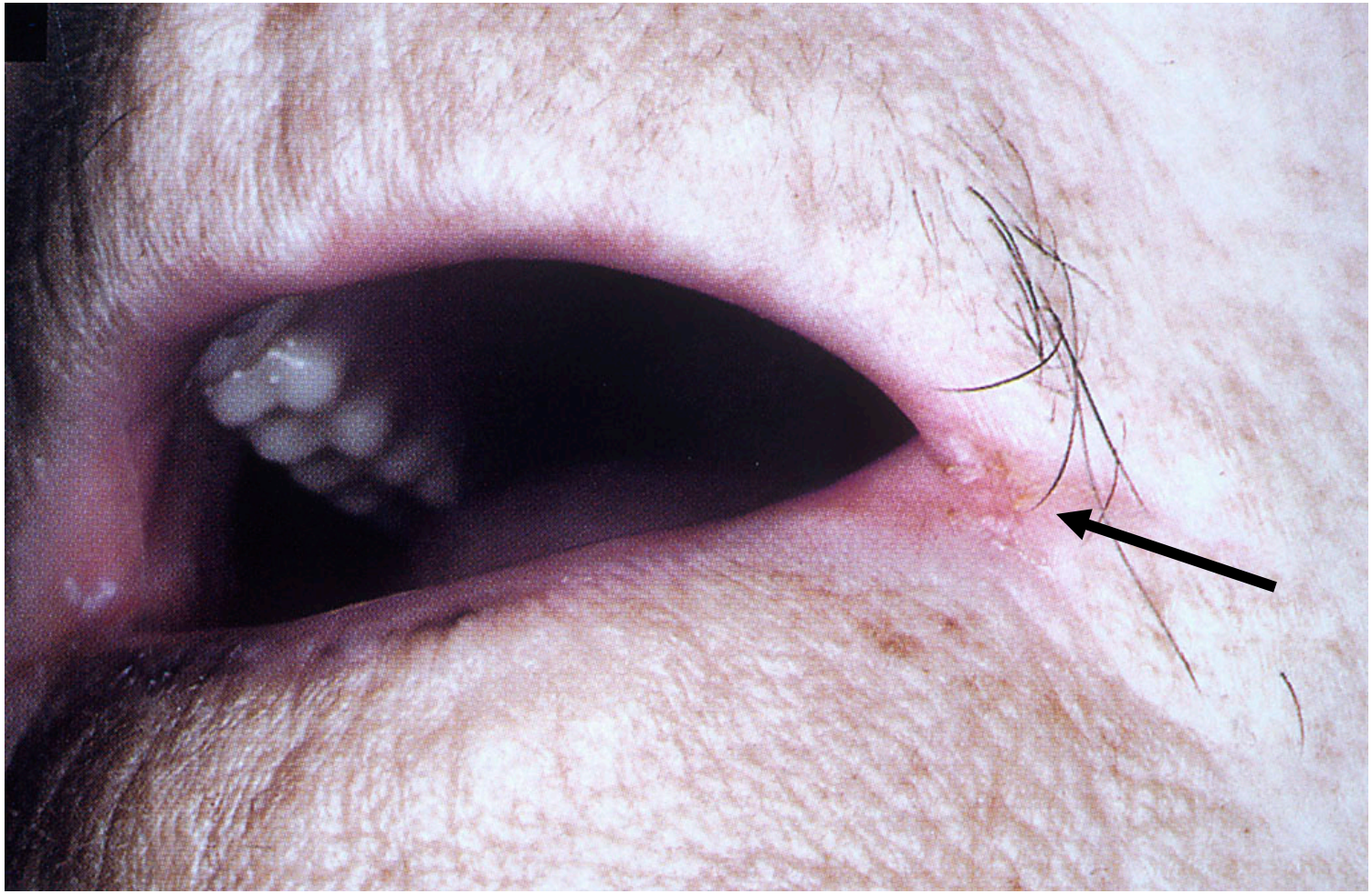
Clinical Clues to Nutrient Malabsorption

Weight loss, fatigue, “out of gas”
Intake of excess calories without weight gain
Diarrhea: bulky, oily stools (fat)
liquid stools (carbohydrates)
Excess flatus
Evidence of vitamin/mineral deficiencies
glossitis, cheilosis (iron/B vitamins)
acrodermatitis (zinc)
dry skin and hair (essential fatty acids)
anemia microcytic - iron deficiency
macrocytic - folate/B-12 deficiency
osteopenia/osteoporosis Vit D/calcium
night blindness Vitamin A
easy bruising Vitamin K

Steatorrhea



Angular Cheilosis

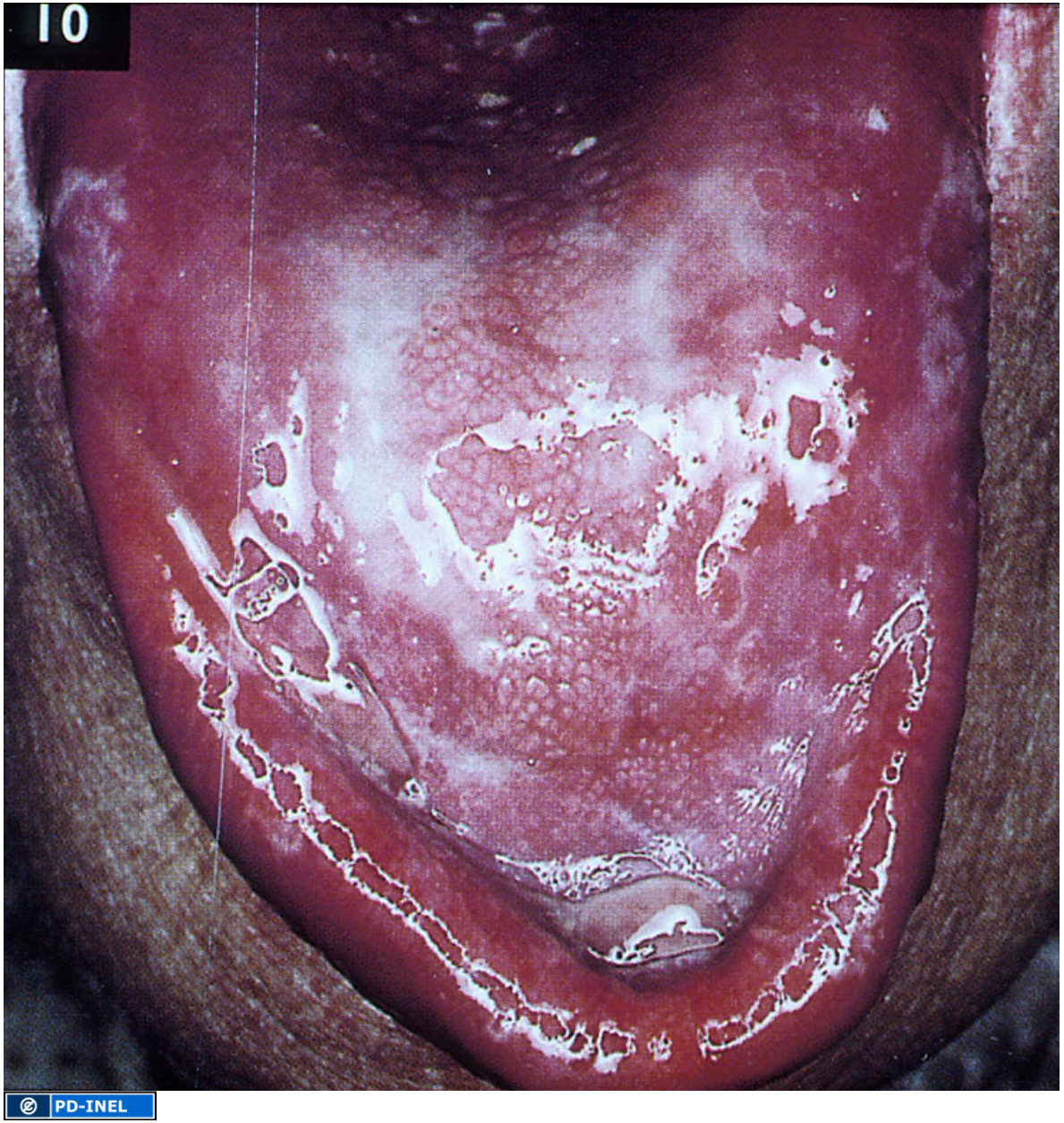


Deficiencies:

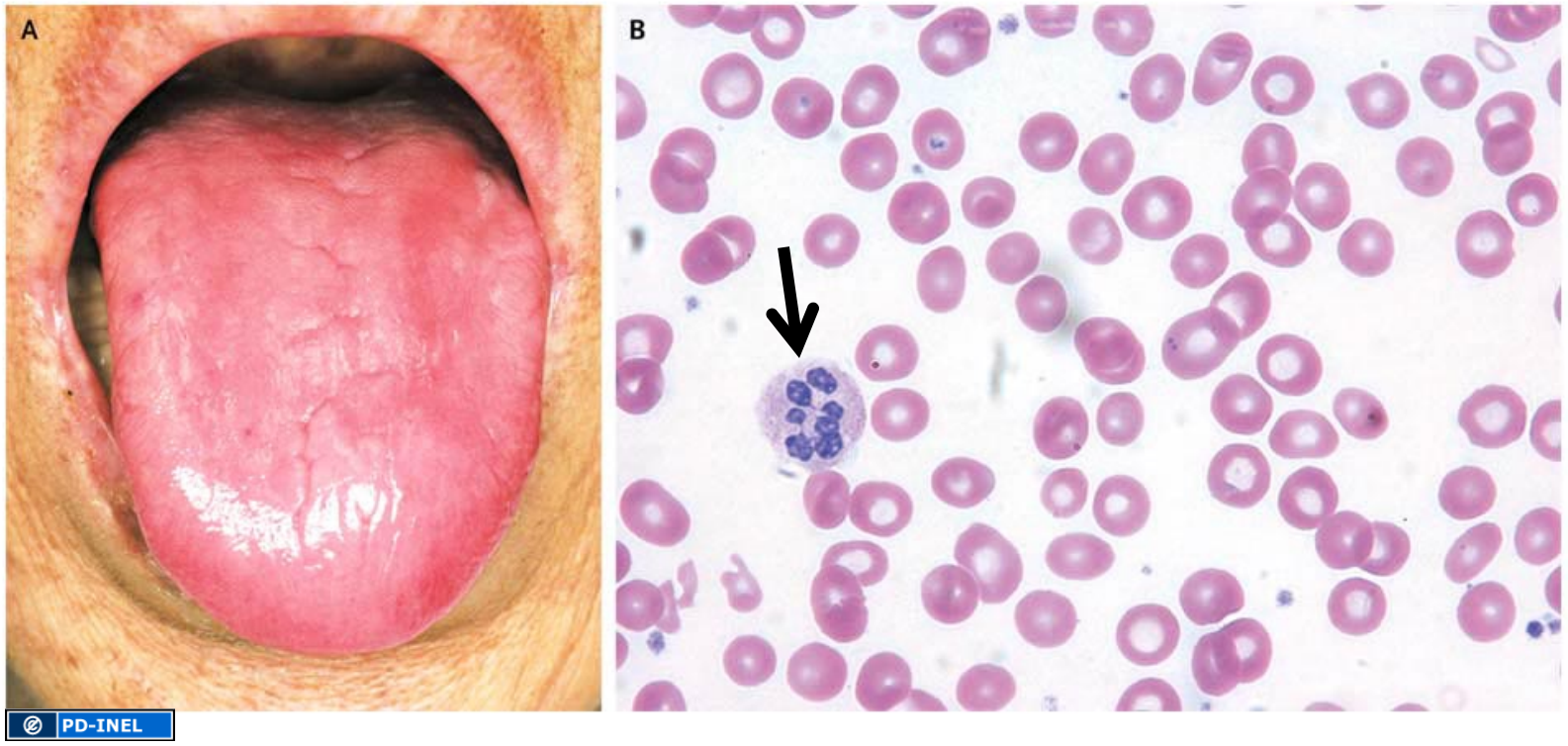
Vitamin B-12
Iron
Folate
B vitamins

Glossitis

Deficiencies of:
- Vitamin B-12
- Iron
- Folate
- Niacin



Red tongue with burning sensation



B-12 deficiency with hypersegmented PMNs

Zinc Deficiency

Acrodermatitis

92 Chronic zinc deficiency resulting in chronic eczematous eruption.

Acrodermatitis

Loss of hair, skin rash and diarrhea due to zinc deficiency

Normal digestion: a play in 3 acts

- Luminal digestion (pancreatic enzymes)
- Mucosal digestion (small bowel brush border enzymes)
- Mucosal absorption (small bowel mucosa, lymphatics)

Examples of Malabsorption

- Luminal Maldigestion: Fat
  - Chronic pancreatitis (Dr. Anderson)
- Mucosal Maldigestion: Disaccharide
  - Lactase deficiency
- Mucosal Maldigestion/Malabsorption: Generalized malabsorption
  - Celiac sprue
  - Bacterial overgrowth

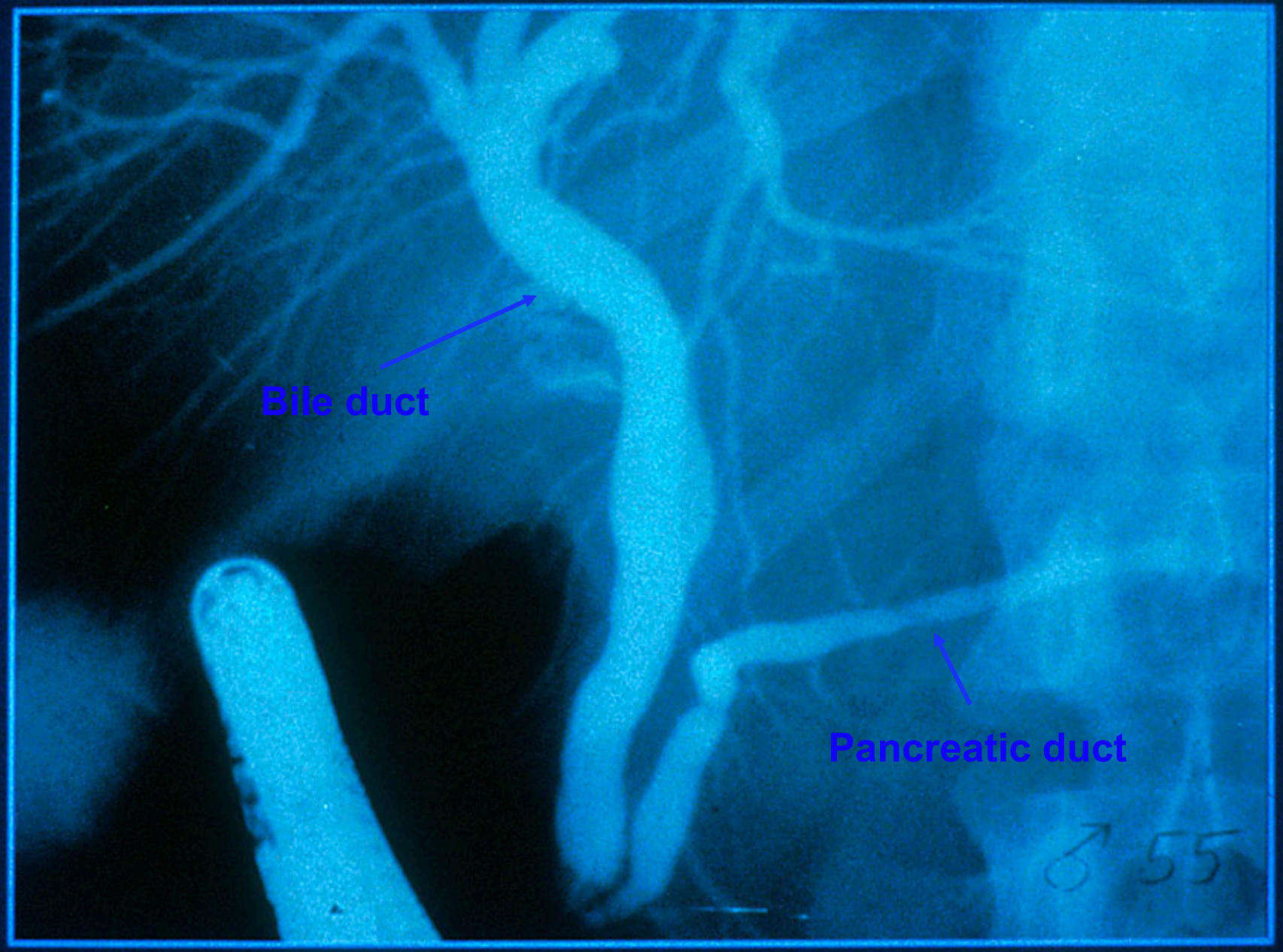
Luminal Digestion of Fat

- Requires pancreatic lipases
- Requires conjugated bile acids (salts) from the liver
- **No small intestinal back-up available**

Chronic Pancreatitis: the disease

- Often due to long-standing alcohol use
- Marked destruction of ducts/acini
- Reduced secretion of digestive enzymes, fluid, bicarbonate
- Lipases most affected
- Anatomic damage assessed by ERCP or endoscopic ultrasound (EUS) or pancreatic calcifications on x-rays

NORMAL ERCP

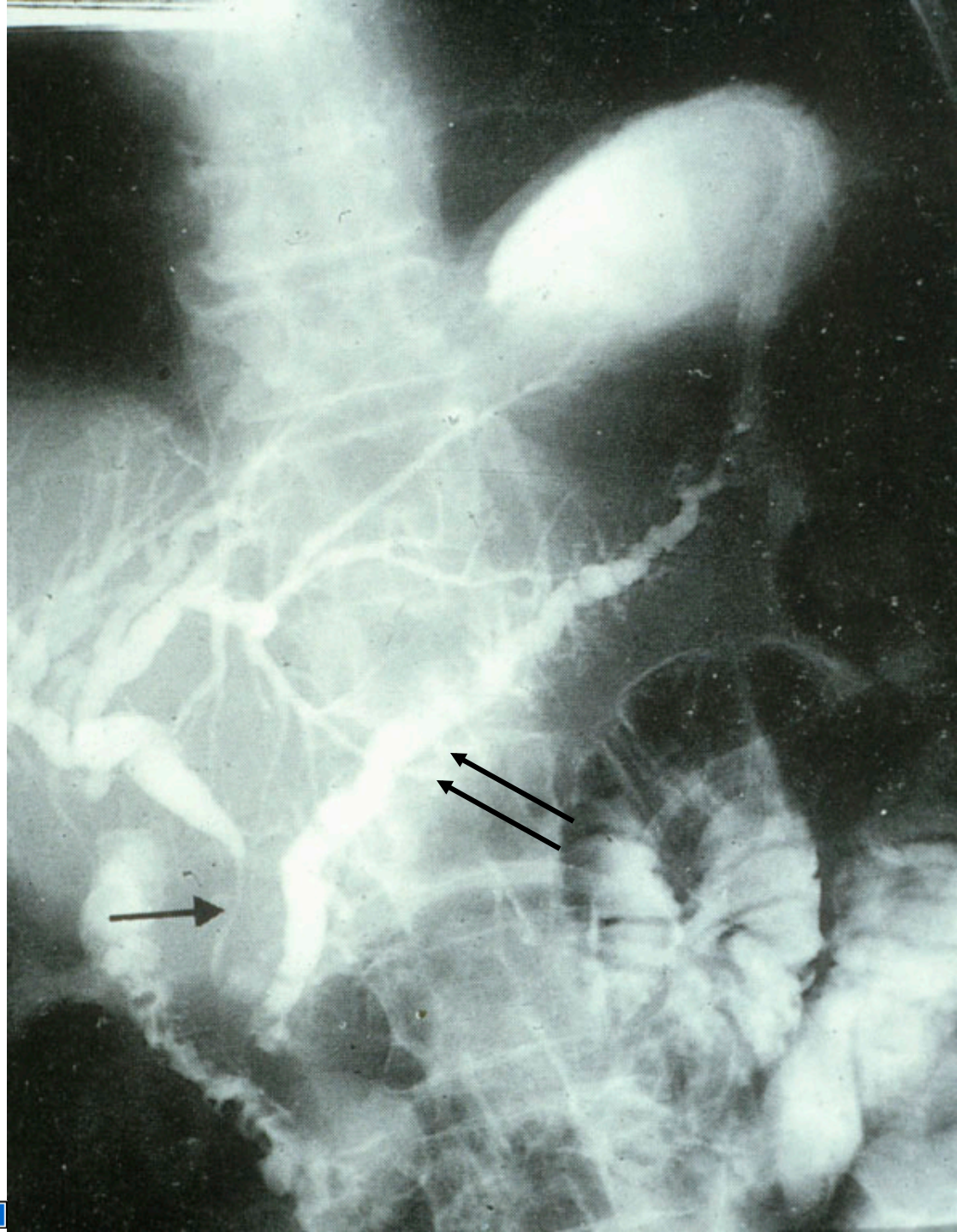


ERCP view of Chronic Pancreatitis

Endoscopic Retrograde CholangioPancreatography

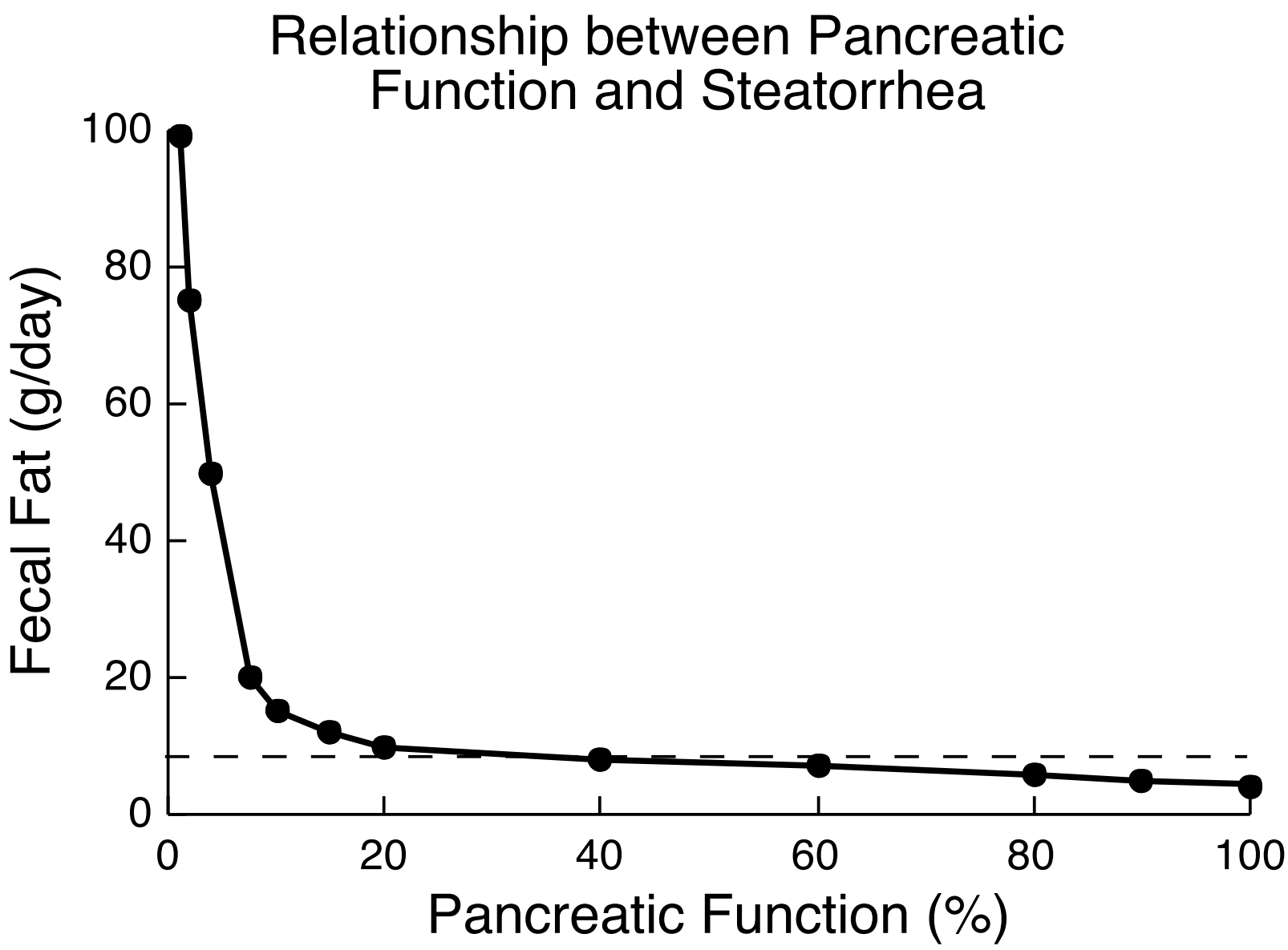
Single arrow points to bile duct compressed by fibrotic pancreas

Double arrow points to dilated pancreatic duct with short stubby side branches



Chronic Pancreatitis: Manifestations

- Weight loss
  - Malabsorption of fat due to loss/inactivation of pancreatic enzymes
- Bulky, oily stool
  - Steatorrhea is predominant abnormality
  - Loss of protein/carbohydrate in stool is much less as back-up mechanisms exist for protein/ carbohydrate digestion
- Fat soluble vitamin deficiency may occur in long-standing severe cases
- Edema/hypoproteinemia
  - Due to malnutrition with decreased hepatic synthesis of albumin/serum proteins


Relationship between Pancreatic Function and Steatorrhea
Fecal Fat (g/day)
100
80
60
40
20
0
0
20
40
60
80
100
Pancreatic Function (%)

Malabsorption due to Luminal Maldigestion of Fat: Differential Diagnosis

Pancreatic insufficiency:	Chronic pancreatitis
Bile salt deficiency:	Loss of terminal ileum: loss of bile salts in stool insufficient bile salts
Bacterial overgrowth:	Deconjugation and loss of bile acids
Gastric hypersecretion:	Acid inactivation of pancreatic enzymes

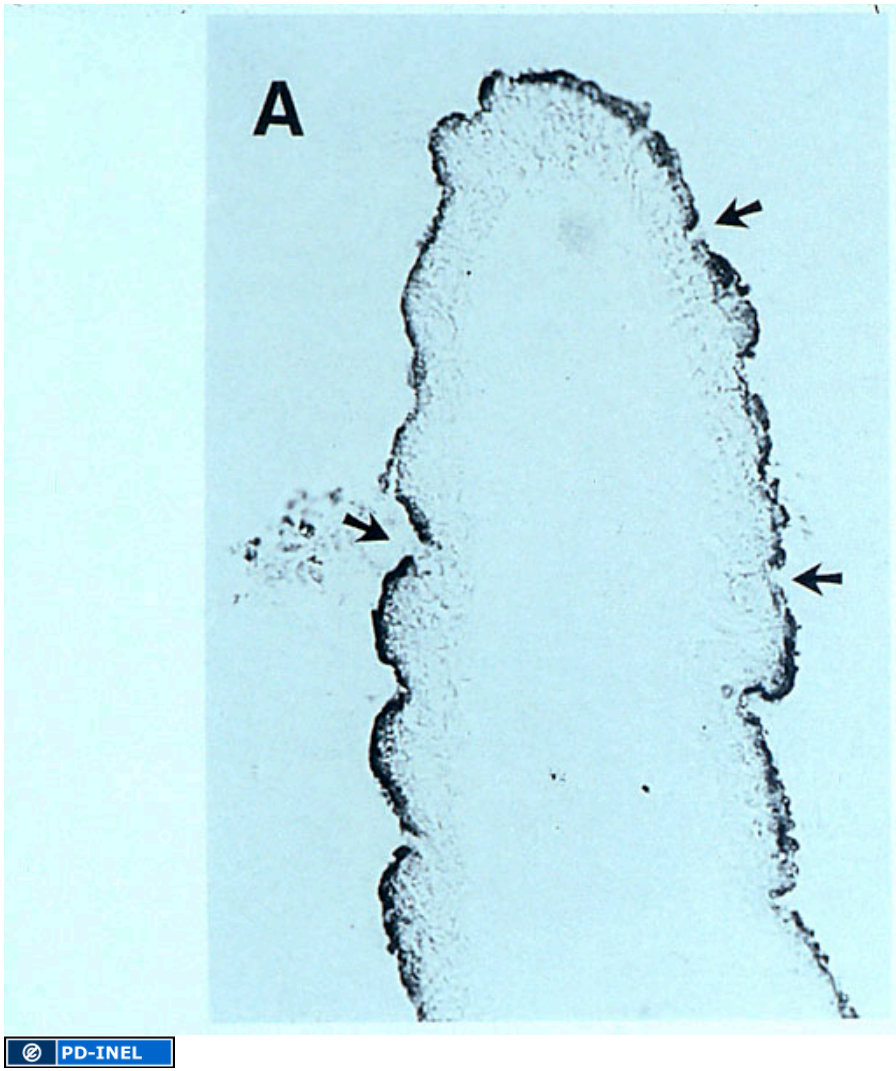
Examples of Malabsorption

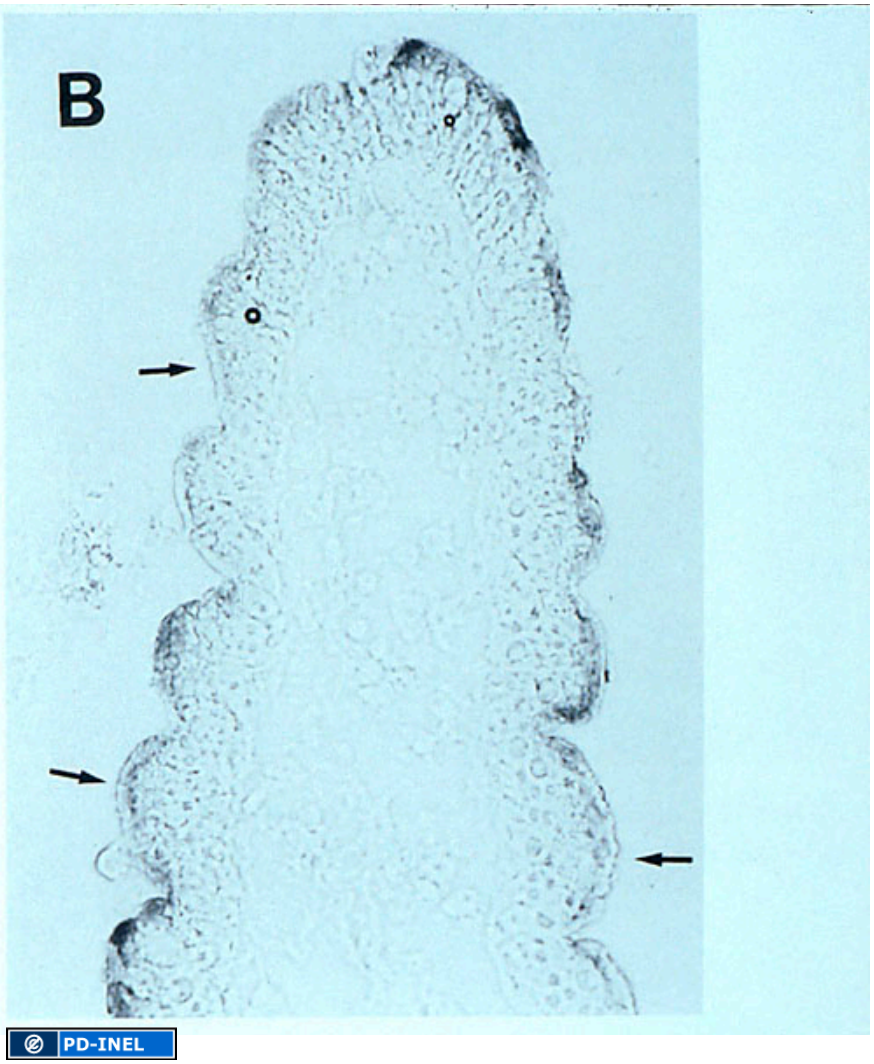
- Luminal Maldigestion: Fat
  - Chronic pancreatitis
- Mucosal Maldigestion: Disaccharide
  - Lactase deficiency
  - Any malabsorbed carbohydrate
- Mucosal Maldigestion/Malabsorption: Generalized malabsorption
  - Celiac sprue
  - Bacterial overgrowth

Lactase Deficiency

- Lactase: enterocyte brush-border disaccharidase found in nursing mammals.
- Lactase splits lactose in milk to the monosaccharides glucose and galactose for absorption.
- Normally little of the enzyme is made by villus enterocytes after weaning
  - exceptions are groups of humans who exhibit unusual persistence of lactase throughout adulthood
  - northern Europeans and other "dairying" cultures
- Symptoms occur upon ingestion of lactose by lactase-deficient individuals.

Lactase-Deficient Patient with low activity enzyme other individuals may also downregulate genes, etc.

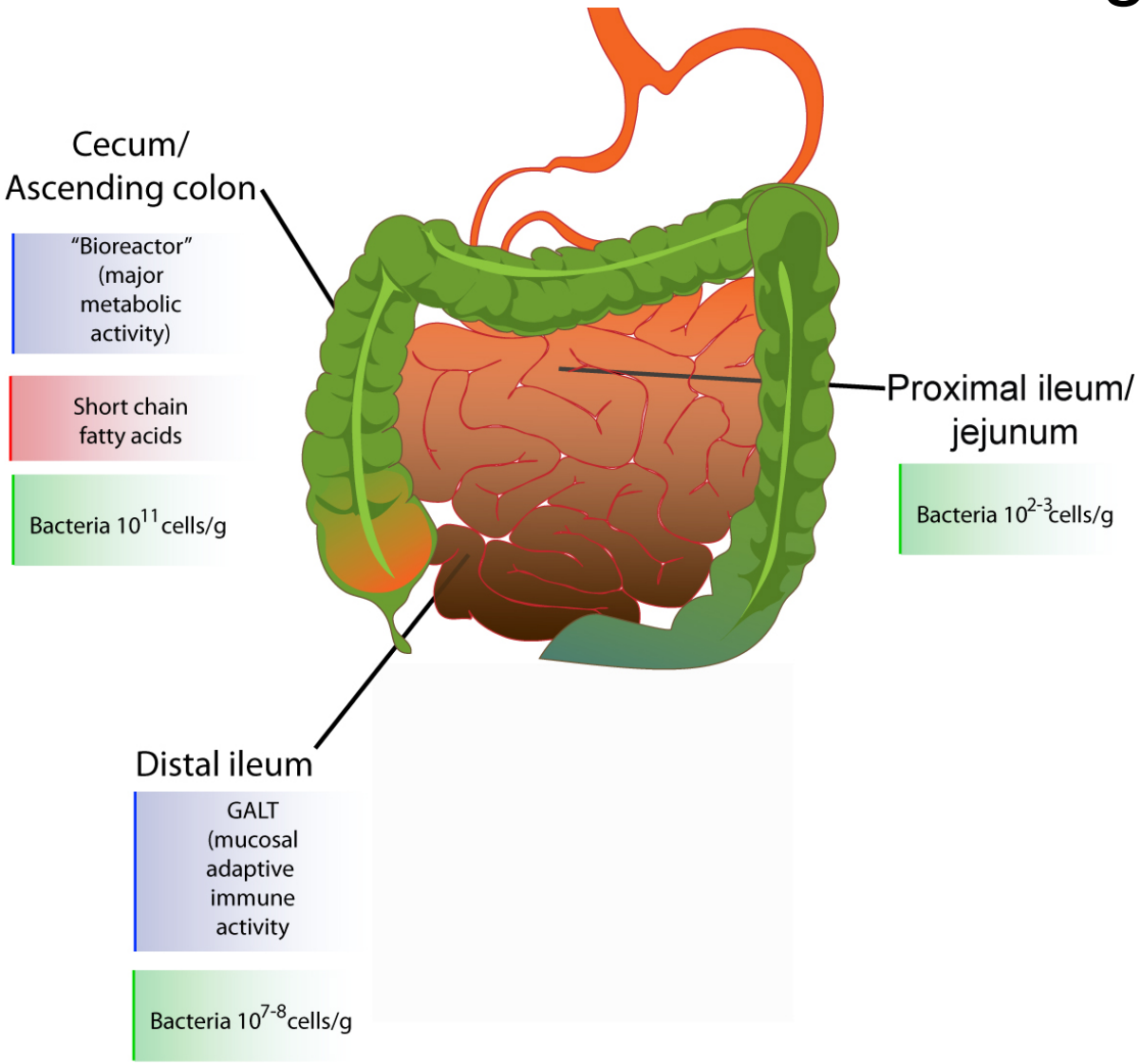




Protein stained
Protein present

Lactase activity stained
Poor enzyme activity

To understand flatus, one must understand the bacterial inhabitants of the gut.



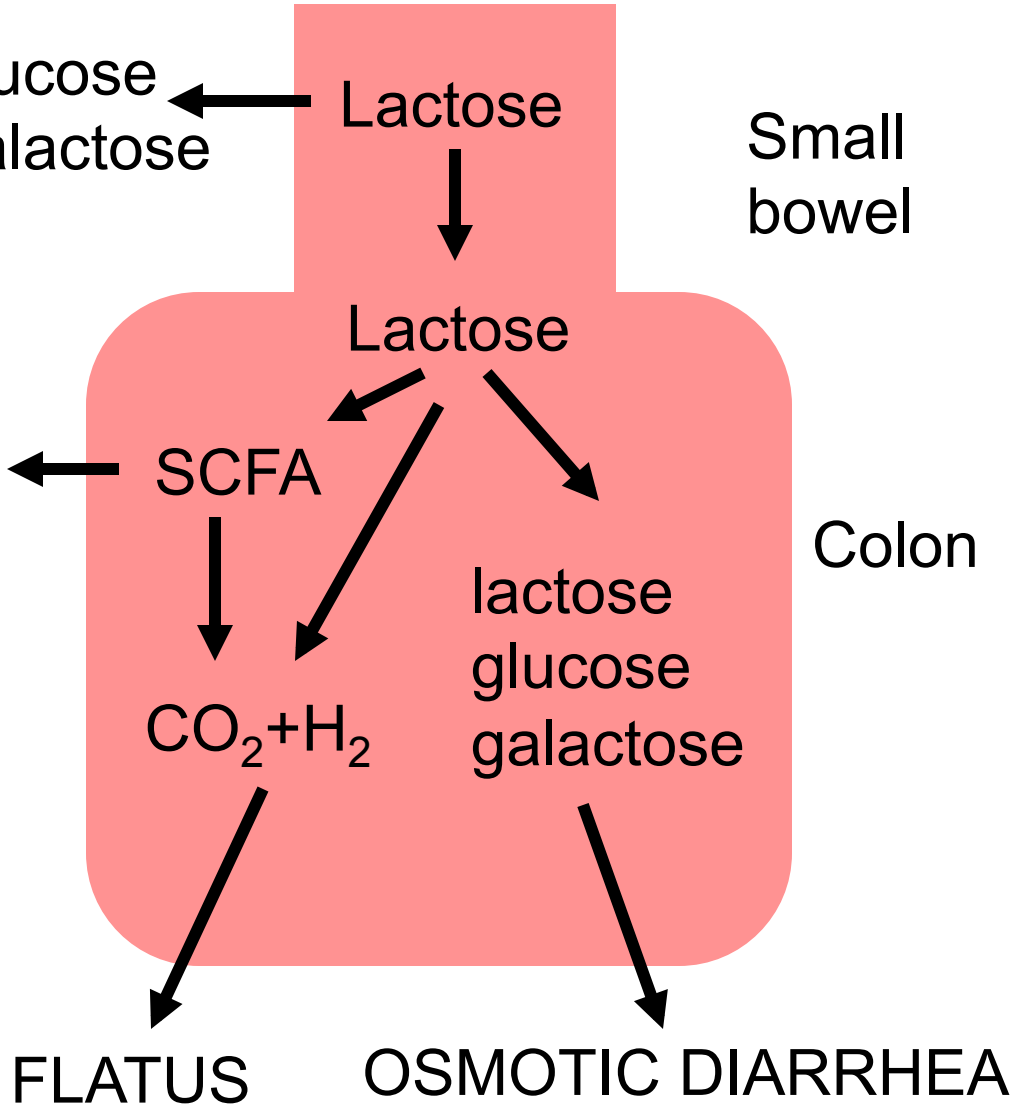
Mechanism of Lactose-Induced Diarrhea and Flatus

Lactase-sufficient
people absorb
>80% of lactose

Lactase-deficient
people absorb
<50% of lactose

6-20 grams malabsorbed
lactose = flatus
(1 g = 44 ml H_2)

≥20 grams malabsorbed
lactose = flatus+diarrhea



Examples of Malabsorption

- Luminal Maldigestion: Fat
  - Chronic pancreatitis
- Mucosal Maldigestion: Disaccharide
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- Mucosal Maldigestion/Malabsorption: Generalized malabsorption
  - Celiac sprue
  - Bacterial overgrowth

Celiac Sprue I

- Immune-mediated destruction of enterocytes in response to ingestion of the protein **gluten** found in wheat and certain other grains. A fraction termed gliadin contains the immunogenic material

- Small intestinal villi are damaged or destroyed - "**flat gut**" appearance.

- Mature digesting and transporting enterocytes are virtually absent.

Celiac Sprue - II

- Patchy disease - usually affects proximal intestine more than distal intestine (? why).
- Mucosal digestion and absorption are both severely impaired.
- Characteristic antibodies used in diagnosis: IgA antibodies to tissue transglutaminase or gliadin.
- Nice review: New England Journal of Medicine 357:1731, 2007

Pathophysiology of Celiac Sprue

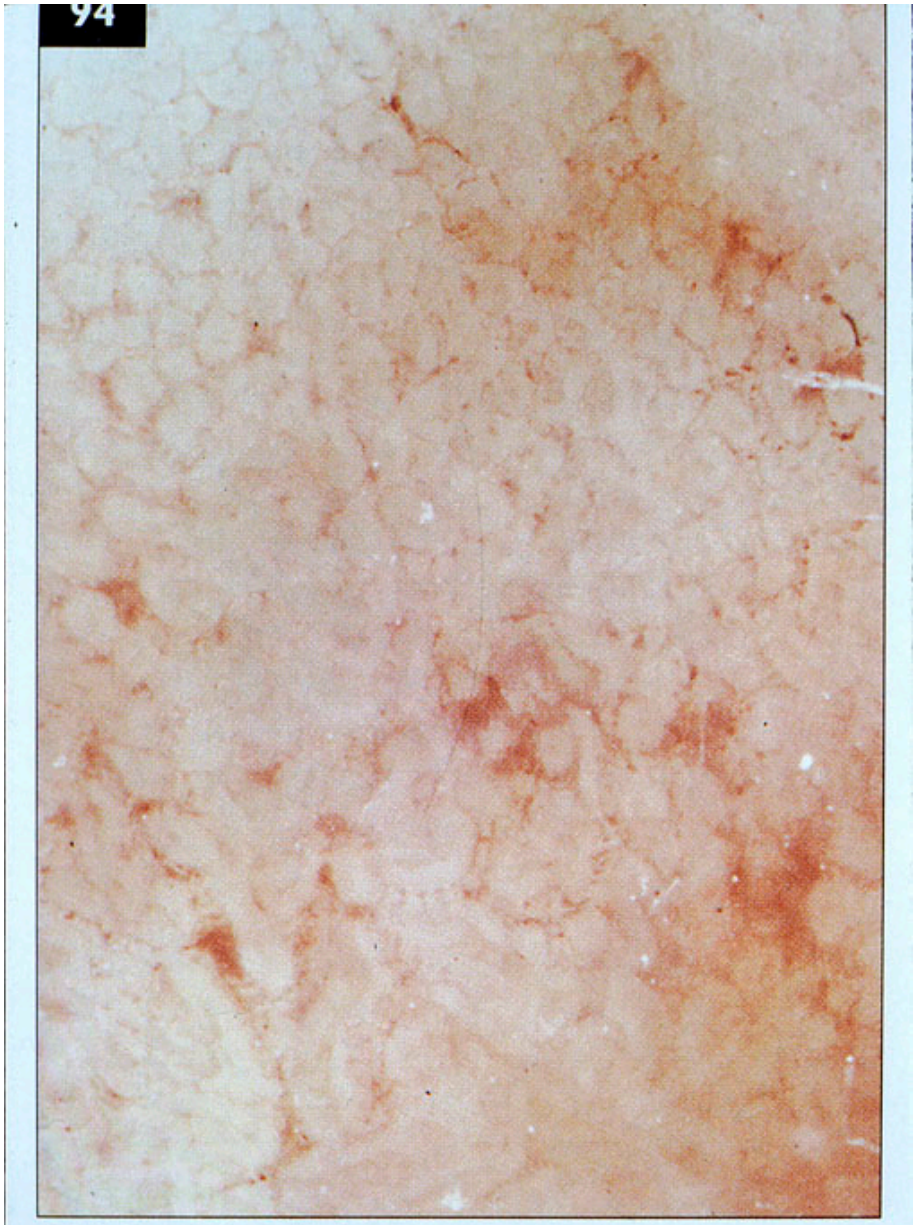
Image of celiac sprue pathophysiology removed

Stereomicroscopic view of small bowel biopsies:

Normal (below)

Celiac sprue (right)

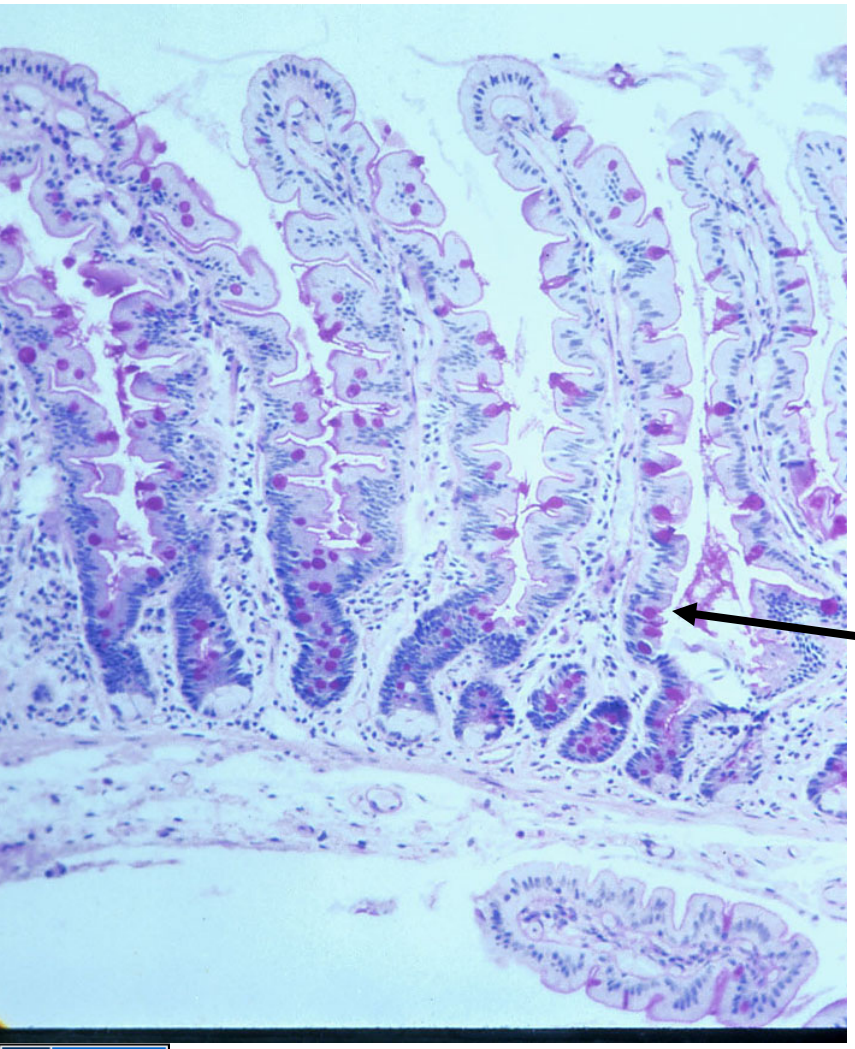
87 Normal dissecting microscope appearances of finger-like villi.



94 Flat jejunal biopsy under dissecting microscope showing no villi and only crypts in coeliac disease.

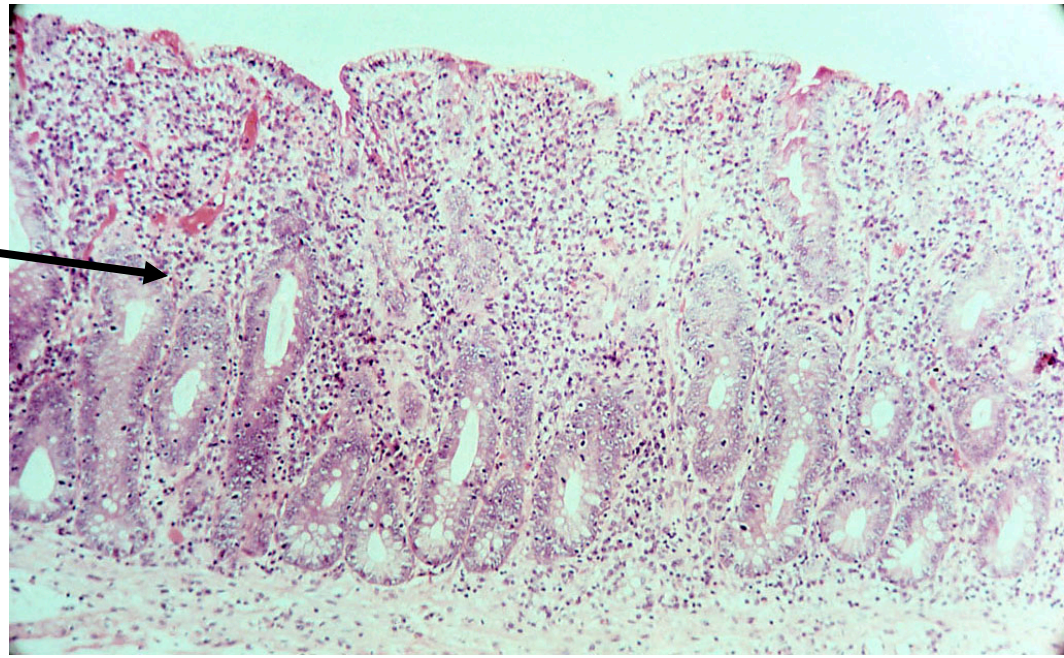
Small Bowel Biopsies

Normal



Celiac Sprue

Villi and mature enterocytes destroyed
Deep crypts (arrows)
Inflammation



Clinical Manifestations of Sprue

- Weight loss, often with increased appetite
- Bulky, oily stools – steatorrhea - fat malabsorption
- Flatus/frothy stools – carbohydrate malabsorption
- Anemia – deficiencies of iron, folate
- Osteopenic bone disease – Vitamin D and calcium malabsorption
- Edema/hypoproteinemia – protein deficiency and malnutrition
- Cheilosis and glossitis – B vitamin deficiencies

Malabsorbed Nutrients in Celiac Sprue

The degree of malabsorption depends on the severity and extent of the disease: how much of the small bowel is affected and how severely?

- Iron (why is this so??)
- Fat
- Fat-soluble vitamins
- Carbohydrate
- Protein
- Water-soluble vitamins
- Other minerals
- (Bile acids - rarely)

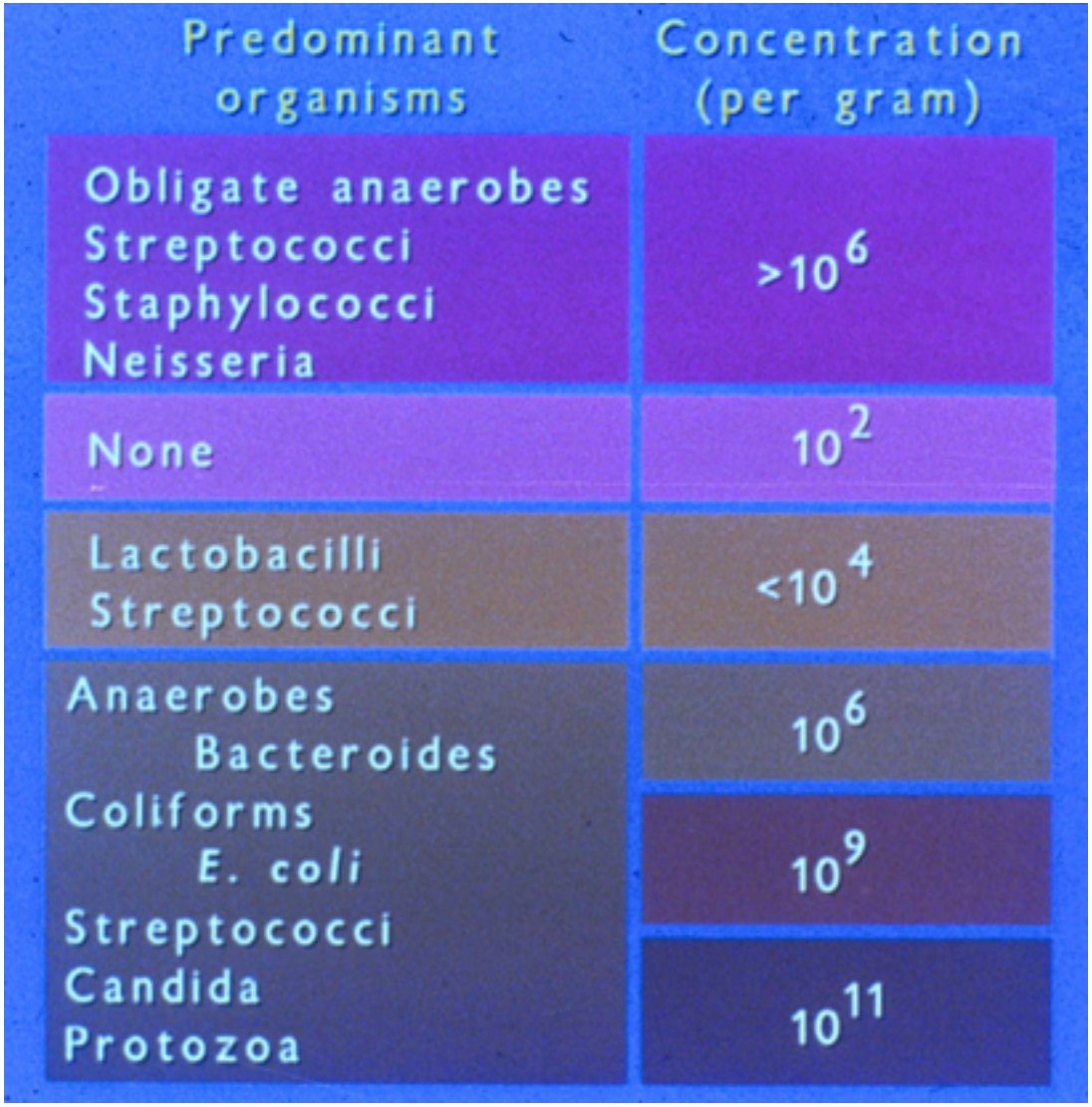
COMPARISON OF MALABSORPTION
Celiac Sprue versus Pancreatic Insufficiency

	Pancreatic Insufficiency	Celiac Sprue
Steatorrhea (gm/day)	48	25
Anemia	0%	21%
Iron deficiency	0%	10-20%
Tetany (low calcium)	0%	40%
Bleeding (low Vit K)	uncommon	25%
Low serum protein	14%	71%

These are examples only and the actual numbers depend on severity of the respective disease.

Bacterial Overgrowth: Background

Distribution of Intestinal Flora



Predominant organisms	Concentration (per gram)
Obligate anaerobes Streptococci Staphylococci Neisseria	$>10^6$
None	10^2
Lactobacilli Streptococci	$<10^4$
Anaerobes Bacteroides	10^6
Coliforms *E. coli* Streptococci	10^9
Candida Protozoa	10^{11}

Anatomical Causes of Small Intestinal bacterial Overgrowth

- Stricture
- Blind pouch
- Entero-enteric anastomosis
- Afferent loop syndrome
- Jejunal diverticula
- Small intestinal dysmotility diseases

Image of anatomical pathologies of small intestine removed

Bacterial Overgrowth-I

- Definition: overgrowth of bacteria in small bowel due to anatomic or motility factors.

- Clinical consequences:
  - Deconjugation of bile acids by bacterial enzymes
    - Loss of deconjugated bile acids in stool
    - Decreased bile acid pool - not enough for lipid digestion/ absorption
  - Damage to enterocytes by bacteria

Bacterial Overgrowth-II

- Clinical consequences:
  - Intraluminal consumption of nutrients by bacteria (competition)
    - Carbohydrates, amino acids
    - Vitamin B-12, iron
  - Damage to small bowel enterocytes causing a sprue-like histologic appearance
  - Mild to severe generalized malabsorption

INVESTIGATION OF MALABSORPTION

1. Consider possibility of malabsorption based on clinical clues

2. Identify nutrient deficiencies

3. Document impaired digestion and/or absorption of nutrients

4. Identify causative process and treat appropriately

Approach to Thinking about Malabsorption

1. How many nutrients?
    - Single nutrient (i.e., Vitamin B-12)
    - Subset of nutrients (i.e., fats)
    - Generalized malabsorption (i.e., several nutrients)

2. What type of nutrient?
    - Fat, carbohydrate, protein, vitamins, minerals or combinations

3. Pathophysiologic process likely to be involved?
    - Luminal maldigestion
    - Mucosal maldigestion
    - Mucosal malabsorption

Tests of Malabsorption: what types are available?

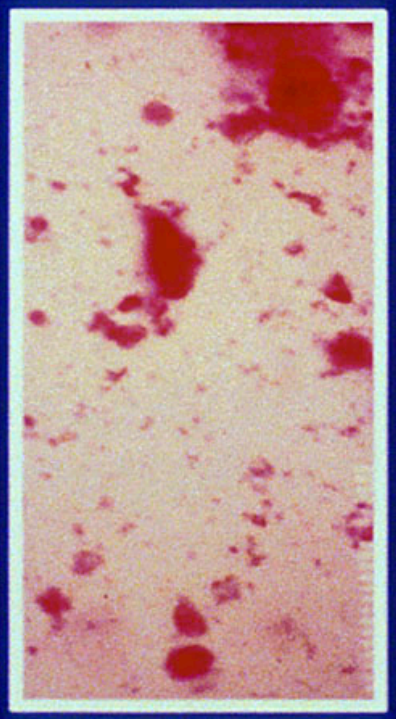
- Screening tests
- Quantitate nutrient malabsorption
- Specific diagnostic tests

Tests of Malabsorption

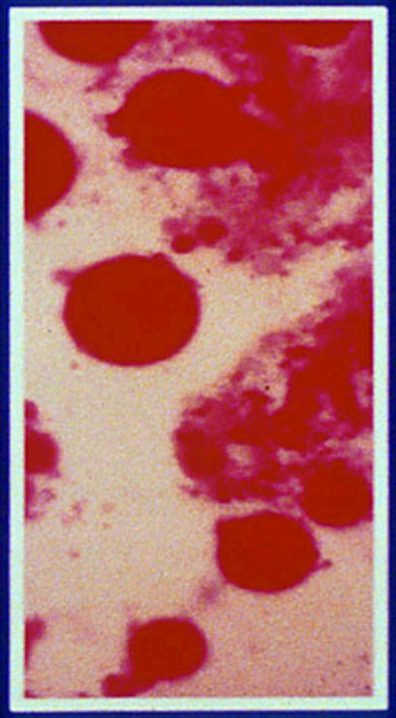
- Screening tests – simple, cheap, fast
  - Stool smear with fat stain
  - CBC for evidence of anemia
  - Cholesterol/carotene blood levels
  - Stool osmotic gap for carbohydrates
  - Weight loss/clinical clues

Example of a positive (right) and negative (left) Sudan fat stain

Magnification = 400 X



NEGATIVE

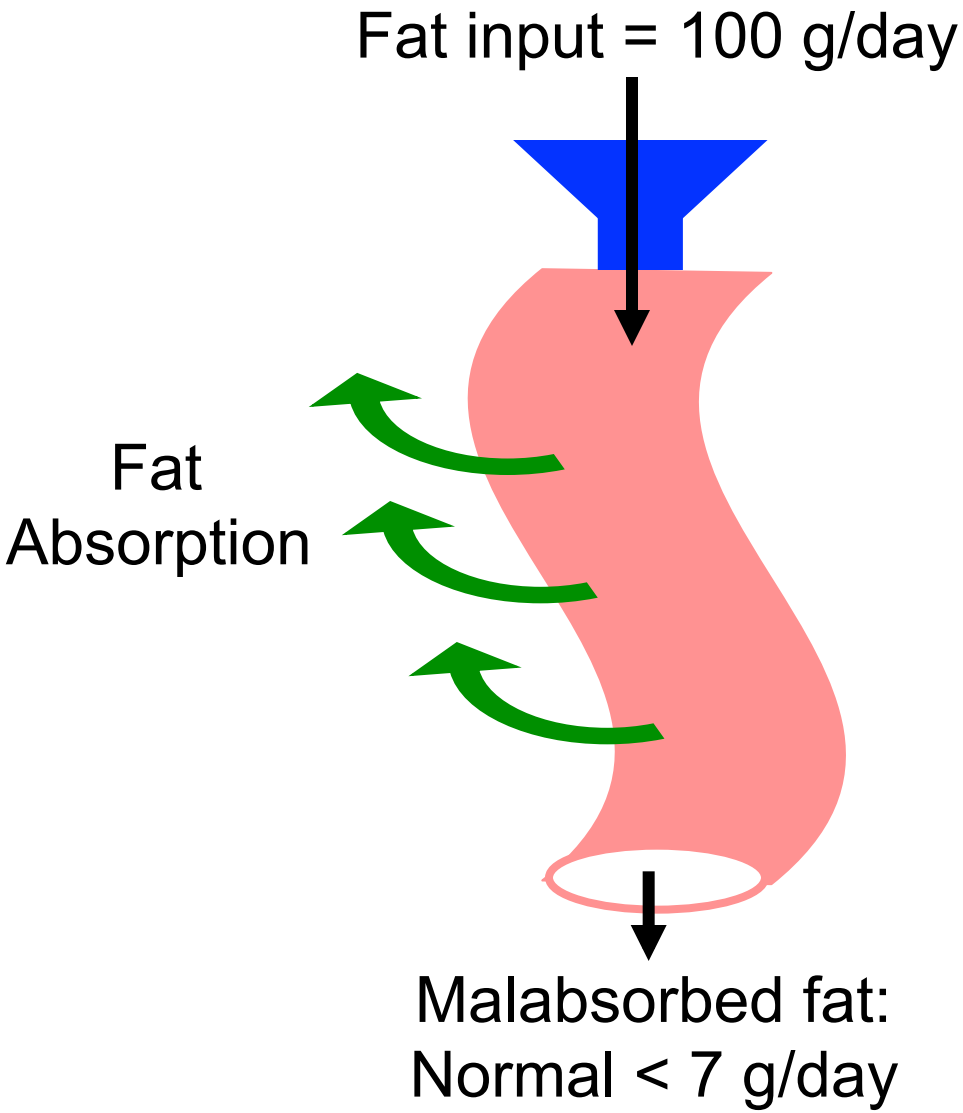


POSITIVE

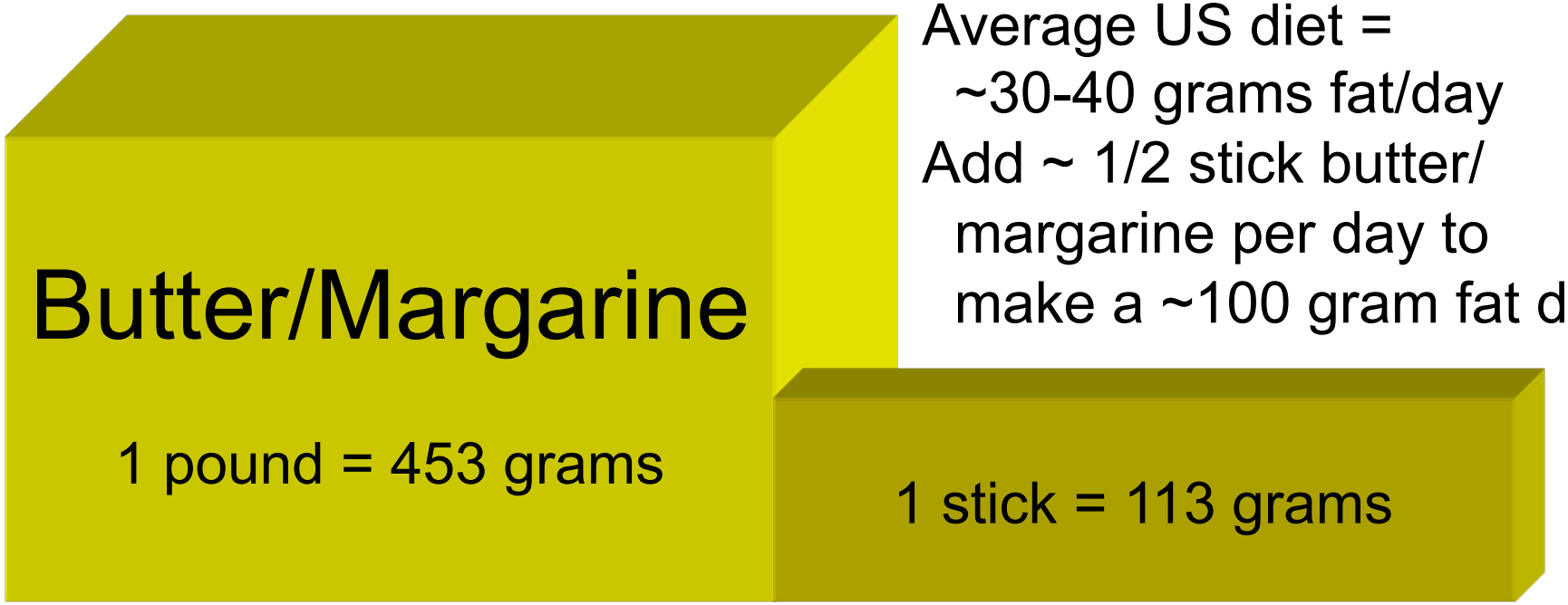
Tests of Malabsorption

- Quantitate nutrient malabsorption: messy, take time, accurate and quantitative
  - 72-hour fecal fat
  - D-xylose excretion (monosaccharide)
  - Schilling's test for B-12 absorption (no longer available)
  - Breath hydrogen test (carbohydrate)

72-hour Fecal Fat Test



100 Gram Fat Diet



Average US diet =
~30-40 grams fat/day
Add ~ 1/2 stick butter/
margarine per day to
make a ~100 gram fat diet

72 hour Fecal Fat Test

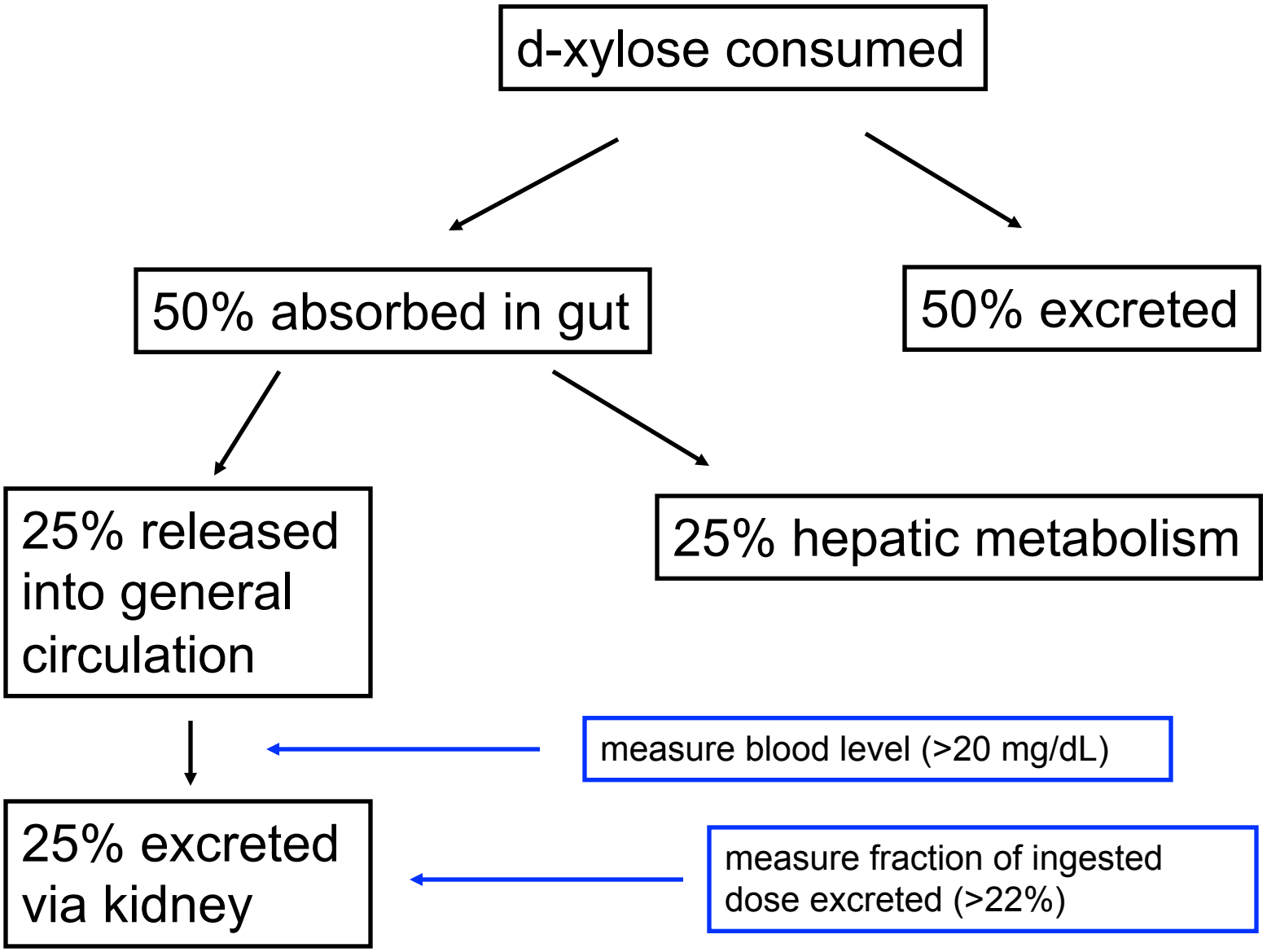
Eat the equivalent of ~1/2 stick of butter/ margarine per day for 4-6 days
Collect stool for the last 3 days in tightly sealed container
Assay for total stool weight, fat content

D-xylose

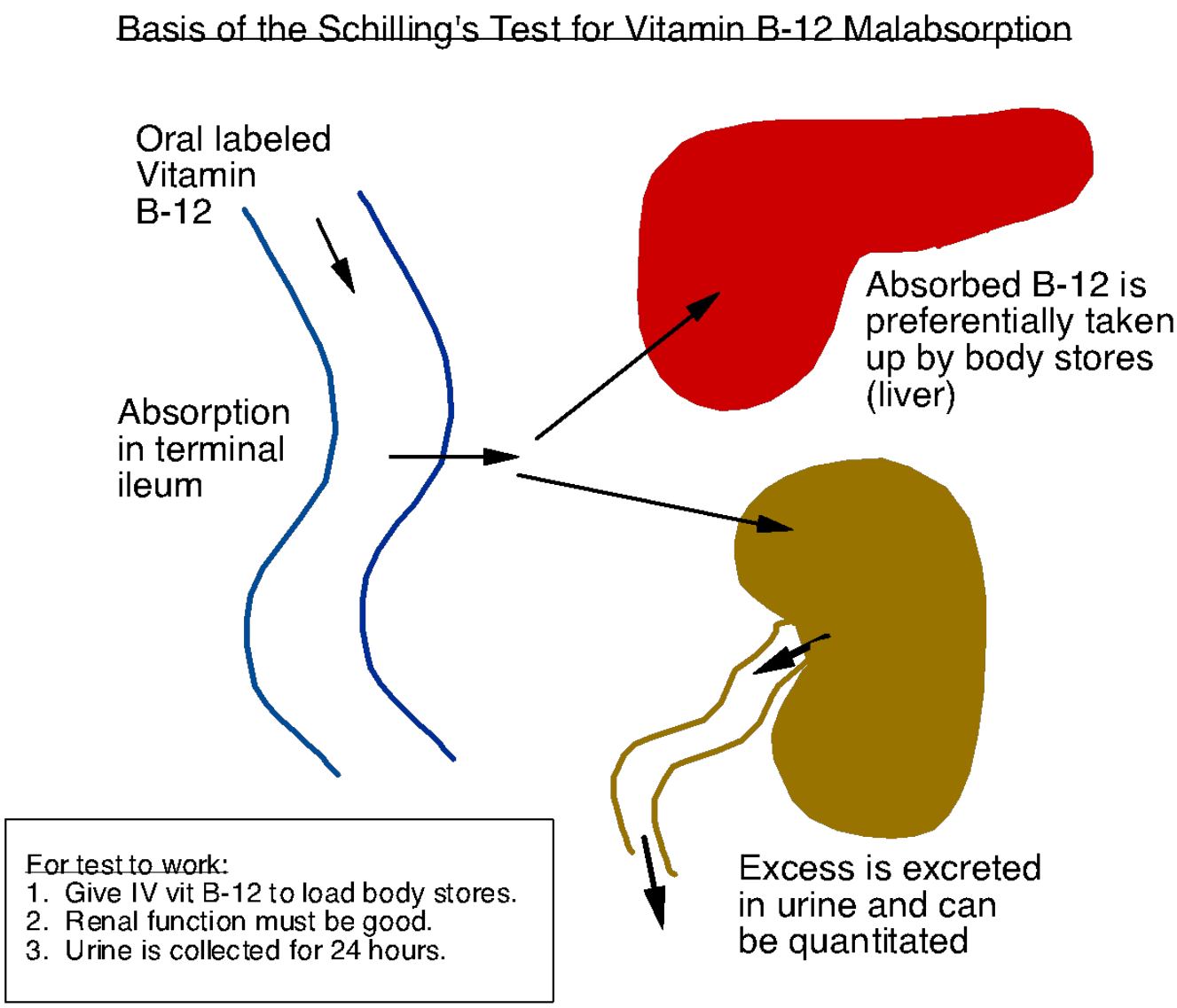
Monosaccharide
used to measure
mucosal absorption
of sugars

Administer 25 grams
orally
Draw blood sample at
2 hours
Collect urine for 5 hours
Analyze d-xylose in blood
and urine

Fate of d-xylose in the body



This test is no longer available as no one makes the radio-labeled cobalt anymore.

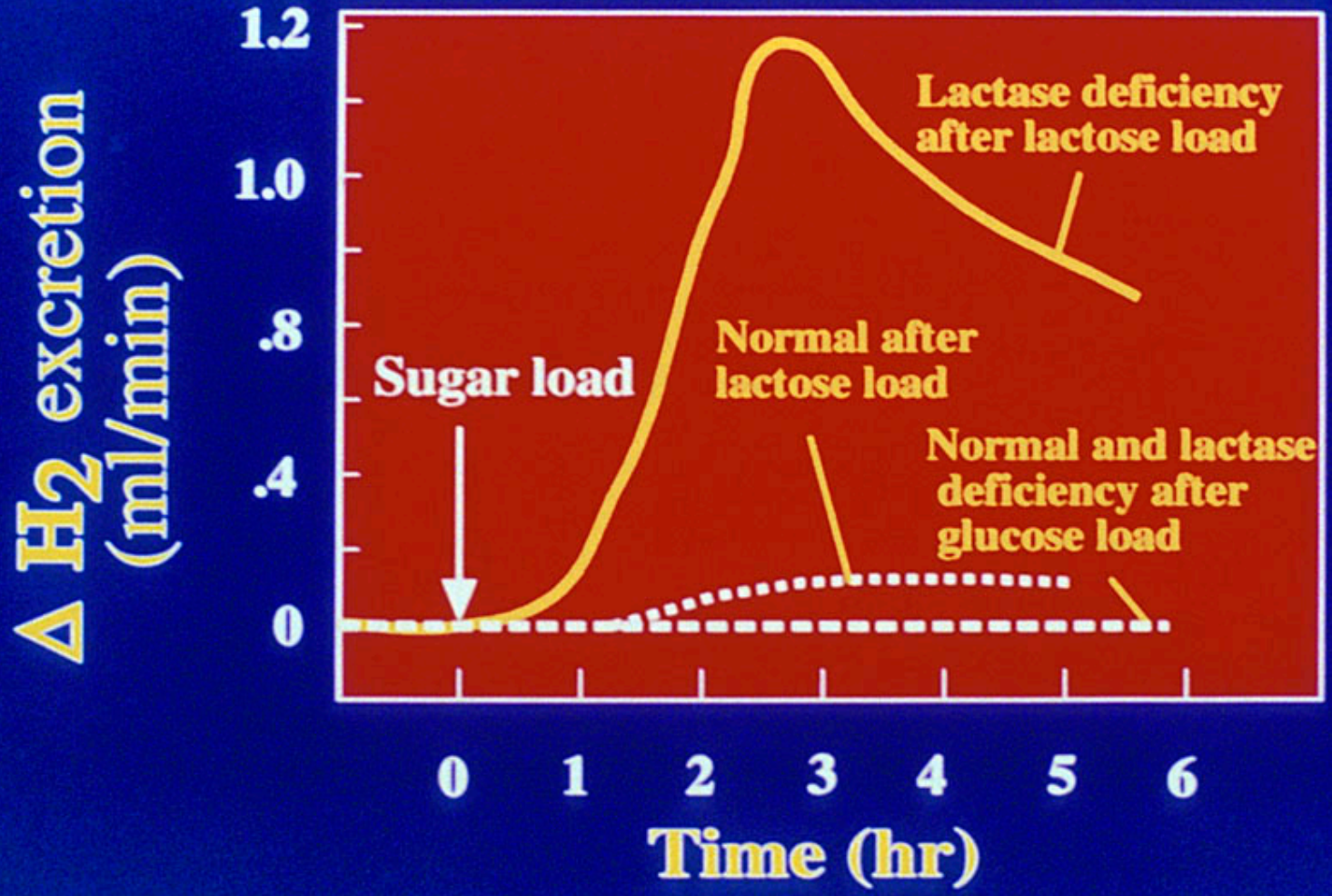


Hydrogen Breath Test for Carbohydrate Malabsorption

- Principle:
  - malabsorbed sugar passes into colon
  - bacteria produce hydrogen gas
  - H_2 diffuses into blood and is excreted by lungs
- Practice:
  - Administer 25-50 grams of glucose or other sugar orally
  - Measure hydrogen in exhaled breath at 2-4 hours
- Variants:
  - Other sugars can be employed to test for specific disaccharidase or transporter defects
    - lactase deficiency
    - glucose-galactose malabsorption

Image of hydrogen breath test mechanics removed

Breath H_2 excretion increases after lactose load in lactase deficiency



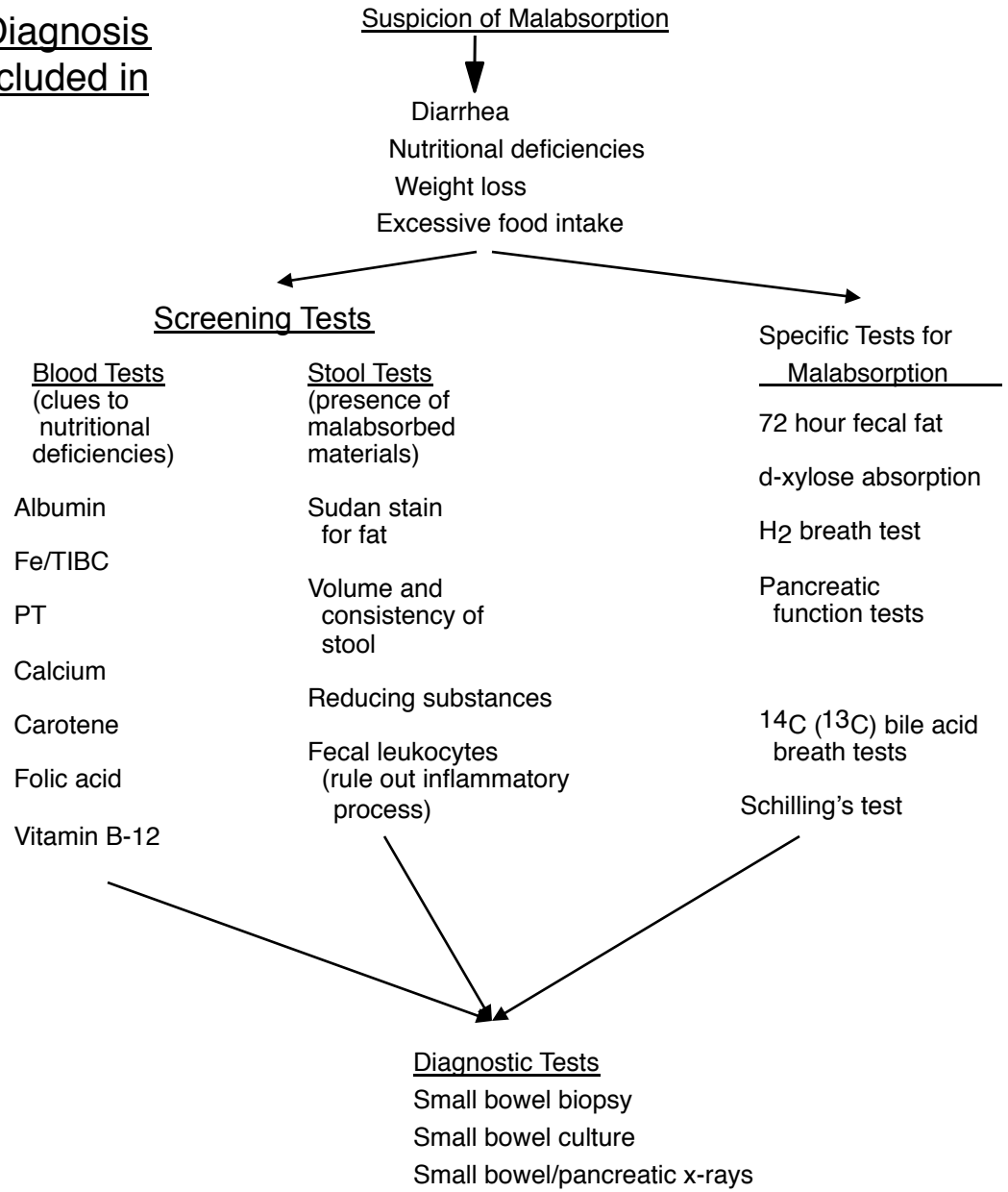
Examples: INTERPRETATION OF TESTS OF MALABSORPTION

Fat malabsorption only:	Luminal maldigestion pancreatic insufficiency bile salt deficiency
Fat and B-12 malabsorption: (have to involve terminal ileum)	Luminal maldigestion due to ileal loss of bile salts and bile salt deficiency Bacterial overgrowth: deconjugation of bile acids and bacterial uptake of B-12
Specific disaccharide malabsorption:	Mucosal maldigestion disaccharidase deficiency
Fat and d-xylose malabsorption: (+/- B-12 malabsorption depending on involvement of TI)	Mucosal malabsorption Celiac sprue Tropical sprue Bacterial overgrowth Severe Crohn's disease Whipple's disease

Tools for Evaluation of Malabsorption: diagnosis of underlying disease once you have identified a small group of possible diseases.

- Radiographs of the small bowel to delineate anatomy
- Endoscopic retrograde cholangiopancreatography (ERCP) to define the anatomy of biliary and pancreatic ducts
- Pancreatic secretory function tests
- Small bowel biopsy and/or antibody tests for celiac sprue
- Quantitative small bowel bacterial culture, bile acid or glucose breath tests for bacterial overgrowth

Approach to Diagnosis Algorithm is included in syllabus



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