# Coeliac Disease

## History of Presenting Illness

TABLE 15. Symptoms of celiac disease

| *Manifestations* | *Probable causes or deficiencies* |
|---|---|
| *Common* | |
| Anemia | Iron, folate, $B_{12}$, pyridoxine |
| Glossitis | Iron, folate |
| Weight loss/weakness | Malassimilation - Negative nitrogen balance |
| Diarrhea/flatulence | Fat and carbohydrate malassimilation |
| Abdominal pain | Increased intestinal gas production secondary to carbohydrate malassimilation |
| *Occasional* | |
| Follicular hyperkeratosis and dermatitis | Vitamin A, folate |
| Pigmentation | Associated adrenal insufficiency |
| Edema | Hypoproteinemia |
| Tetany | Vitamin D, calcium, magnesium |
| Osteomalacia | Vitamin D, calcium |
| Purpura | Hypoprothrombinemia (vitamin K) |
| *Rare* | |
| Spinal cord degeneration | $B_{12}$ |
| Peripheral neuritis | $B_{12}$, vitamin E, thiamine, pyridoxine |
| Psychosis | $B_{12}$ |
| Malignancy (usually small bowel lymphoma) | Unknown |

***In adults it usually occurs between 20 and 60 years.***

***Sole presentation nowadays may be a microcytic hypochromic anaemia which cannot be otherwise explained***

***diarrhea is usually mild:***
fewer than three bowel movements per day in most.

***Malabsorption diarrhoea: WORST SMELL EVER***

**Fatigue is the most frequent symptom at presentation.**

**Weight loss is usually only ~10kg**

***A clue to the diagnosis of celiac disease is the development of lactose intolerance in person whose heritage is northern European.***

***It only takes ONE GLASS OF MILK to induce diarrhoea and flatulence in a lactose-intolerant person.***

## Differential Diagnoses

**Bacterial Overgrowth Syndrome**
**Collagenous and Lymphocytic Colitis**
**Crohn Disease**
**Cytomegalovirus Colitis**
**Eosinophilic Gastroenteritis**
**Gastroenteritis, Bacterial**
**Gastroenteritis, Viral**
**Giardiasis**
**Hypoalbuminemia**
**Hypocalcemia**
**Hypokalemia**
**Hypomagnesemia**
**Hypothyroidism**
**Immunoglobulin A Deficiency**
**Inflammatory Bowel Disease**
**Iron Deficiency Anemia**
**Irritable Bowel Syndrome**
**Malabsorption**
**Protein-Losing Enteropathy**
**Jejunoileitis**
**Intestinal lymphoma**

## Findings on Examination

- **Abdominal examination = protuberant and tympanic abdomen** due to distension with fluids and gas.
- **Ascites** occasionally
- **Evidence of weight loss**, including muscle wasting or loose skin folds
- **Orthostatic hypotension**
- Peripheral edema
- **Ecchymoses**
- **Hyperkeratosis** or **dermatitis herpetiformis** (itchy vesicles on elbows)
- Cheilosis and glossitis
- Evidence of peripheral neuropathy
- **Chvostek sign:** tapping on facial nerve over mastoid process causes a tic of facial muscles
- **Trousseau sign**: when the cuff is inflated to just over the systolic pressure, the hand will spasm

# Tests and Investigations

***For it to be called COELIAC DISEASE,***
***you have to demonstrate***
***SMALL BOWEL MUCOSAL VILLOUS ATROPHY that IMPROVES UPON GLUTEN WITHDRAWAL***

***WHAT ELSE LOOKS LIKE COELIAC DISEASE @ BIOPSY:***
Nothing, if its from a white western adult. Otherwise,

tropical sprue,

diffuse lymphoma of small bowel,

immunoglobulin deficiency syndromes

Zollinger-Ellison syndrome (gastrin-secreting tumour

**IN INFANTS:**
soy protein intolerance, cow's milk protein intolerance and viral gastroenteritis produce a similar appearance

## Full Blood Count

**Anemia** is present in less than 50% of adult patients.
Also want to make sure that the **coagulopathy is due to malnutrition and vitamin K depletion, not thrombocytopenia**

## Serum Ferritin.

**iron deficiency is the most common laboratory abnormality..**

## Serum Biochemistry

Depletion of minerals (zinc, magnesium) and ions (potassium)
( **occurs only with severe disease** )
**Malnutrition = decreased serum albumin.**

## RBC Folate

**Folate deficiency is uncommon, but happens**

## Hydrogen Breath test

the absorptive cell lesion also results in secondary lactase deficiency; thus, the **$H_2$-lactose breath test may be abnormal in celiac disease.**

## Stool Examination

Steatorrhea can be confirmed by a **72-hour fecal fat study**.
It is usually mild (10-20 g/24 hours) and may be absent in some patients.
**Severity of steatorrhoea correlates with the extent of the intestinal lesion**,
PLUS you look for **ova, cysts, parasites, Leucocytes and BLOOD**

## Barium Swallow radiography (IGNORE AS IT IS USELESS)

Barium studies of the small bowel may show dilation of the bowel and slight thickening of the mucosal folds. Intraluminal signs of malabsorption with flocculation, segmentation and clumping of the barium (features due to excess amount of fluid present within the lumen) are variable and not common. (The new barium suspensions now used have made this a rare finding.) **Radiographic findings in celiac disease are not specific for this syndrome of malabsorption.**

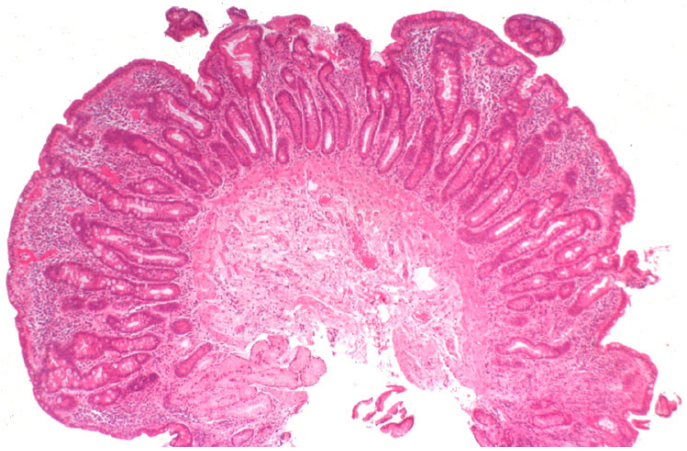
## Serum Anti-Endomyseal Antibodies

**Anti-endomysial IgA antibody** : antibodies against reticulin in monkey oesophageal smooth muscle..
**The most sensitive and specific test (>98%)**

# SMALL BOWEL BIOPSY is the gold standard: so get in there

**= can be obtained endoscopically from the distal duodenum (at least four forceps biopsies).**

You don't need to do another biopsy to prove that a gluten-free diet made it better



Looking for*:*

- ***SUBTOTAL VILLOUS ATROPHY***
- flat surface
- hyperplastic lengthened crypts
- increased cellularity
- more plasma cells and lymphocytes
- proximal small bowel most severely involved

# Management: STOP EATING GLUTEN!

THIS DIET IS LIFE-LONG:
Mention to the patient – persistent non-compliance may be associated with small bowel malignancy

*which requires avoiding wheat, rye, barley and oats*

**PLUS: may want to think about replacing + supplementing** haematinics and other micronutrients

## Nutritional approaches to GI disease

**Gluten is found in**

- wheat (wheat flour is ~8% gluten)
- rye and barley
- wheaten cornflour,
- malt
- some thickeners
- oats (contaminated with traces)

**elastic properties of the wheat gluten protein permit the baking of leavened bread.**

many foods on the market that are gluten-free are **not labelled as such**

A person on a normal diet consumes about 10-14g of gluten per day.

**Gluten-free flours:**

- rice,
- soy,
- maize,
- besan (chickpea)
- potato
- Arrowroot,
- buckwheat,
- lupin,
- maize cornflour,
- millet,
- modified maize starch,
- polenta,
- psyllium,
- rice,
- sago,
- seeds,
- sorghum
- tapioca

## Prognosis: EXCELLENT provided gluten is withdrawn

Vast improvement within weeks if not days

## Epidemiology

Commonest cause of malabsorption in the western world! 1:250 to 1:75

**Frequency:**

- **Internationally:** Celiac sprue is prevalent in some European countries with temperate climates. For example, the frequency of the disease is between 1 in 250 persons and 1 in 300 persons in Italian and Irish populations. In comparison, the disease is rare in Africans or Asians.

**Mortality/Morbidity:**

- increased risk for lymphomas and adenocarcinomas of the intestinal tract.
- Untreated pregnant women are at risk of miscarriage
- There is risk of congenital malformation of the baby.
- celiac sprue @ childhood = FAILURE TO THRIVE and short stature
  (!!30% have clubbing and 20% can have constipation. How very weird)

**Race:** Celiac sprue is **most prevalent in Europeans and is rare in Africans and Asians.**

**Sex:** Incidence of celiac sprue is **slightly higher in females.**

**Age:** The **age distribution of patients with celiac disease is bimodal,**

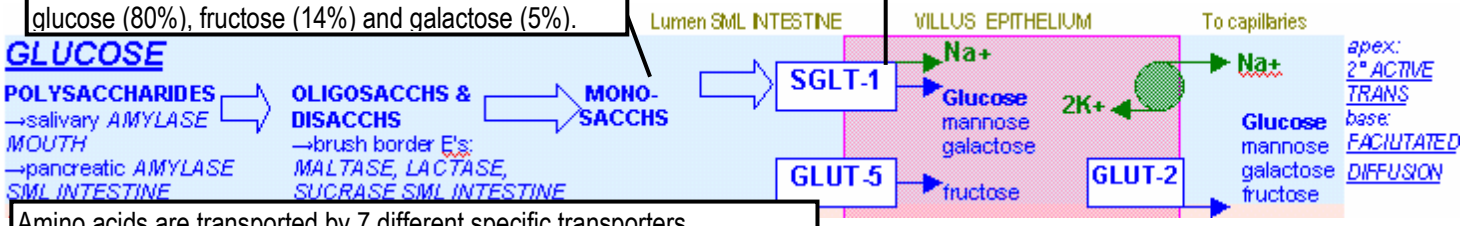
- ***first peak is at 8-12 months***
- ***second peak in the third to fourth decades.***

# Nutrient Absorption and Transport

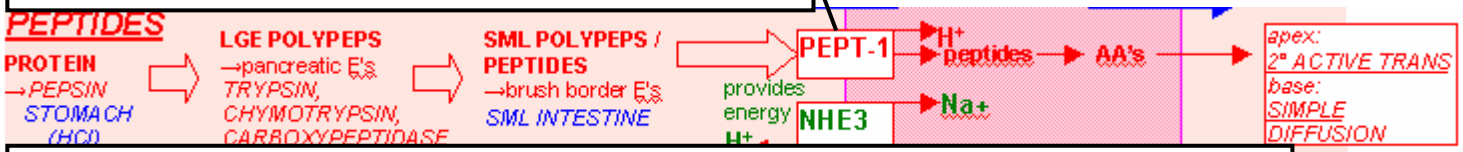
**For most vitamins,**
**JEJUNUM IS WHERE IT ALL HAPPENS**
**Except for weird vitamin B12**

SGLT uses Na+ concentration gradient,
But GLUT-5 is **passive**

glucose (80%), fructose (14%) and galactose (5%).




Amino acids are transported by 7 different specific transporters.
Some are Na+ coupled, some are not.




**CHOLESTEROL has its own transporter: then, esterified in enterocyte; → secreted into portal blood**


## *Trace nutrients: Water soluble vitamins*

**RIBOFLAVIN** → Released from proteins by stomach acid → **Absorbed by SATURABLE TRANSPORT SYSTEM @ proximal JEJUNUM**

**NIACIN** → **FACILITATED or PASSIVE transport @ JEJUNUM**

**B6** → dephosphorylated → **FACILITATED or PASSIVE transport @ JEJUNUM**

**B12** → Released from proteins by stomach acid : binds to R-proteins in saliva → Liberated from R-proteins by pancreatic proteases Links with intrinsic factor @ duodenum → Absorbed via a specific receptors in terminal ILEUM Then bound to transcobalamine for transport in plasma

**Vitamin C** → Converted to dihydro-derivatives → **Energy-dependant facilitated transport**

**FOLATE** → Cleaved from polyglutamates by upper jejunal brush border CONJUGASES (!!conjugase action impaired by alcohol) → **Energy-dependant facilitated transport**

## *Fat soluble vitamins*

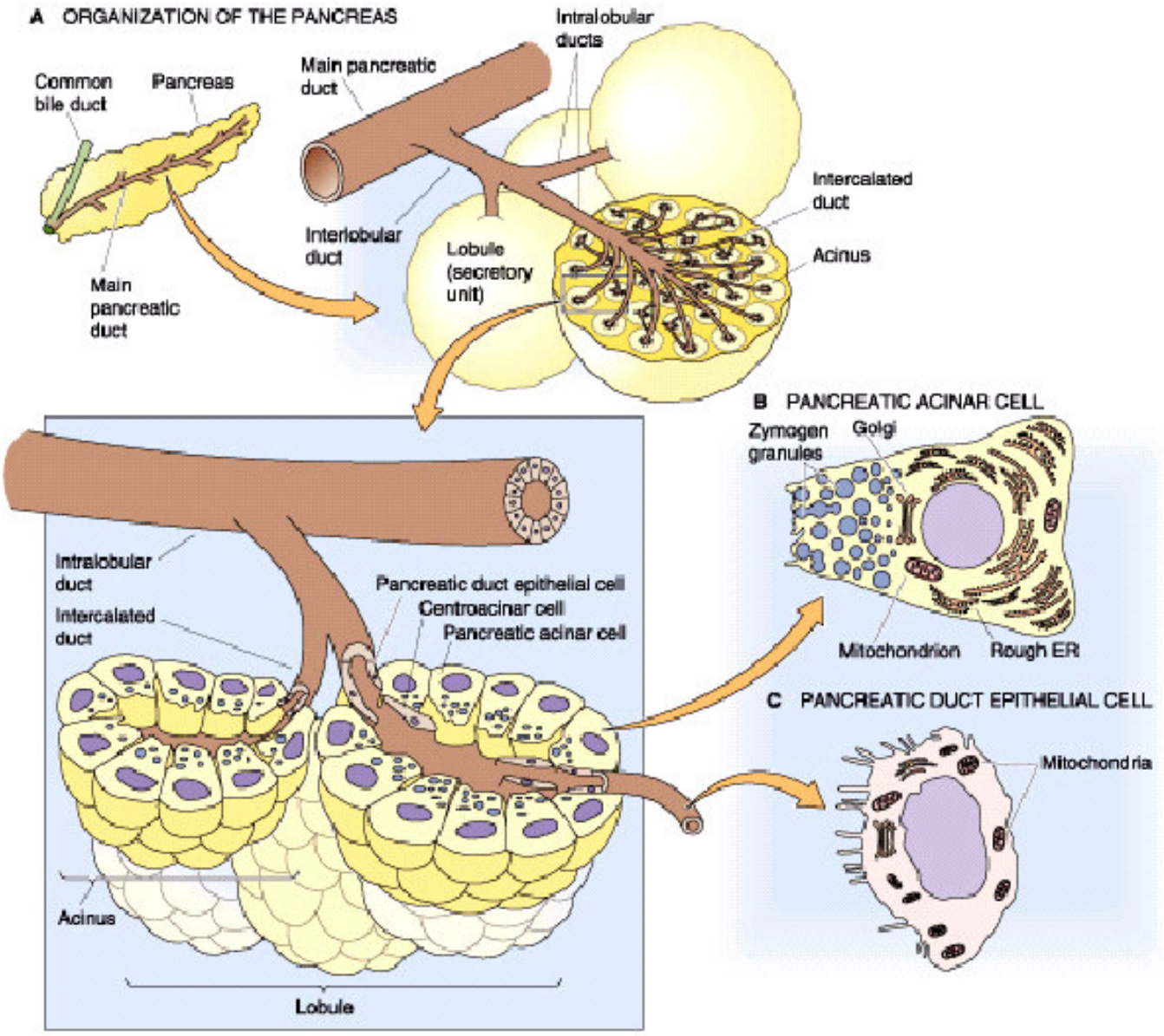
incorporated in **bile salt micelles** prior to absorption by the enterocytes usually in the **upper jejunum.**

Vitamin A is not as reliant on bile andpancreatic enzymes
Vitamin D is absorbed in the upper jejunum presumably by diffusion.
Vitamin E absorption is very dependent on adequate micelle formation
Vitamin K requires both bile and pancreatic enzymes for absorption.

## *Trace metals*

**Most trace metals are absorbed by passive diffusion**

Iron bonds to a membrane receptor protein, and absorption may be facilitated by a cytosolic apotransferrin. Iron absorption is impaired by certain foods, eg milk protein, tea and coffee, phytates, and enhanced or impaired according to iron storage status.

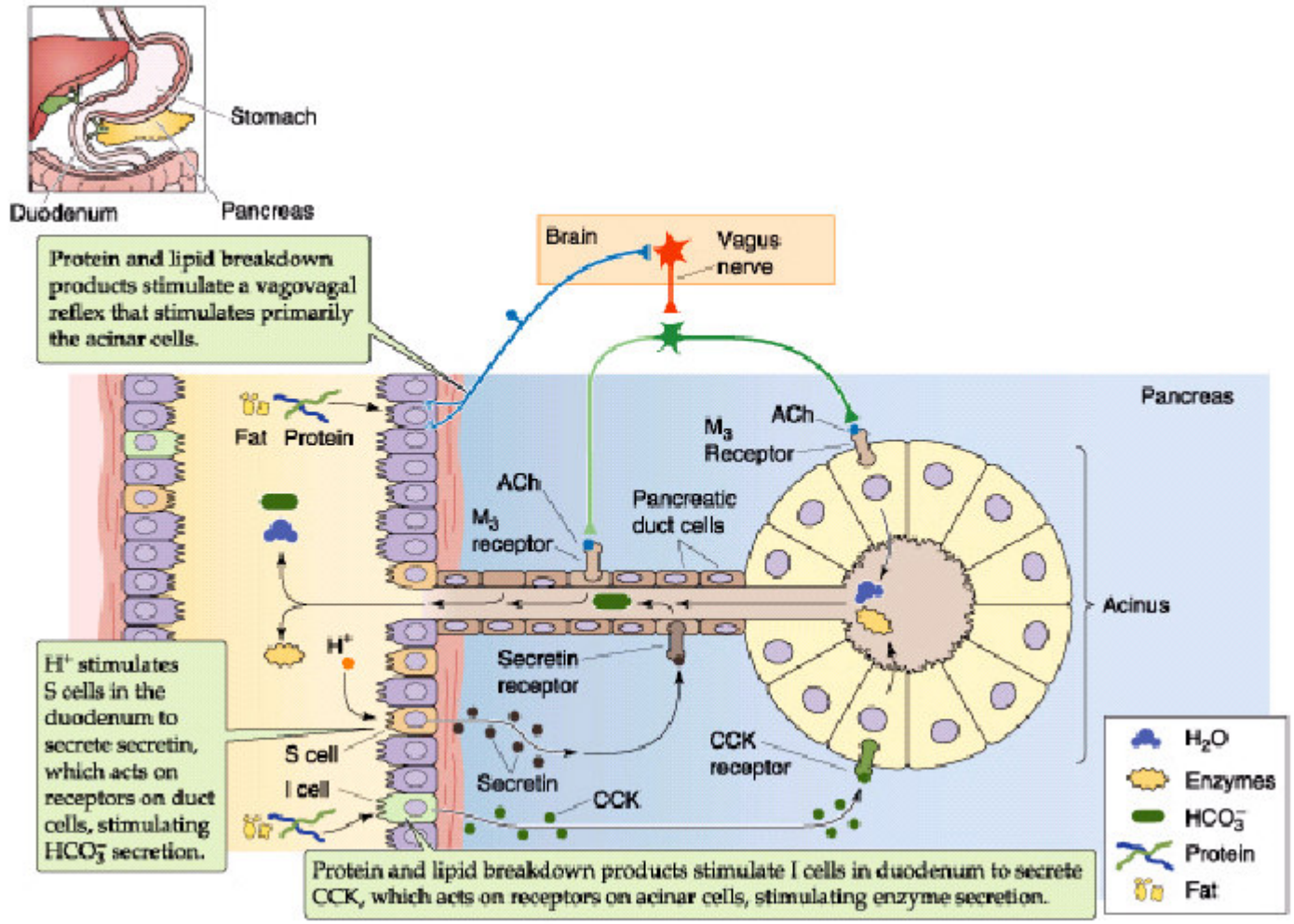


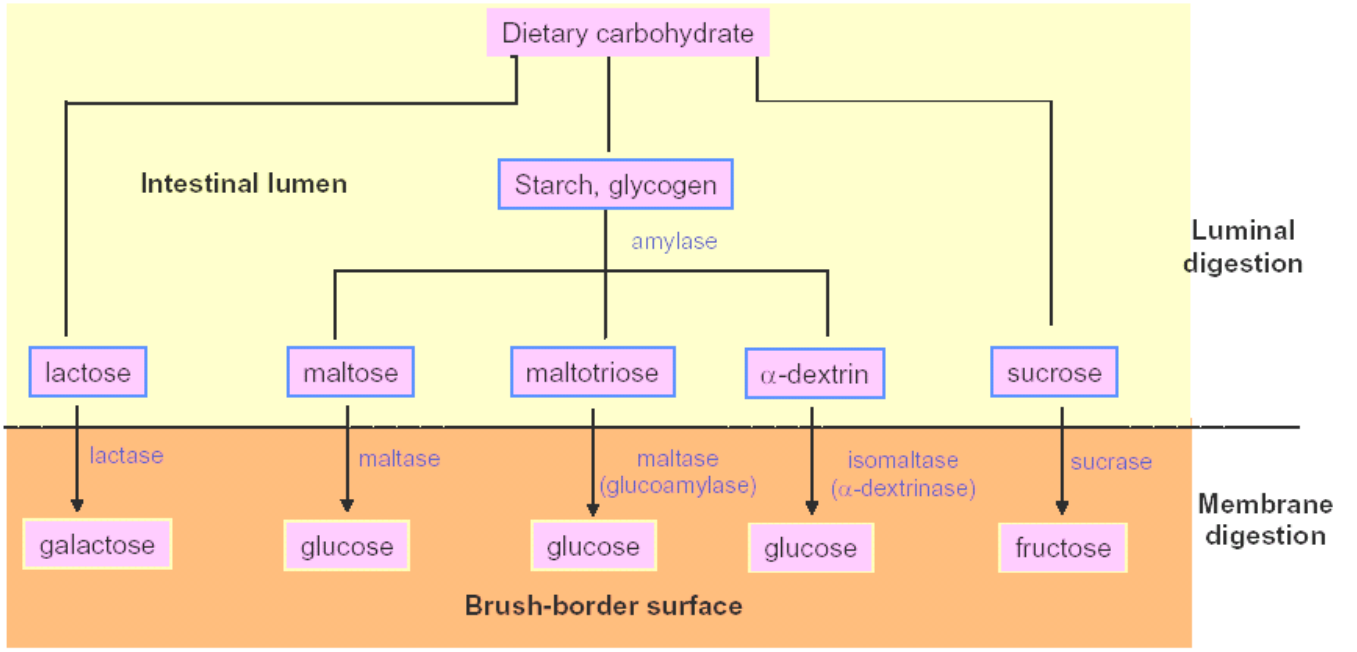

Most pancreatic enzymes are activated in the lumen- **EXCEPT amylase and the lipases**

| | | |
|---|---|---|
| Trypsinogen | **Enteropeptidase** → | Trypsin + peptide |
| Chemotrypsinogen | trypsin → | Chemotrypsin + peptide |
| Proelastase | trypsin → | Elastase + peptide |
| Procarboxypeptidase | trypsin → | Carboxypeptidase + peptide |
| Phospholipase A | trypsin → | Phospholipase A + peptide |

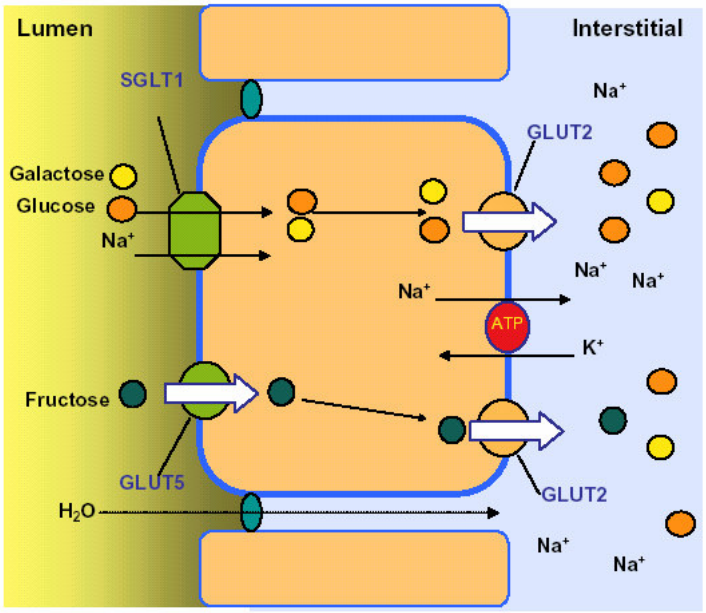
Amylase and lipases are secreted as active enzymes

**B INTESTINAL PHASE**

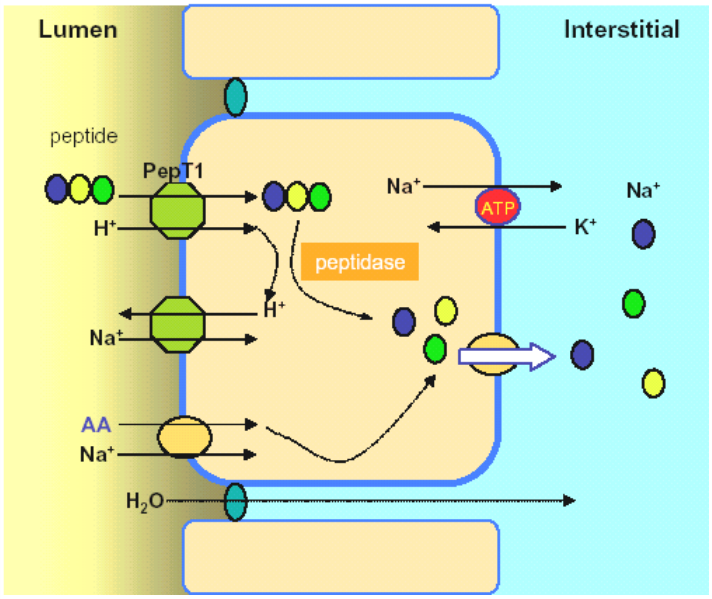


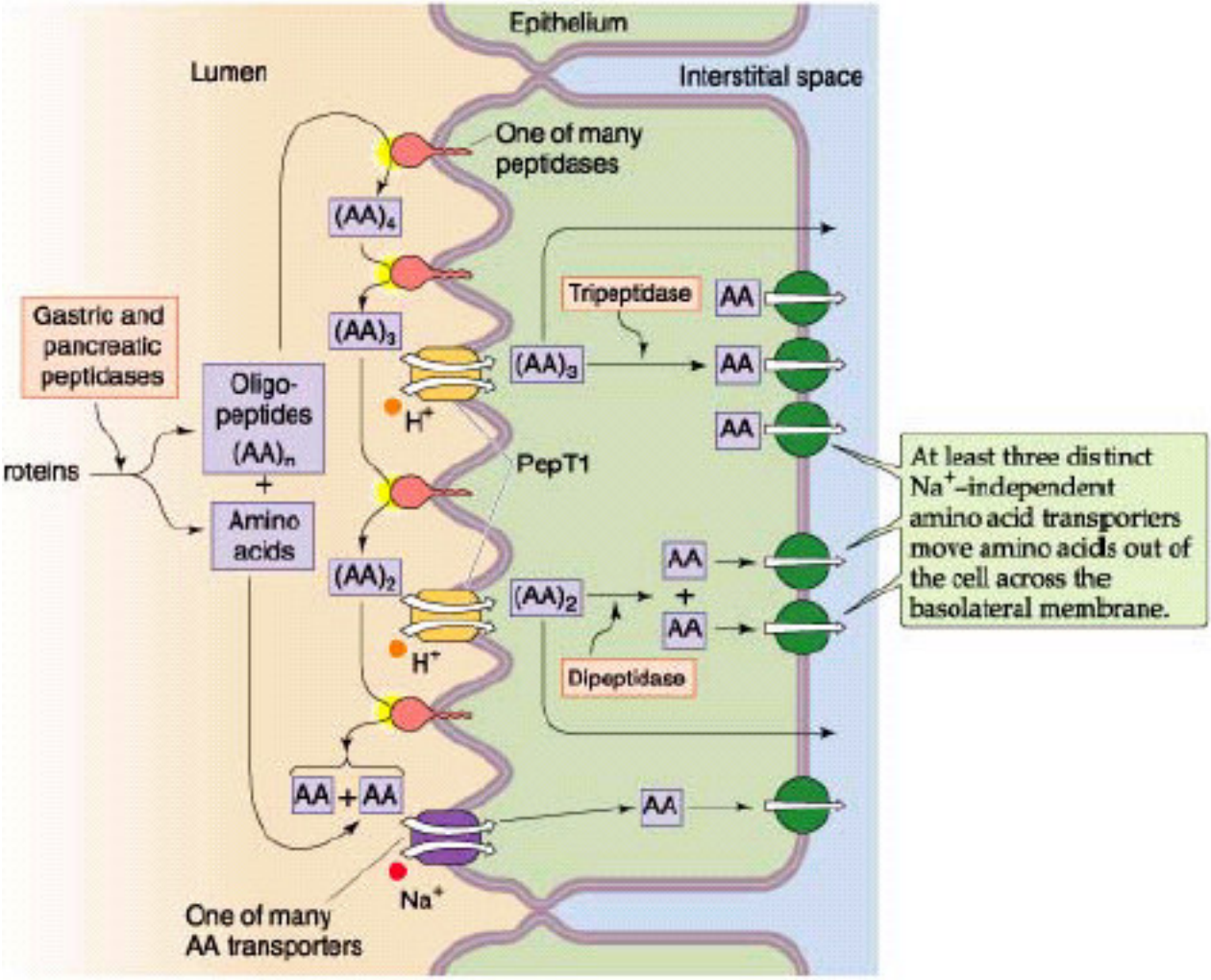



## Carbohydrate absorption

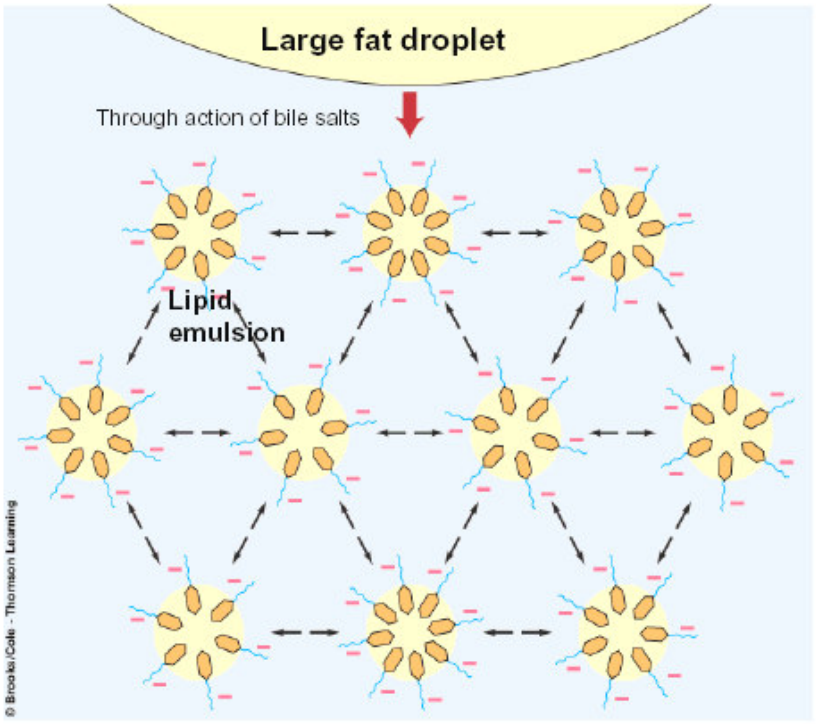


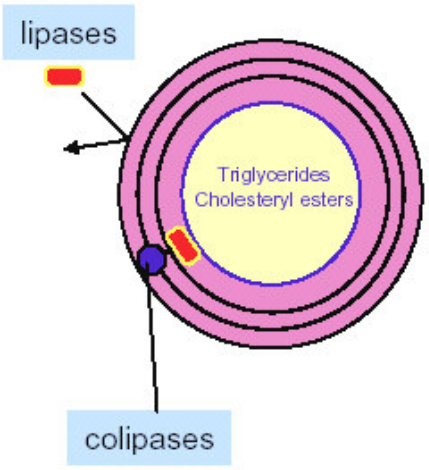

## Protein absorption



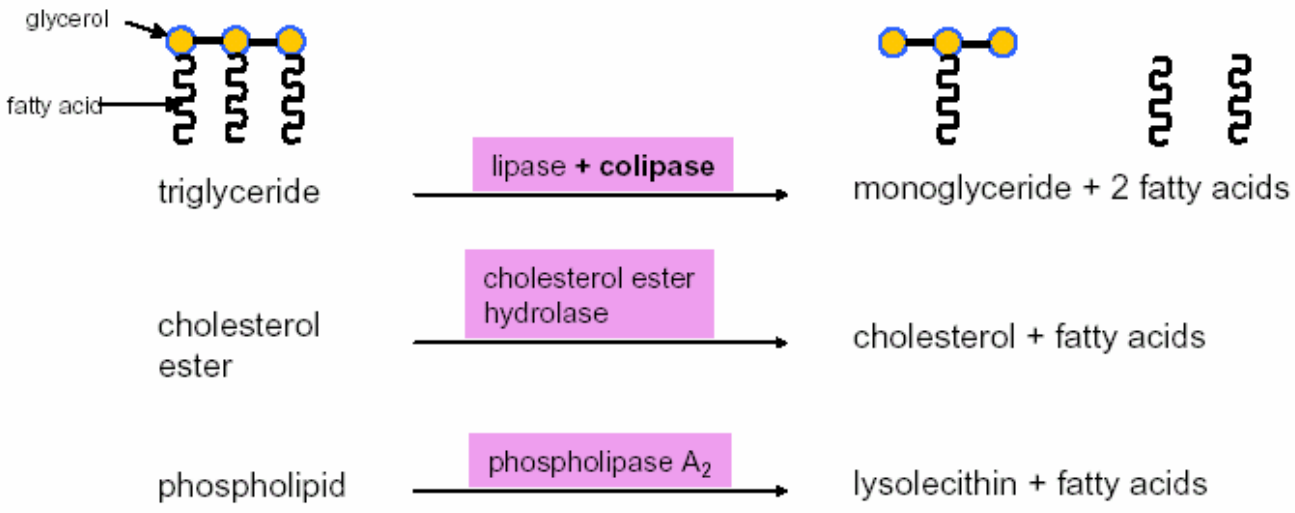



# Emulsification of lipid

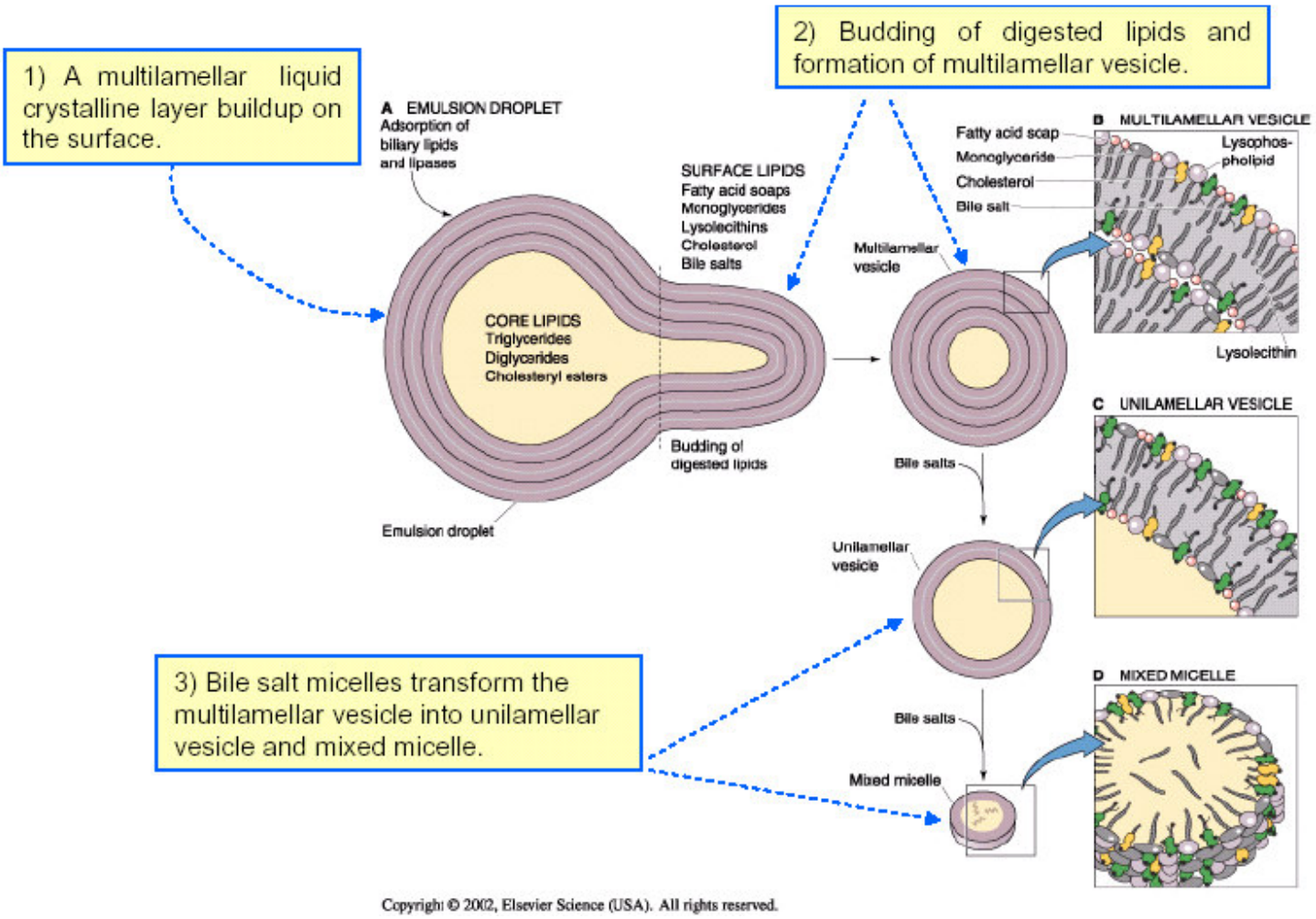



# Pancreatic lipases

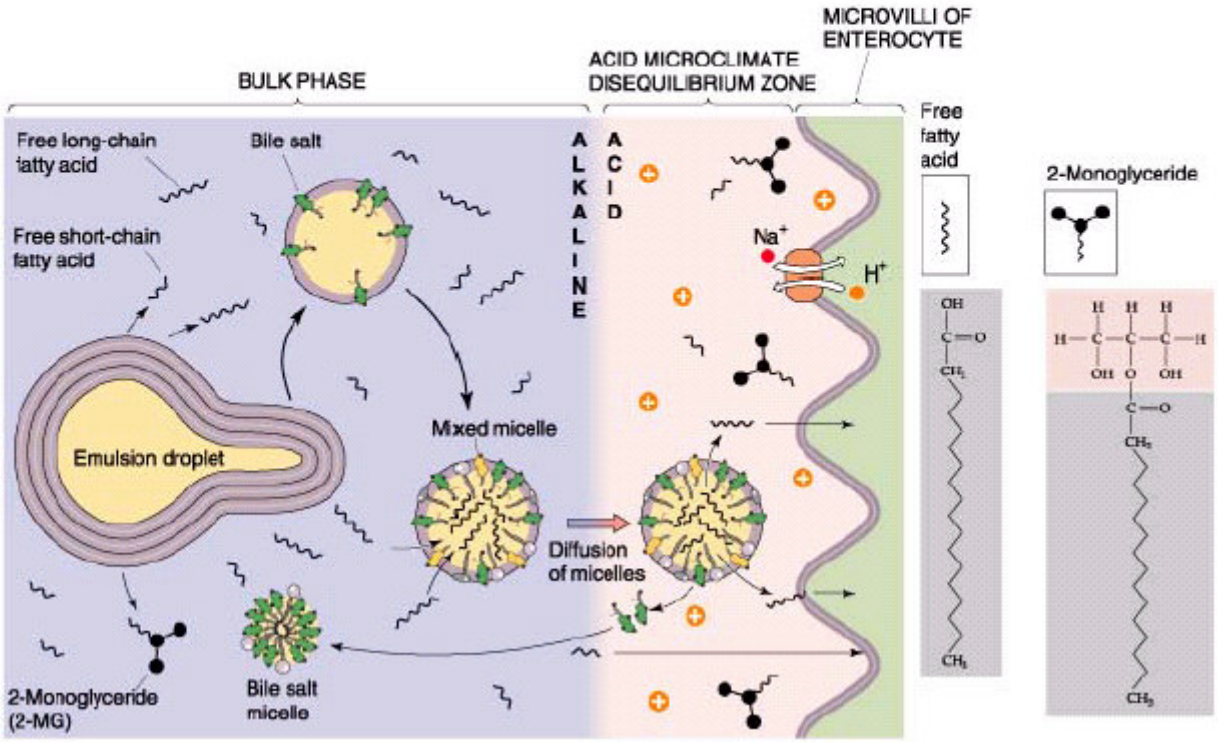


# Breakdown of emulsion droplets

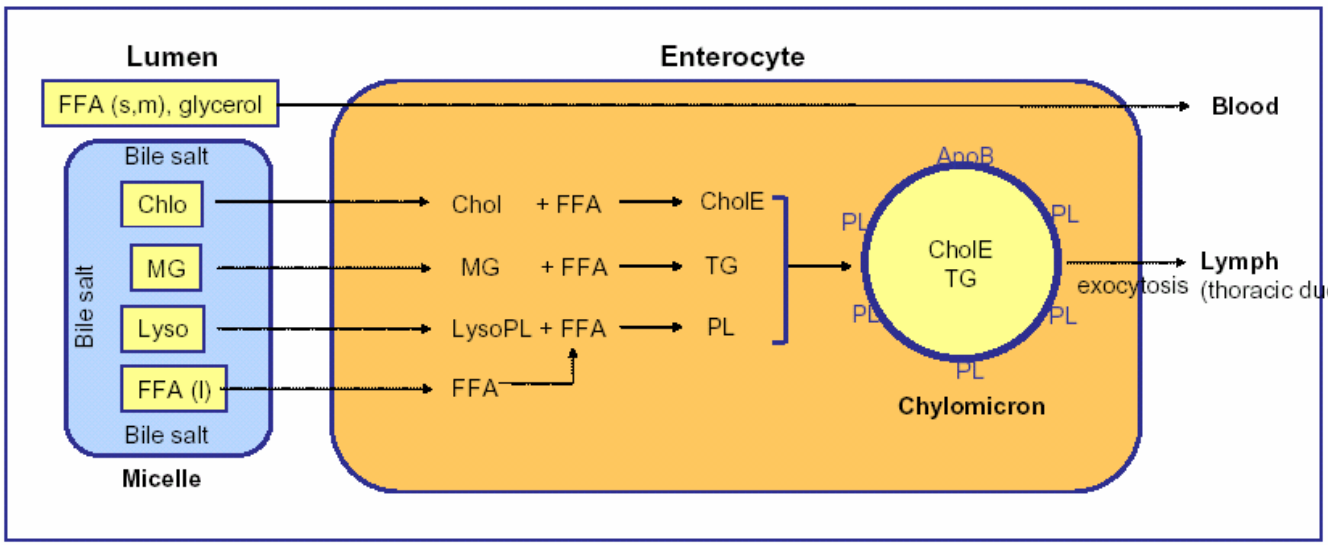





# Micellar transport of lipolytic products



# Absorption of lipids

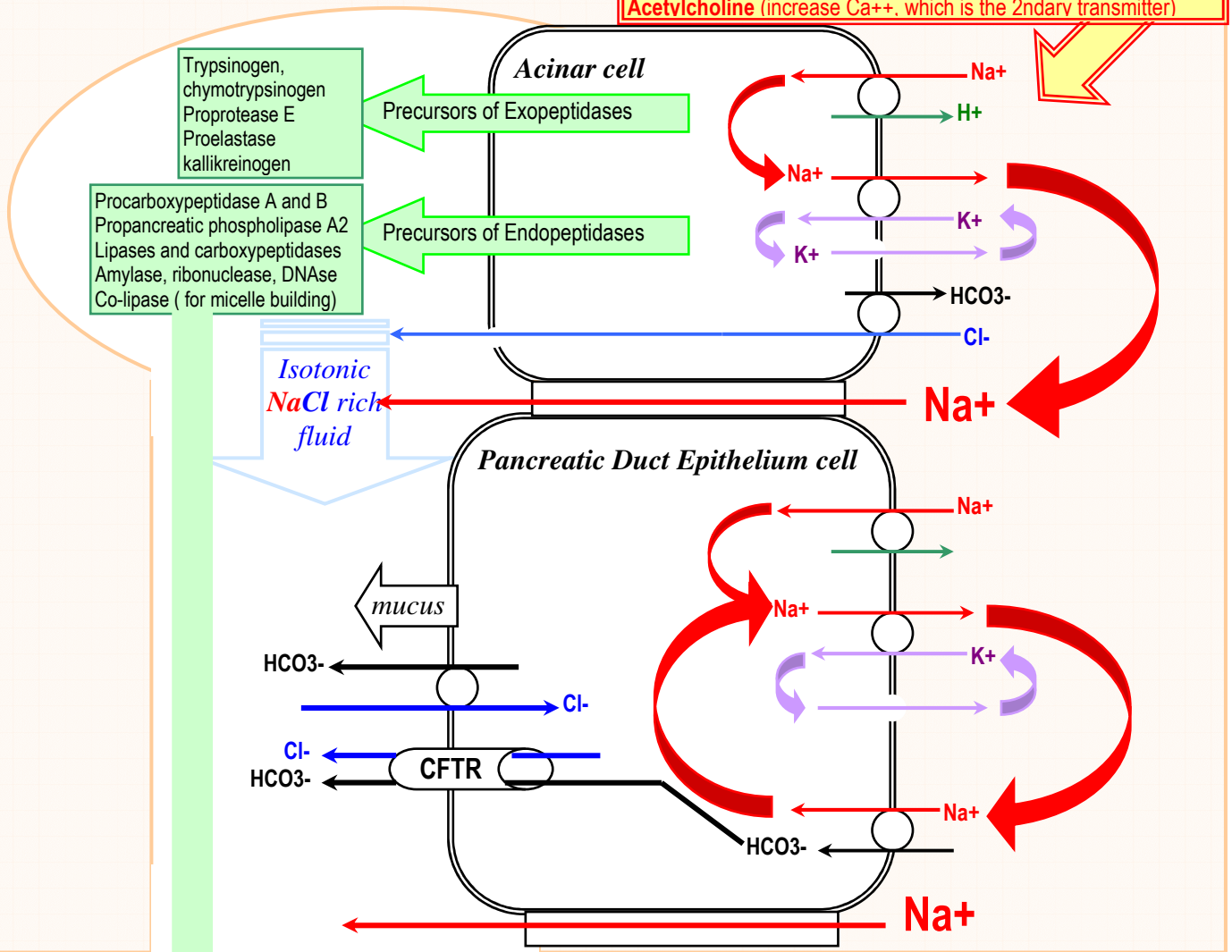



## Function of Exocrine Pancreas

2 litres of pancreatic juice per day.

**96% of the total weight of the pancreas is exocrine**

**ACINAR** Secretory stimulus: from **Cholecystokinin** and **Acetylcholine** (increase Ca++, which is the 2ndary transmitter)




**@ gut lumen:**
brush border enzymes activate **TRYPSIN** → **TRYPSIN** then activates all other pancreatic enzymes

## FAILURES OF PANCREATIC FUNCTION:

For example cystic fibrosis: **pancreatic lipase requires a steady alkaline pH,** but if the CFTR protein cant channel HCO3-, the duodenum stays acidic and the lipase doesn't work, **hence→ FAT MALABSORPTION**

Patients with pancreatic insufficiency present with diarrhoea and often describe their stools as containing "bacon fat", "melted butter" or "olive oil".

NOTHING LIKE COELIAC DISEASE!! → where malabsorption is of the fatty acids, not whole triglycerides

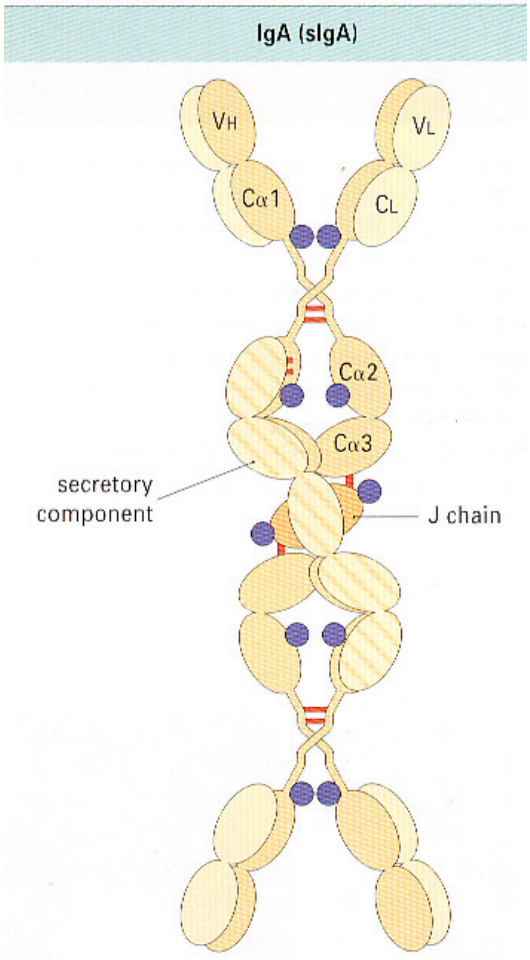
# Mucosal Immunity: Mucosa-associated lymphoid tissue (MALT)

IgA

*Whole idea of MALT is that ITS NOT ENCAPSULATED like the lymph nodes.*

*FOUND IN LAMINA PROPRIA and SUBMUCOSA: @ GASTRO, RESPIRATORY and GENITOURINARY tracts*

- **The tonsils** contain a considerable amount of lymphoid tissue, often with many large germinal centres.
- **The bronchi** contain diffuse lymphoid aggregates and respiratory epithelium contains dendritic cells for uptake, transport and processing of antigens.
- **Peyer's patches of the lower ileum** are particularly prominent diffuse accumulations of lymphoid tissue are seen in the lamina propria of the intestinal wall. They form **follicles with segregation of lymphocytes** into T and B cell areas.



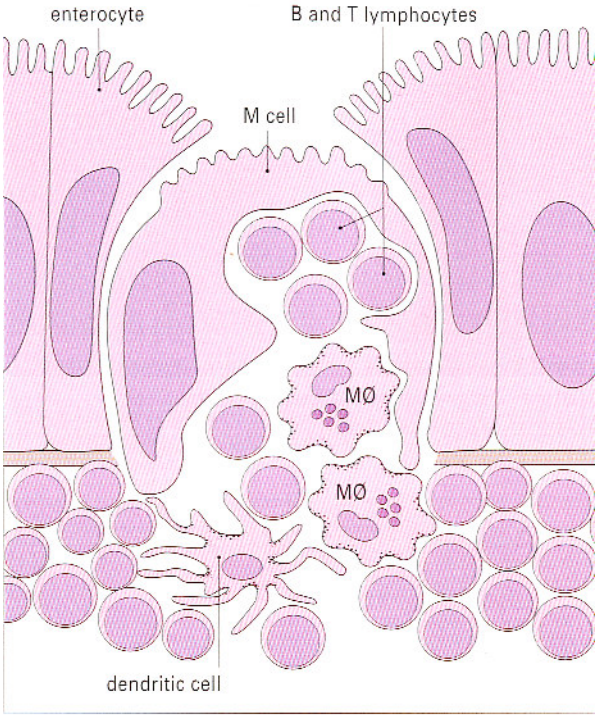




Fig. 2.61 The intestinal FAE contains M cells. Note the lymphocytes and occasional macrophages (MØ) in the intracellular pocket. Endocytosed antigens are passed via this pocket into the subepithelial tissues.

## *HOW EVERYTHING WORKS:*

***Peyers patch is COVERED BY A DOME OF EPITHELIUM.***
***This dome is composed of "M" CELLS (microfold cells)***
**These cells TOTALLY ENVELOP the B and T lymphocytes!**
**Their job is to allow the antigens to penetrate through into the lymph**

## *IgA IMMUNITY*

**Secreted by B cells in the mucosa**
**Actively transported through the epithelium:**

- Internal surface of epithelium has special receptor
- **The receptor + IgA complex is endocytosed**
- **Gets transported in vesicles**
- **@ the LUMEN MEMBRANE, enzymes cleave the receptor**
- **the IgA is released, bound to the secretory component**
- **Protected from destruction by the secretory component**

## *Mucosal T cells :*

**→ MAIN FUNCTION seems to be virus surveillance: they are mainly CD8 cytotoxic T-cells**

## *Recirculation and homing*

***Cells activated in the mucosa migrate to regional lymph nodes and then "home" back to mucosal surfaces via the thoracic duct and blood stream.***

This tissue-specific recirculation is dependent on recognition of adhesion molecules (of the selectin and integrin family) expressed on MALT-derived lymphocytes and on endothelial cells of the mucosal postcapillary venules.

**Thus, antigen stimulation at one mucosal site can elicit an antibody response at other surfaces as well.**

**Overview of Spectrum of non-infectious diarrhoea** : *worth ignoring*

Inflammatory bowel disease is the term used to describe ulcerative colitis and Crohn's disease. These are chronic, relapsing conditions of unknown aetiology affecting the gastrointestinal tract. Onset can be at any age, but with a peak from late teens to mid-30s.

**Aetiology**

The cause of either condition is unknown. Factors implicated in Crohn's disease include smoking, genetic factors and intraluminal bacteria. Mucosal inflammation with activation of the immune system is a feature of both diseases.

**Ulcerative colitis**

*Pathology:* affects only the large intestine. Always involves the rectum and usually a variable length of colon proximal to this in continuity. The inflammation is confined to the mucosa. Neutrophils prominent in the inflammatory infiltrate.

*Clinical features:* typically presents with diarrhoea containing blood and mucus. Patients with proctitis may have bleeding only. Pain is a feature of severe disease. Toxic megacolon and perforation may result. Extraintestinal manifestation can develop, affecting joints, skin, eyes and liver. The risk of colorectal cancer is increased in patients with extensive disease after 7-10 years.

*Diagnosis:* sigmoidoscopy or colonoscopy, with biopsy. Barium enema occasionally used as the alternative. Infectious causes of colitis must be excluded by stool microscopy and culture.

*Treatment:* In active disease depends upon the extent of involvement and degree of inflammation. Corticosteroids are used rectally for left-sided disease, orally if more extensive, more active or unresponsive, and intravenously in severe cases. 5-aminosalicylic acid (5-ASA) compounds, sulphasalazine, mesalazine and olsalazine, of benefit in mild-moderate disease, but their main role is in maintenance therapy. Immunosuppressants (azathioprine, 6-mercaptopurine) are used for resistant disease or for their steroid-sparing effect. Cyclosporine may have a limited role in severe colitis where surgery is not possible.

Maintenance therapy with 5-ASA compounds reduces the relapse rate by 50% or more. Treatment should be continued indefinitely. Azathioprine/6-MP can also be used for maintenance.

Surgery, usually ileal pouch-anal anastomosis, is required in approximately 20% of patients. Indications include severe active disease, chronic unresponsive disease, cancer risk or overt cancer.

**Crohn's disease**

*Pathology:* can involve any part of the gastrointestinal tract, most commonly the ileum, colon or both. Discontinuous involvement, with characteristic "skip" lesions. The inflammation is transmural, leading to wall thickening. Fistulae may develop and are specific for Crohn's disease. Histologically there is a mononuclear infiltrate with the characteristic granulomas present in 70%.

*Clinical features:* In small bowel disease the main symptom is pain. Patients with colitis develop diarrhoea, but with bleeding in only 50%. Fistulae may develop between loops of intestine or between intestine and skin or other organs. Systemic symptoms such as fatigue, fever and weight loss are also common in Crohn's disease. Perianal complications occur in 25%. Extraintestinal manifestations may develop as in ulcerative colitis.

*Diagnosis:* a high index of suspicion is required. Colonoscopy with biopsy and small bowel radiology are generally used. Other investigations depend on the site of involvement.

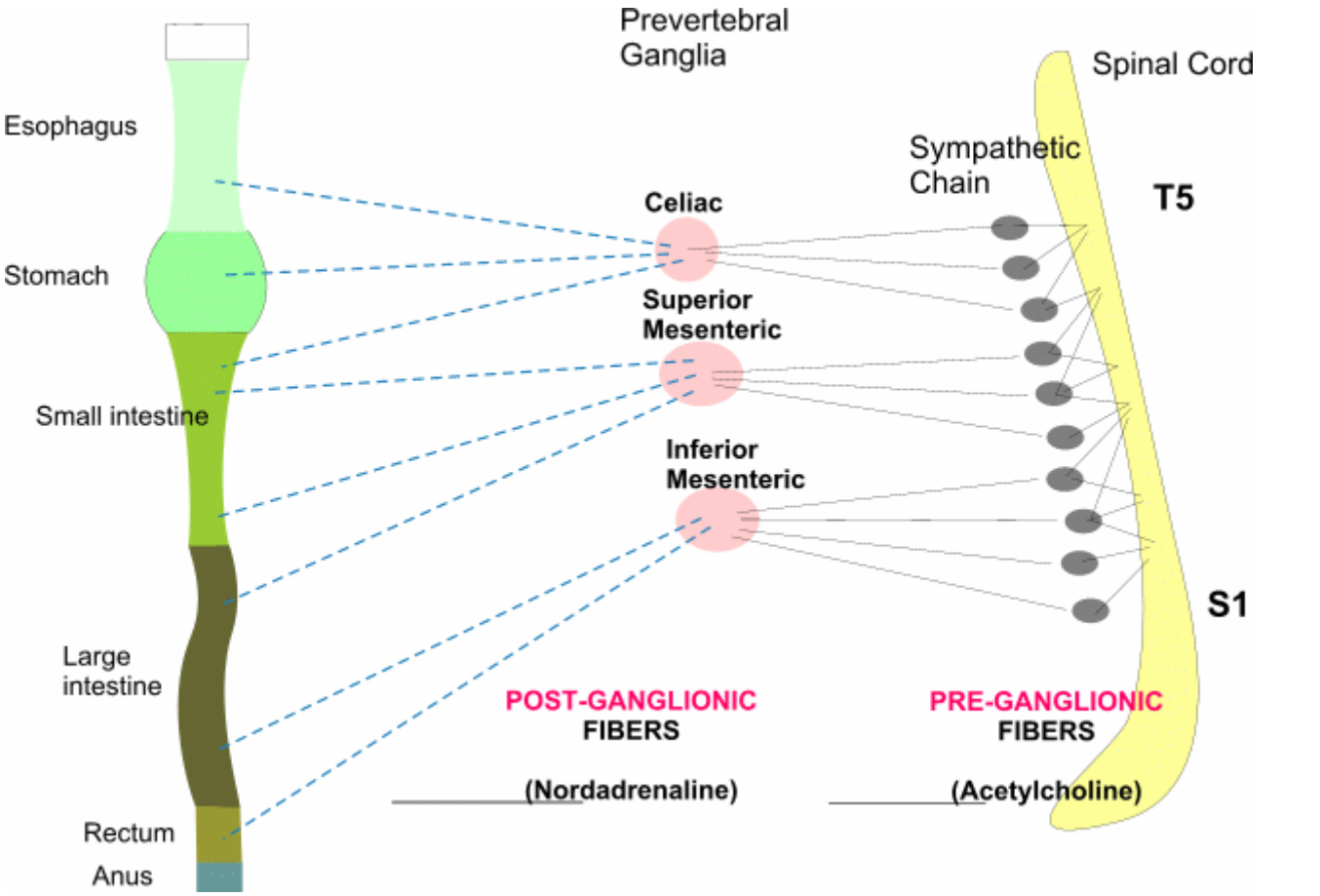
*Treatment:* active disease is treated with corticosteroids. Azathioprine or 6-MP are also used as in ulcerative colitis. Oral mesalazine in high dose may be of benefit in ileal inflammation. In resistant disease methotrexate has been tried. Cessation of smoking is essential because of its adverse effect on the course of the disease. New treatments include broad-spectrum antibiotics and anti-tumour necrosis factor (infliximab).

Maintenance therapy with oral mesalazine is used in ileal disease. Immunosuppressants can also be used in selected patients.

Surgery is needed in up to 80% of patients, especially those with small bowel involvement. This is mostly segmental resection of the most inflamed areas, with a conservative approach. Strictureplasty is performed on small bowel strictures. Surgery is not curative, with approximately 50% of patients requiring a subsequent operation.

*Prognosis:* although these are chronic diseases, most patients can lead productive lives. Only a small proportion are disabled by the condition. Death from inflammatory bowel disease is rare.

# INNERVATION OF THE GUT




***CHRONIC DIARRHOEA: a synopsis of pathophysiology :*** ***4 BASIC MECHANISMS***

## OSMOTIC

Poorly absorbed nutrient drags water into the lumen

**DIAGNOSIS:**

**It will stop with fasting,**

…or with removal of the offending solute

**CAUSES:**

Lactase deficiency

Ingestion of excess **mannitol, sorbitol, etc**

Even fibre can do it

Magnesium, laxatives, antacids

## EXUDATIVE

associated with mucosal damage that leads to **an outpouring of mucus, blood, & plasma proteins**

(eg. - chronic ulcerative colitis, radiation enteritis)

**WILL NOT STOP WITH FASTING**

***WHERE IS IT COMING FROM? SMALL BOWEl, LARGE BOWEL, OR STEATORRHOEA?***

**SMALL BOWEL:**

Large volume

Liquid

No blood or mucus

May have undigested food

Audible gurgling

Periumbilical PAIN

**LARGE BOWEL:**

Small volume but frequent

Blood AND mucus

Straining, tenesmus

(constant urge)

pain @ lower abdomen

**STEATORRHOEA:**

Bulky, pale, oily, **STINKY**

**Floating!!**

**Either liver or pancreas:**

**are they YELLOW?**

**Is there PRURITIS** (bile duct obstruction)

## MOTILITY

### Too fast

**Thyrotixicosis**

**Post-abdominal surgery**

### Too slow

**Bacterial overgrowth**

**Primary intestinal hypomotility**

**Scleroderma (constrictions)**

**Diabetic autonomic neuropathy**

## SECRETORY

results from **active secretion of electrolytes & water** from the intestinal epithelium

eg. – CHOLERA TOXIN

**Fasting does not relieve this type.**

*Secretory is not a common type.*

*→ secretory gastric carcinoma, VIPoma, laxative abuse, loss of 100cm of terminal ileum*

# PATHOGENESIS of Coeliac Disease and Lactose Intolerance