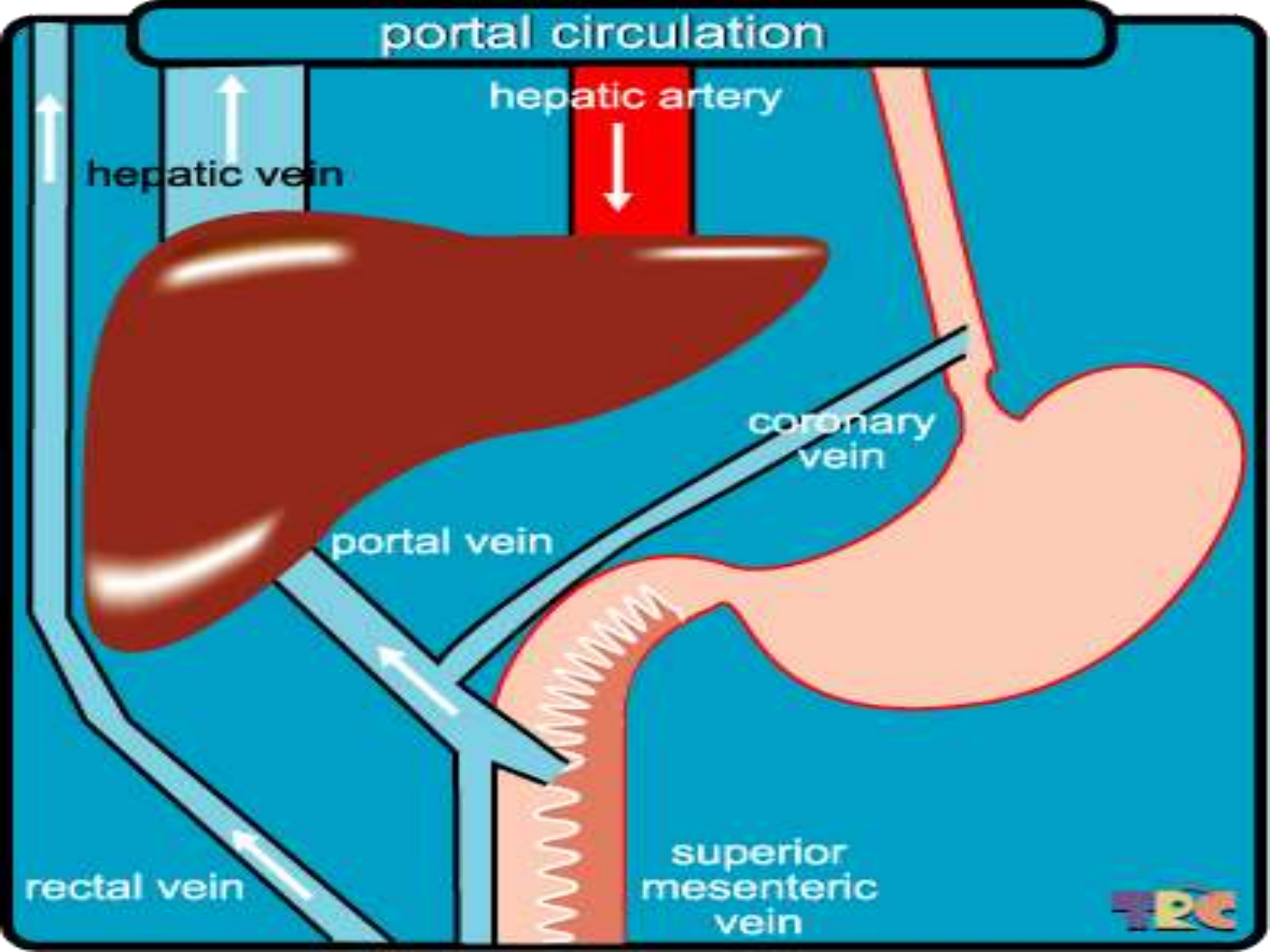
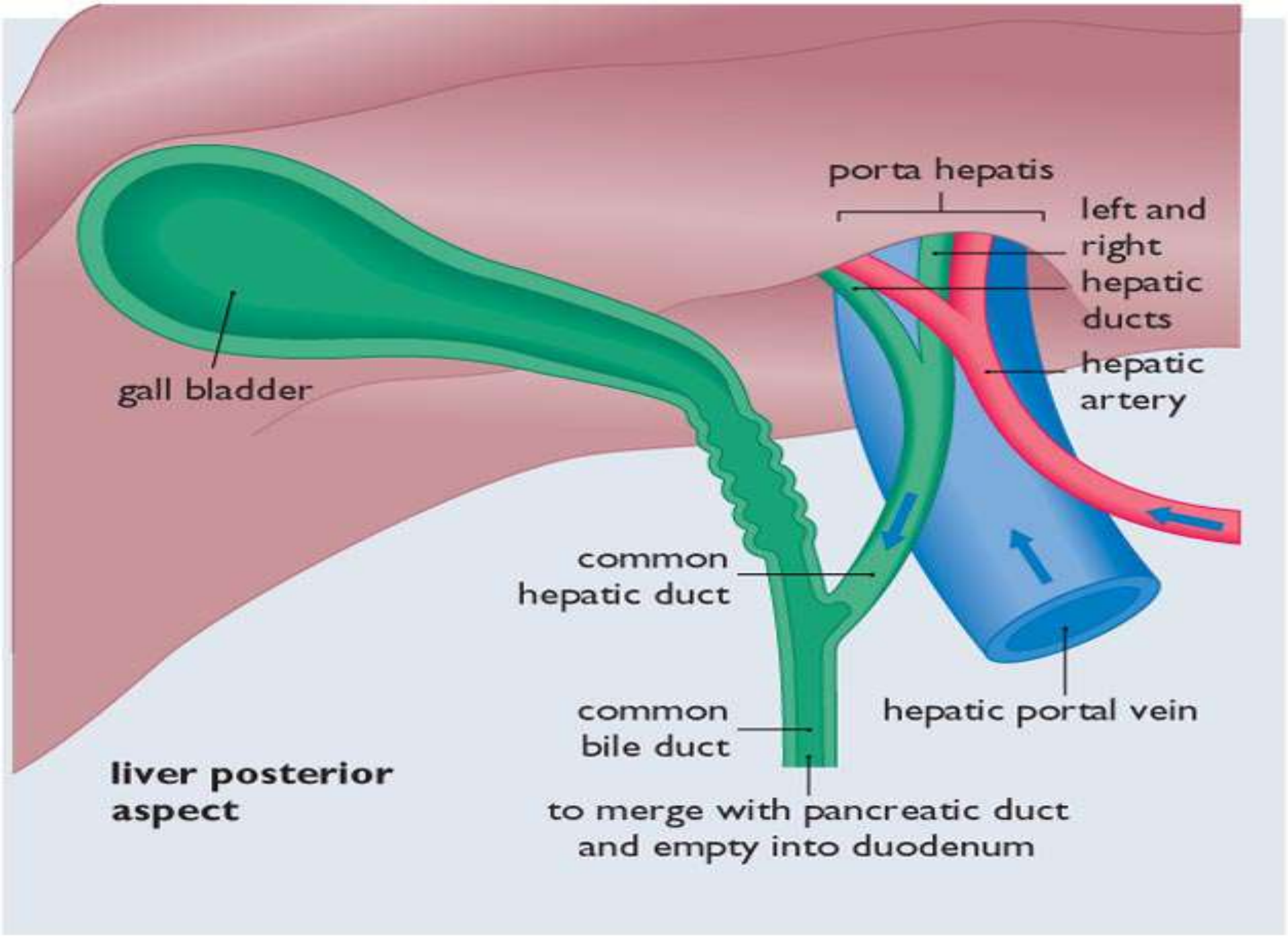
BIOTRANSFORMASI OBAT

NOOR WIJAYAHADI


portal circulation
hepatic artery
hepatic vein
coronary vein
portal vein
rectal vein
superior mesenteric vein



FUNGSI HATI

➔ **metabolism of CHO, fat, protein, and drugs**

1) **Storage of vitamins and trace elements**
2) **Bio-transformasi obat → Konversi beta-carotene, folate, and vitamin D menjadi aktif**
3) **Bile formation and excretion**
4) **Sodium and water homeostasis**

Anabolic functions

1) **Control of blood glucose: glycogenesis, glycogenolysis, glycolysis, gluconeogenesis.**
2) **Protein and amino acid metabolism: synthesis of a number of proteins; albumin, transferrin, prealbumin, retinol-binding protein, coagulation...**
3) **Lipid metabolism: synthesis of triacylglycerols, lipoproteins, cholesterol, LCAT, and bile acids.**

Catabolic functions

1) Oxidation of fatty acids: energy source
2) Detoxification of ammonium and drugs
3) Phagocytosis of bacteria and endotoxin from the GI tract
4) Conjugation and excretion of bilirubin
5) Catabolism of aldosterone

Nutrient storage

1) Glycogen
2) Fat-soluble vitamins
3) Vitamin B12
4) Magnesium
5) Metals: zinc, iron, copper

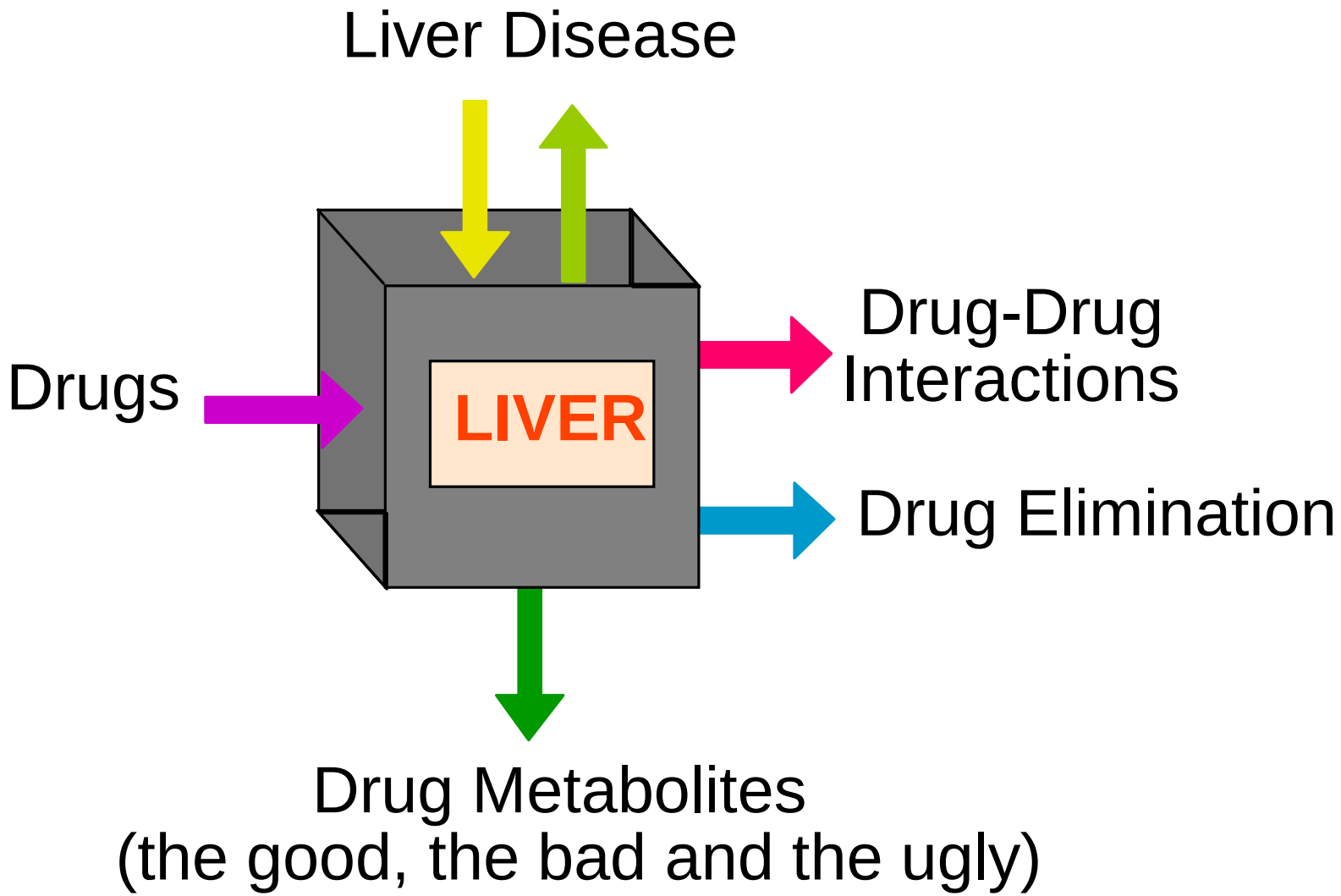
Conversion

1) **Carotene → vitamin A**
2) **Folate → 5-methyltetrahydrofolate**
3) **Pyridoxine → pyridoxal-5-Phosphate**
4) **Vitamin D → 25-hydroxyvitamin D**

Homeostatic function

1) **Water and sodium homeostasis**
2) **Maintenance of normal plasma volume**

Drugs and the Liver



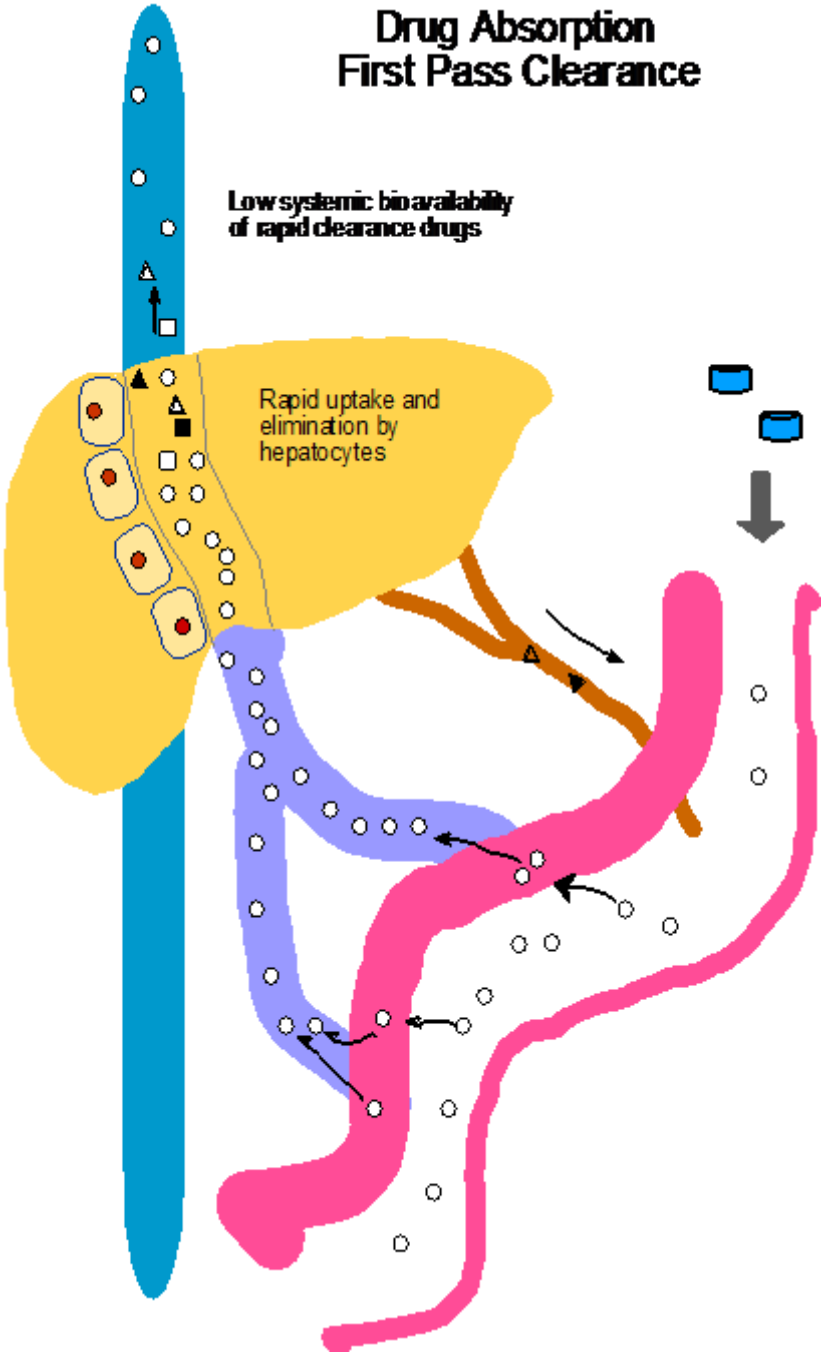
High Extraction Drugs:

Drugs/xenobiotics rapidly cleared in a single pass through the liver.

Consequences can be good or bad:

Oral administration of drugs/ xenobiotics is inefficient – must administer IV/IM.

However, enterohepatic circulation of bile acids is efficient.



Metabolisme Obat di Hepar

Phase I Reactions

OXIDATION
REDUCTION
HYDROLYSIS

Phase 2 Reactions

Glucuronidation

Sulfate Conjugation

Acetylation

Glycine Conjugation

Methylation

Transulfuration

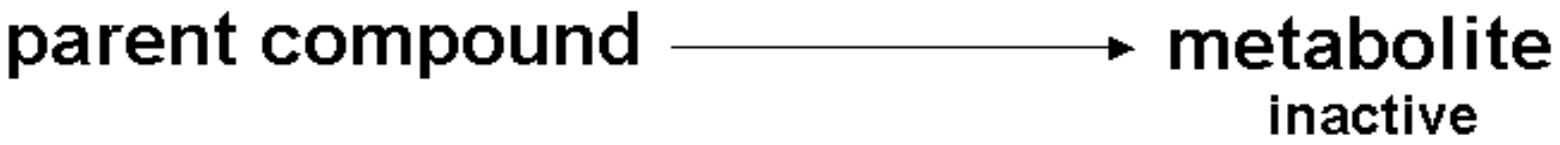
Glutathione Conjugation

Mercapturic Acid Synthesis

IMPLIKASI PADA METABOLISME OBAT

1. Termination of drug action
2. Activation of prodrug
3. Bioactivation and toxication
4. Carcinogenesis
5. Tetratogenesis

1. Termination of Drug Action



atropine → tropic acid and tropine

propranolol → hydroxypropranolol

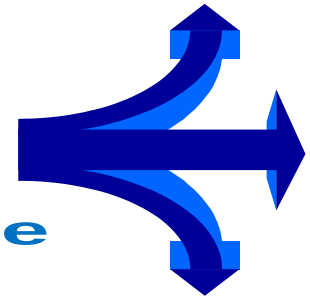
(active) (active)

2. Activation of Prodrug

Terfenadine → **Fexofenadine**

Drugs with Active Metabolites

DRUG	ACTIVE METABOLITE
allopurinol	oxypurinol
amitriptyline	nortriptyline
codeine	morphine
diazepam	oxazepam
procainamide	N-acetyl PA
prednisone	prednisolone
primidone	phenobarbitone
aspirin	salicylate



3. Bioactivation and Toxication

Parent compound ⟶ **metabolit**

toxic

Parasetamol ⟶ **metabolit 1 (NABQ)**

4. Carcinogenesis

Parent compound → **Metabolit**

Carcinogen

- **3,4 Benzopyrene**
- **Aflatoxin**
- **N-Acetylaminoflluorene**

→ **Metabolites (Carcinogen)**

5. Teratogenesis

Parent compound → **metabolit**

teratogenic

Talidomid → **metabolit teratogen**

Drug Induced liver Disease

Hepatocelular damage	Drug
Microvesicular fatty change	Tetracycline, salicylates.
Macrovesicular fatty change	Ethanol, methrotexate.
Massive necrosis	Acetaminophen, insoniazid.
Hepatitis, acute and chronic	Methyldopa, phenytoin.
Cholestasis	Anabolic steroids, oral contraceptives.

Efek sakit parenchym hati terhadap half -life berbagai obat

Half-life memanjang

- Amobarbital
- Carbenicillin
- Klorampenikol
- Diazepam
- Hexobarbital
- Isoniazid
- Lidocain
- Meperidine
- Meprobamate
- Fenobarbital
- Prednisone
- Rifampin
- Fenilbutazon*
- Pentobarbital*
- Tolbutamide*

Half-life tetap

- Asam salisilat
- Chlorpromazine
- Dicumarol
- Fenitoin
- Fenilbutazone*
- Pentobarbital*
- Tolbutamide*

* Half-life memanjang atau tetap

Aliran Darah di Hati

- Obat dengan angka first-pass atau ratio-ekstraksi tinggi (hepar melakukan metabolisme besar-besaran bahkan lebih dari jumlah obat bebas dlm plasma dan eritrosit) a.l.: propranolol,meperidine dan lidocain, akan **mengalami perubahan kadar plasma yg cukup bermakna dgn adanya perfusi organ yang menurun** (aliran darah lewat hepar berkurang).Sebaliknya tidak demikian halnya dgn obat yg ratio ekstraksi-nya rendah.a.l. antipyrine, ratio-ekstraksinya 0.1. (Lidocain 0.9).
- Obat semacam lidocain ini disebut

  liver blood-flow dependent.

Efek toksik obat terhadap hati

Toksisitas obat dpt terjadi o.k over-dosis hiper-sensitivitas,atau berhubungan dengan metabolit nya. Beberapa obat penting berpotensi toksik thd hepar.

- **Hepatitis akut**:paracetamol (Acetaminophen) ,tetrasiklin,Isoniazid,salisilat, ethanol,ferrosulfas (dosis besar).
- **Cirrhosis**: MTX,arsen,ethanol.
- **Cholestasis**:Estrogen.
- **Neoplasma**:kontrasepsi oral

Efek toksik obat terhadap hati

- Selain karena over-dosis,toksisitas dapat terjadi karena **hipersensitivitas.**Secara klinis maupun histologis manifestasinya dpt berupa penyakit hepatoseluler, cholestasis atau gabungan keduanya.Secara klinis bisa berupa hepatitis akut atau kronik aktif.
- Mekanisme reaksi tersebut tidak diketahui dengan pasti.

Interaksi farmakodinamis obat

Pada keadaan sakit hepar, furosemide atau thiazide menimbulkan kehilangan kalium dan alkalosis yang memicu timbulnya ensefalopati hepatik.

Demikian juga morphin,sedatif analgetik dan tranquilizer.

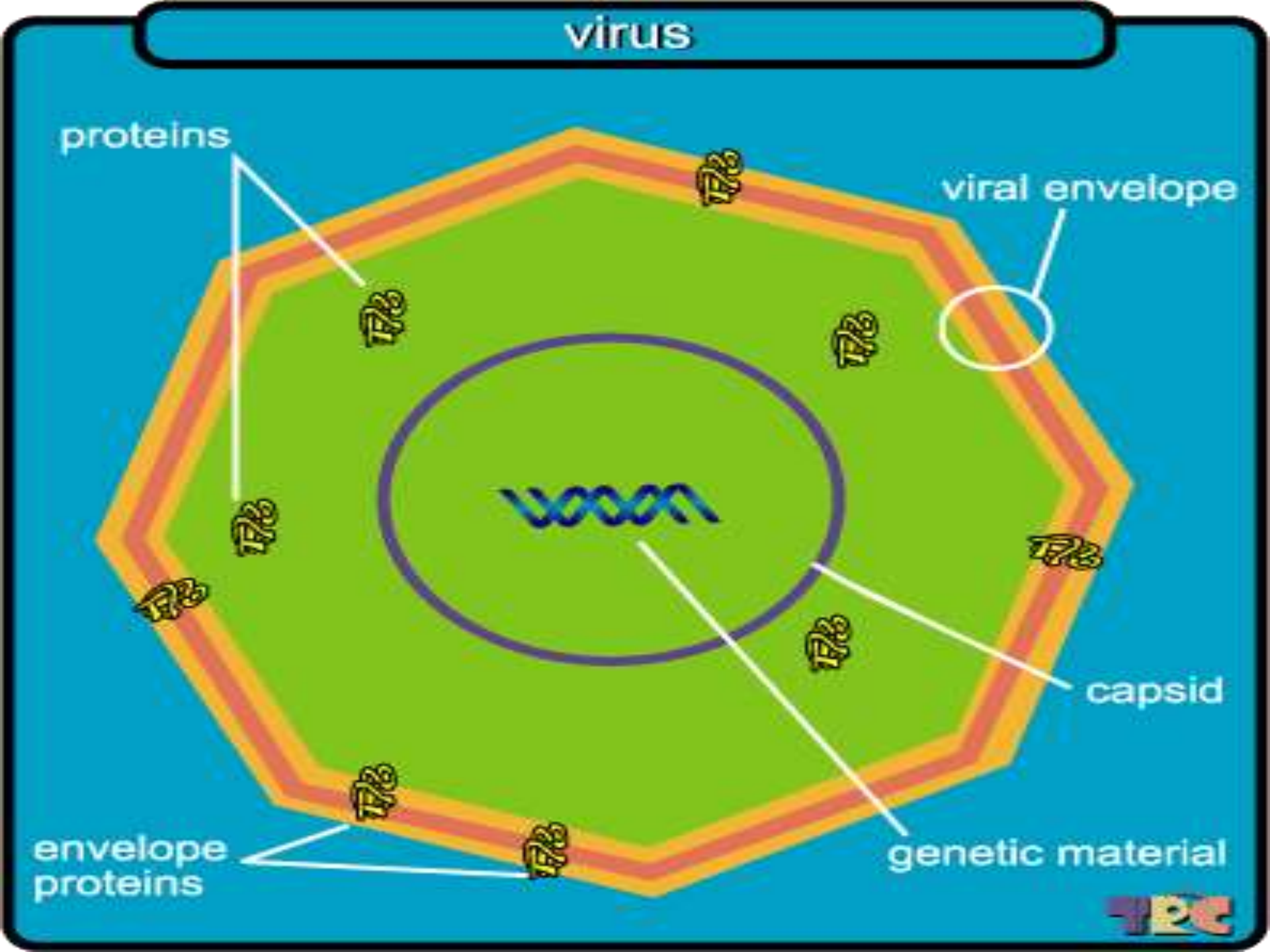
Hipoglikemik drug memicu koma hipoglikemikum .

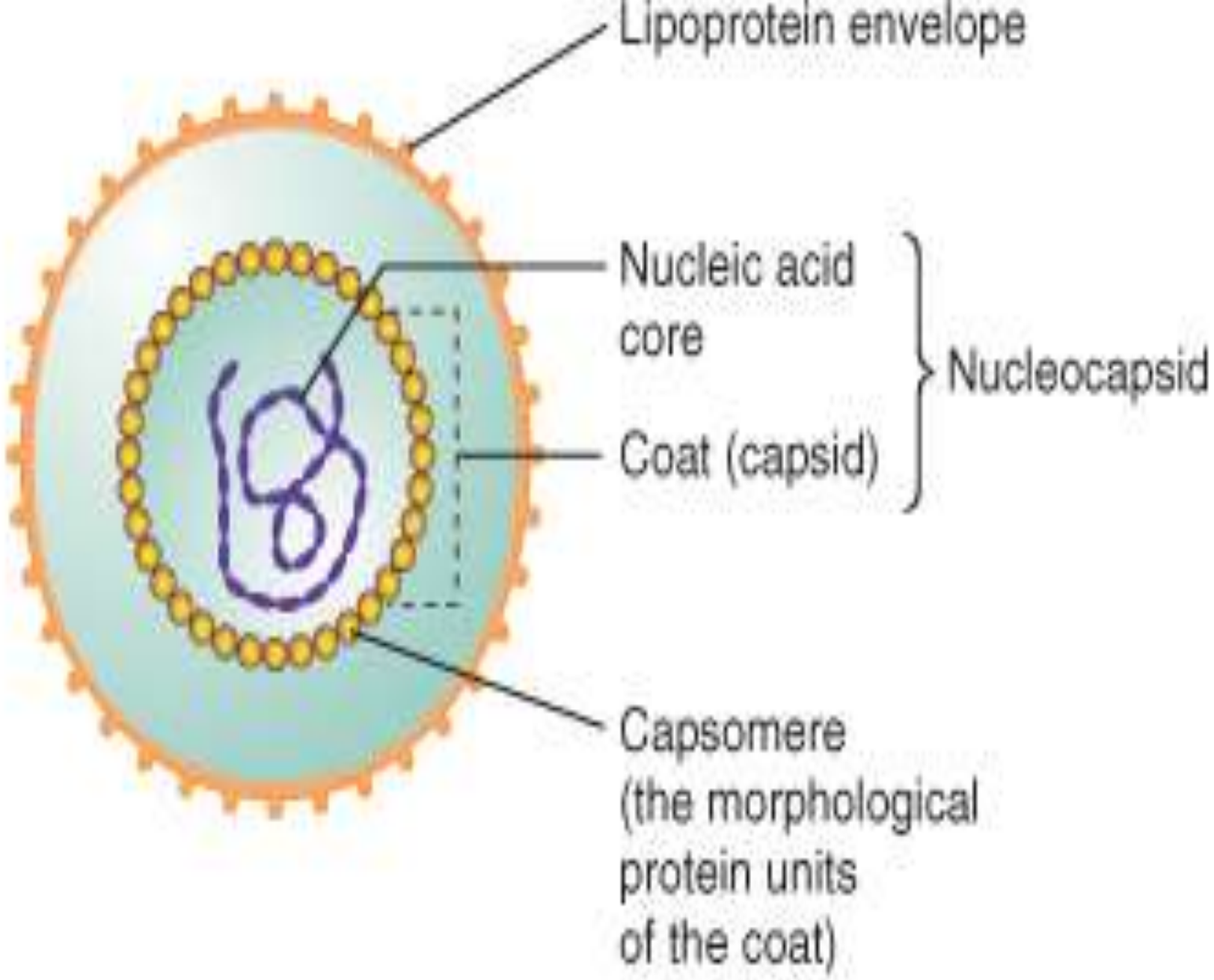
Kemampuan memproduksi faktor penjendalan berkurang pada penyakit hepar,

ANTIVIRAL

Virus

- **Virus ➔ material genetik (DNA / RNA)**
  + nucleocapsid / membran
- **Terlalu kecil ➔**
  sintesa protein, energi dan replikasi tergantung sel inang


virus
proteins
viral envelope
capsid
genetic material
envelope proteins

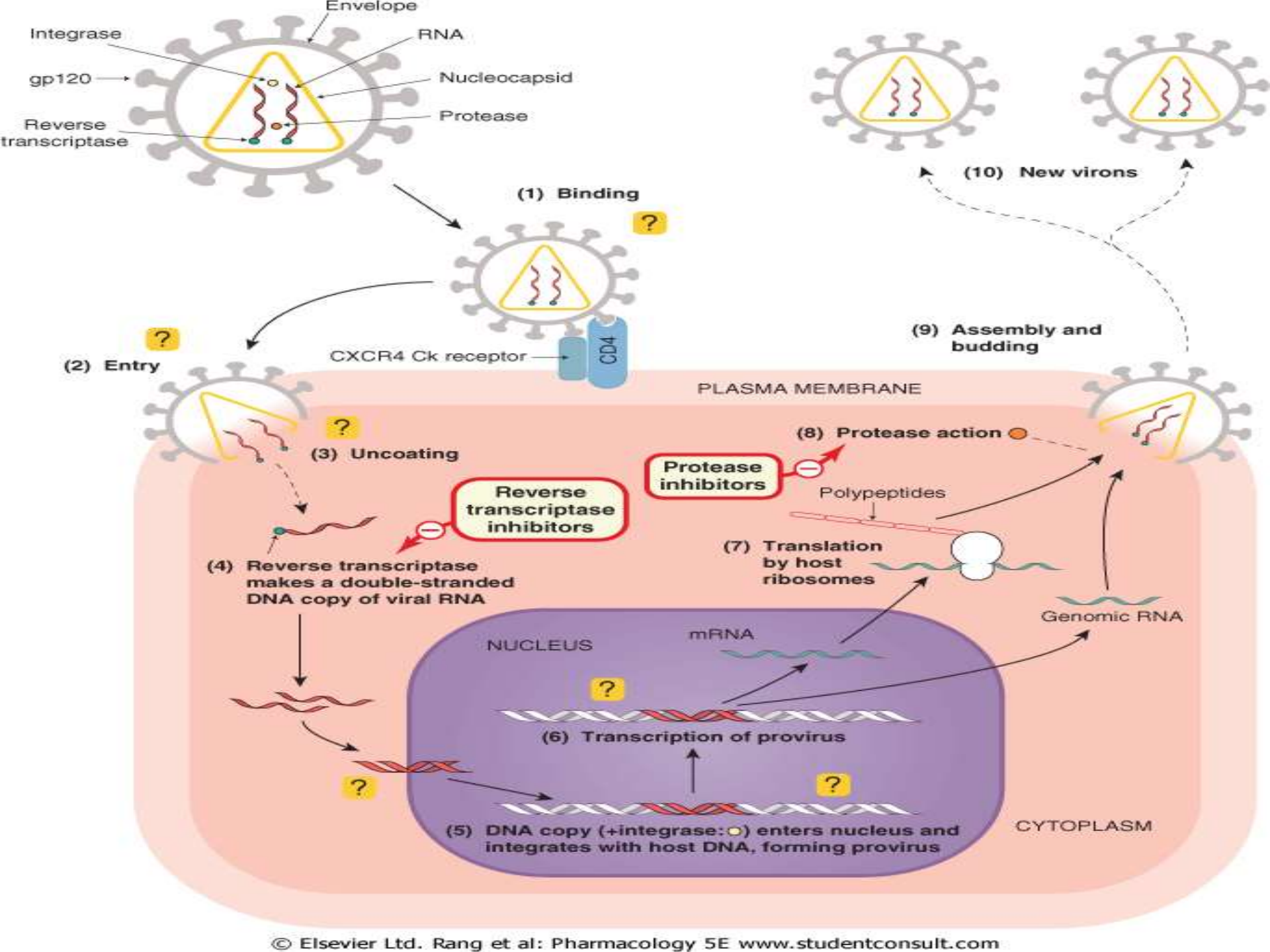


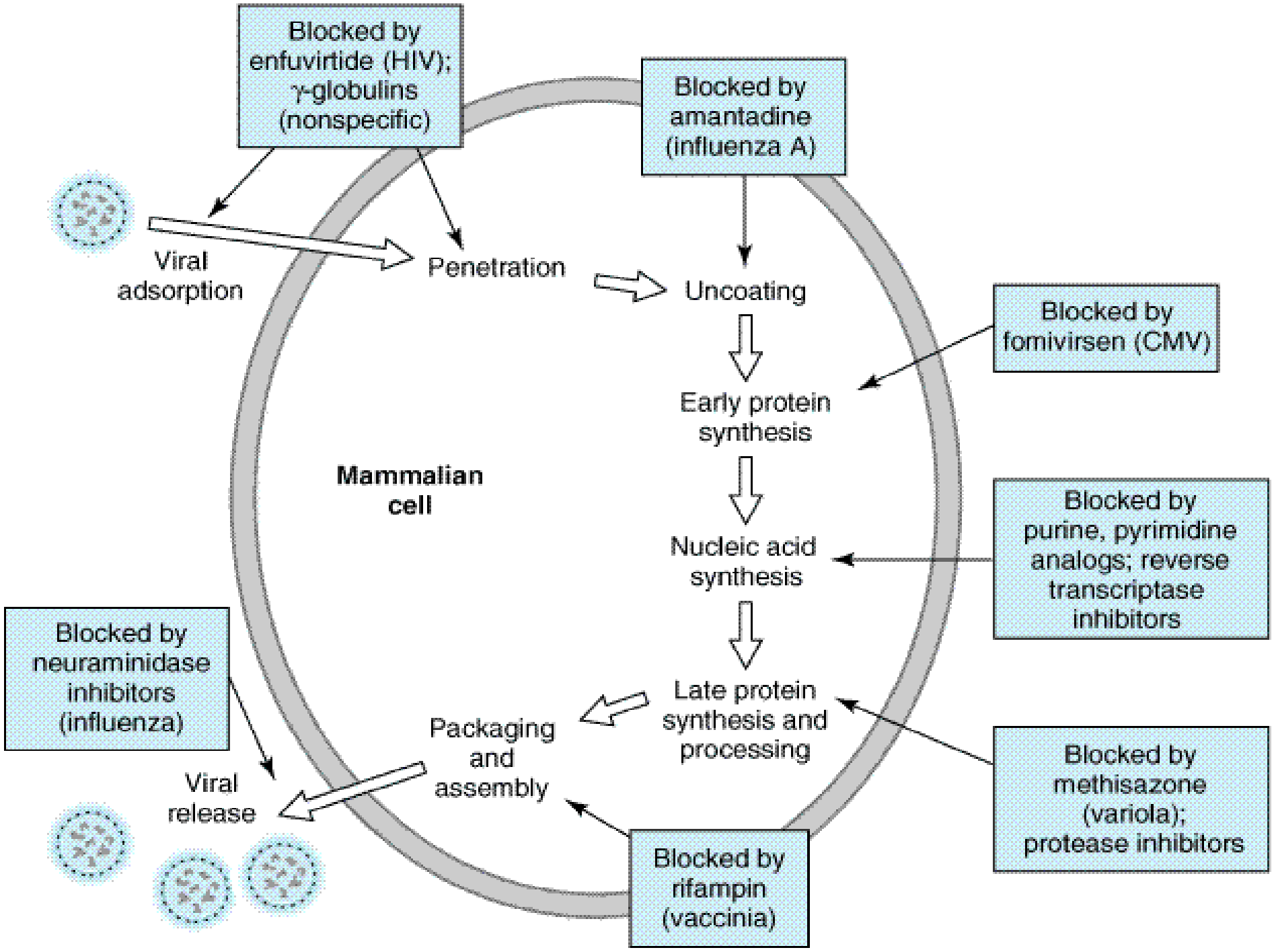
Tahapan replikasi virus:

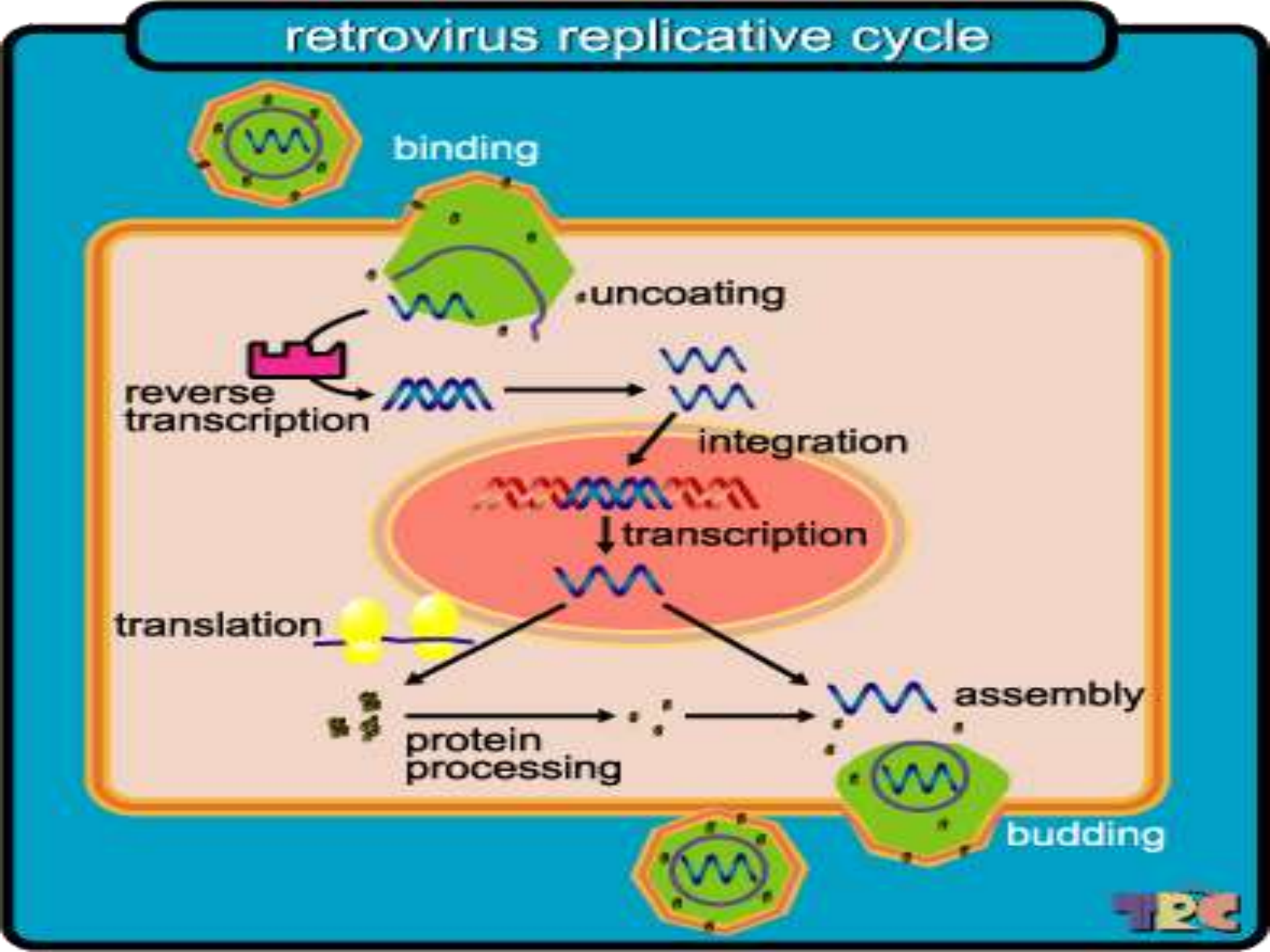
- **(1) pelekatan + penetrasi ke sel inang**
- **(2) uncoating asam nukleat virus**
- **(3) sintesis early regulatory proteins**

  (nucleic acid polymerase)
- **(4) sintesis RNA / DNA**
- **(5) sintesis late structural proteins**
- **(6) assembly (maturation) of viral particles;**
- **(7) pelepasan ke luar sel.**

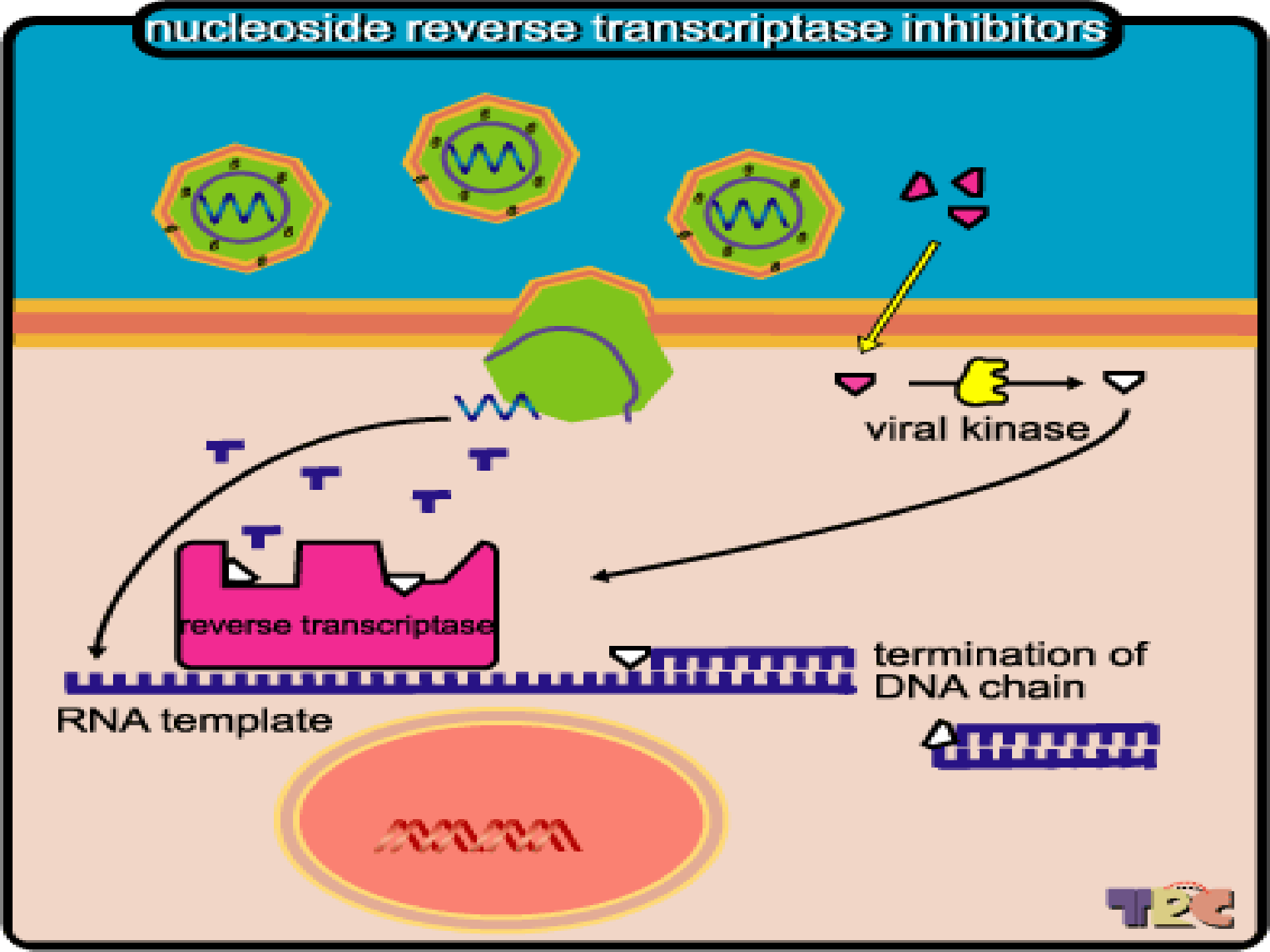
Obat Antiviral ➔ mempengaruhi tiap tahapan




Blocked by enfuvirtide (HIV); γ-globulins (nonspecific)
Blocked by amantadine (influenza A)
Viral adsorption
Penetration
Uncoating
Blocked by fomivirsen (CMV)
Early protein synthesis
Mammalian cell
Nucleic acid synthesis
Blocked by purine, pyrimidine analogs; reverse transcriptase inhibitors
Blocked by neuraminidase inhibitors (influenza)
Late protein synthesis and processing
Packaging and assembly
Viral release
Blocked by methisazone (variola); protease inhibitors
Blocked by rifampin (vaccinia)


retrovirus replicative cycle
binding
uncoating
reverse transcription
integration
transcription
translation
protein processing
assembly
budding

nucleoside reverse transcriptase inhibitors



1. NRTI

- = Nucleoside reverse transcriptase inhibitors (NRTIs)

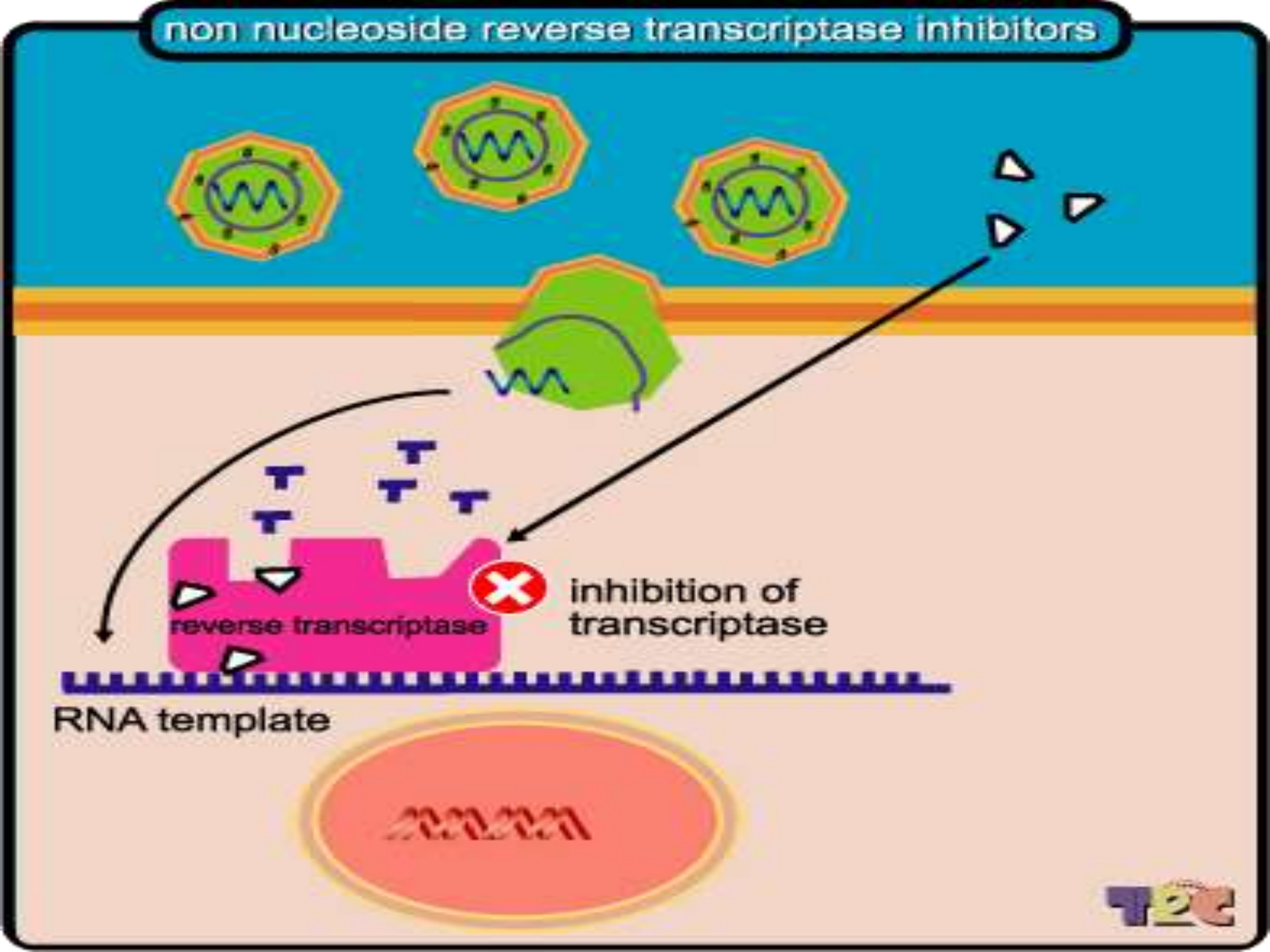
  ➔ analog natural RNA dan DNA nucleotida

- ***Zidovudine* (AZT)** = analog timidin
  - Mengalami phosphorilasi 3x ➔ lebih aktif

    1. Berkompetisi dengan timidin alami

       ➔ sintesis dna terputus

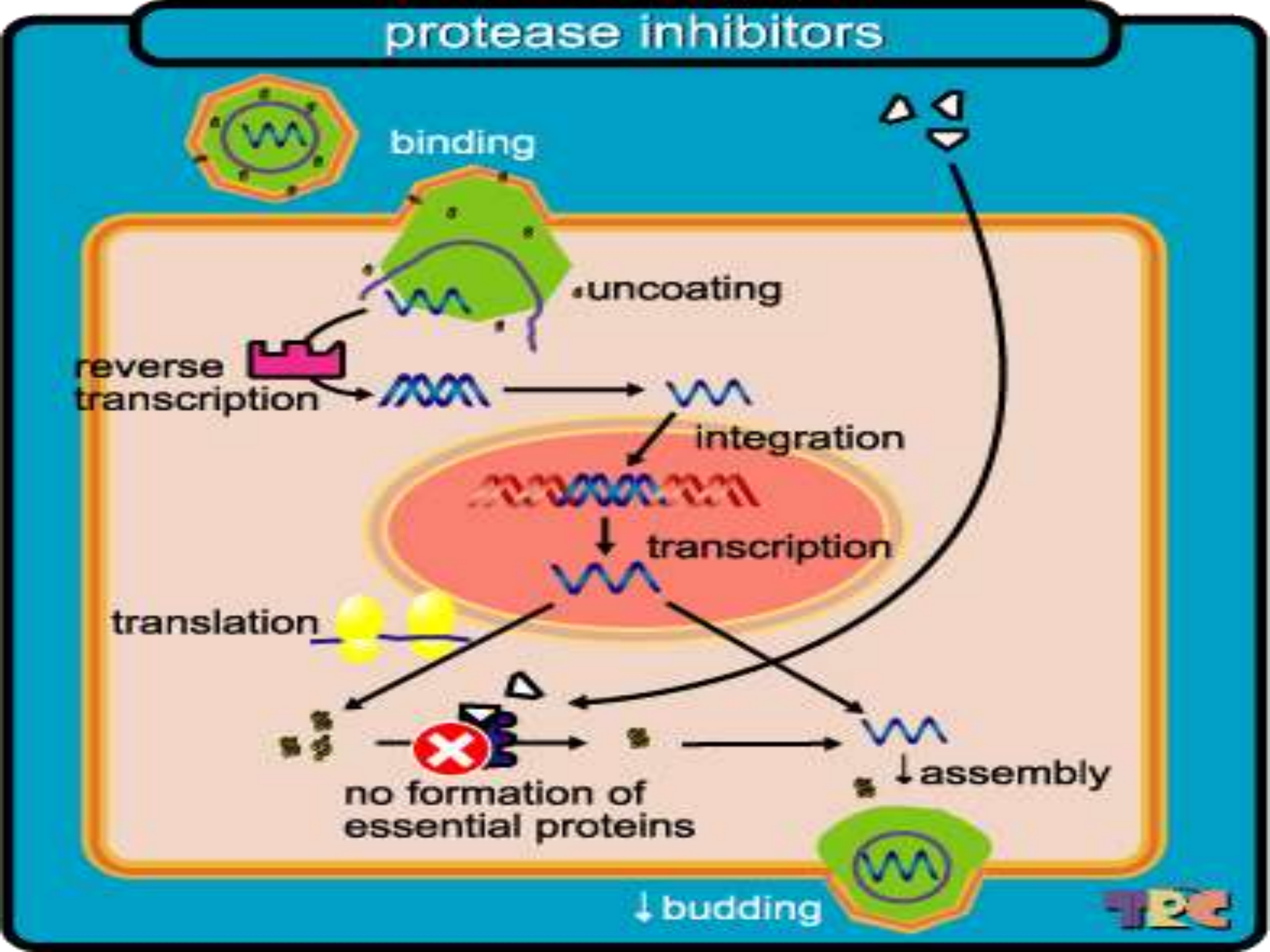
    2. Hambat enzim reverse transcriptase.
  - Dosis tinggi ➔ myelotoksik
  - Dosis normal ➔ gangguan gastrointestinal
  - Zidovudine disukai karena tidak neurotoxic dan penetrasi ke SSP baik
- ***Lamivudine*** (3TC)
  - Kekurangan : cepat terjadi resistensi
  - Juga efektif vs **Hepatitis B virus**


non nucleoside reverse transcriptase inhibitors
reverse transcriptase
inhibition of transcriptase
RNA template

2. NNRTI

- ***Nevirapine*, *delavirdine* and *efavirenz***
- **Berikatan dengan enzim reverse transcriptase**

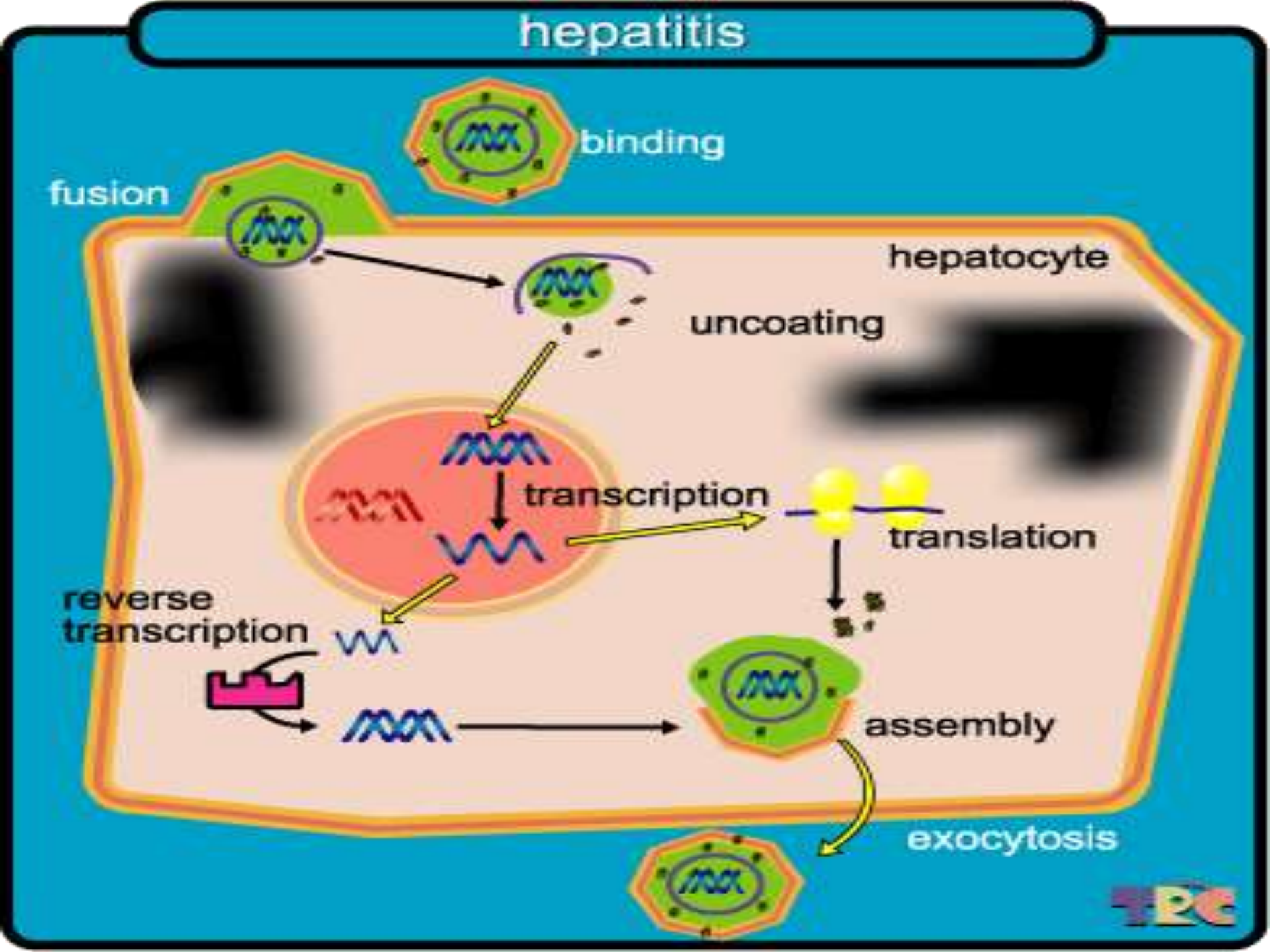
  ➔block aktifitas polymerase
- **Beda dengan NRTI, NNRTI tidak perlu diaktifasi di dalam sel**
- **Pemakaian tunggal tidak efektif. Kombinasi dengan NRTI ➔ sangat efektif**
- **Dimetabolisme enzim sitokrom hepar ➔ berinteraksi dengan pemakaian obat lai (astemazole, midazolam, cyclosporine, rifampin and erythromycin)**
- **Nevirapine ➔ serious hepatotoxic ➔ fungsi hepar perlu dimonitor**


protease inhibitors
binding
uncoating
reverse transcription
integration
transcription
translation
no formation of essential proteins
assembly
budding

3. Protease Inhibitors

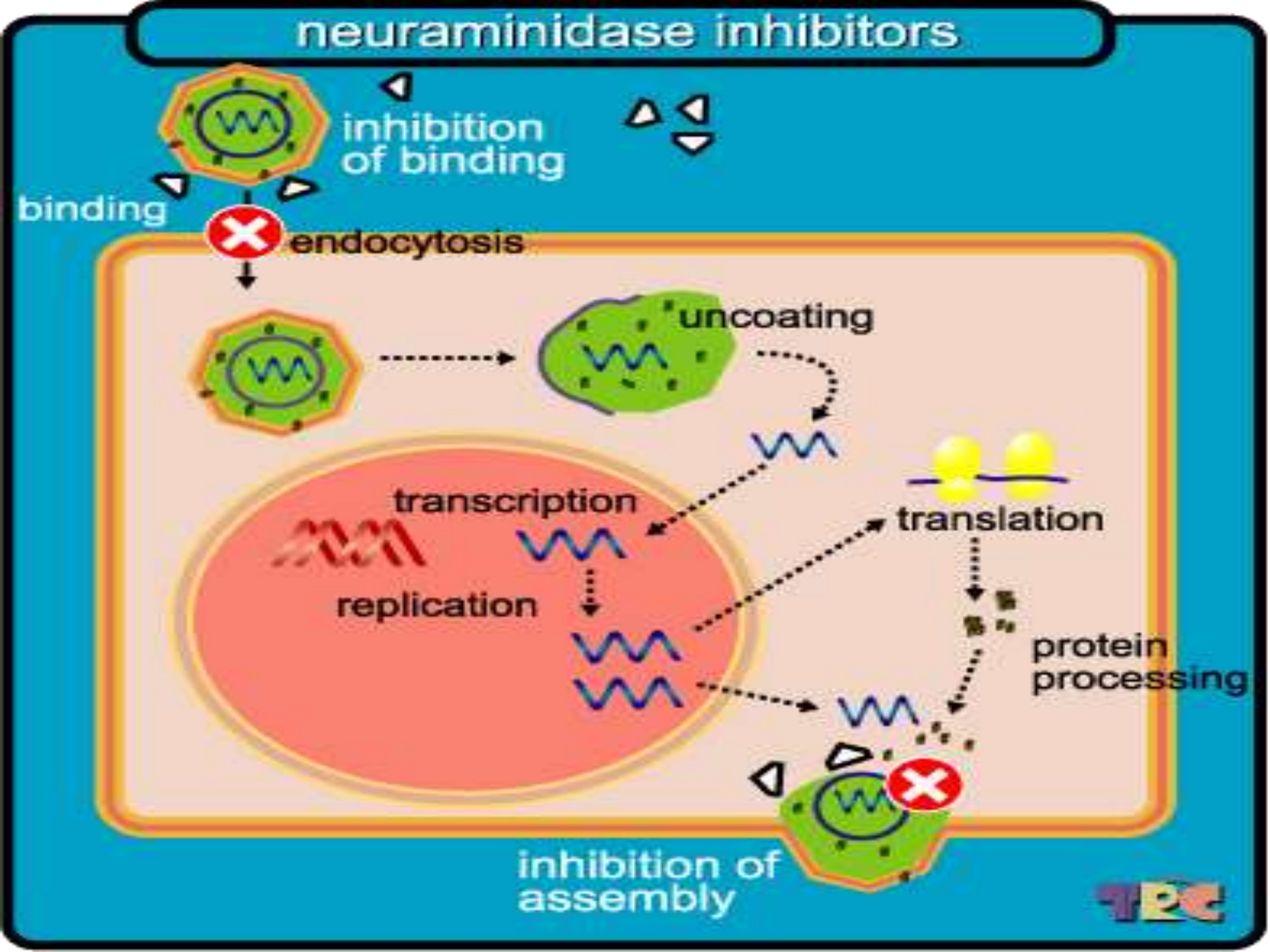
- *Saquinavir, ritonavir* and ***indinavir***
- Hambat enzim protease virus ➔ anakan virus imatur & tidak fungsional ➔ cegah infeksi sel lainnya.
- ESO ➔ gangguan gastrointestinal

  pemakaian lama ➔ lipodistrofi & dislipidemia.
- Hambat kerja enzim hepar ➔ interaksi dengan obat lain


hepatitis
binding
fusion
hepatocyte
uncoating
transcription
translation
reverse
transcription
assembly
exocytosis

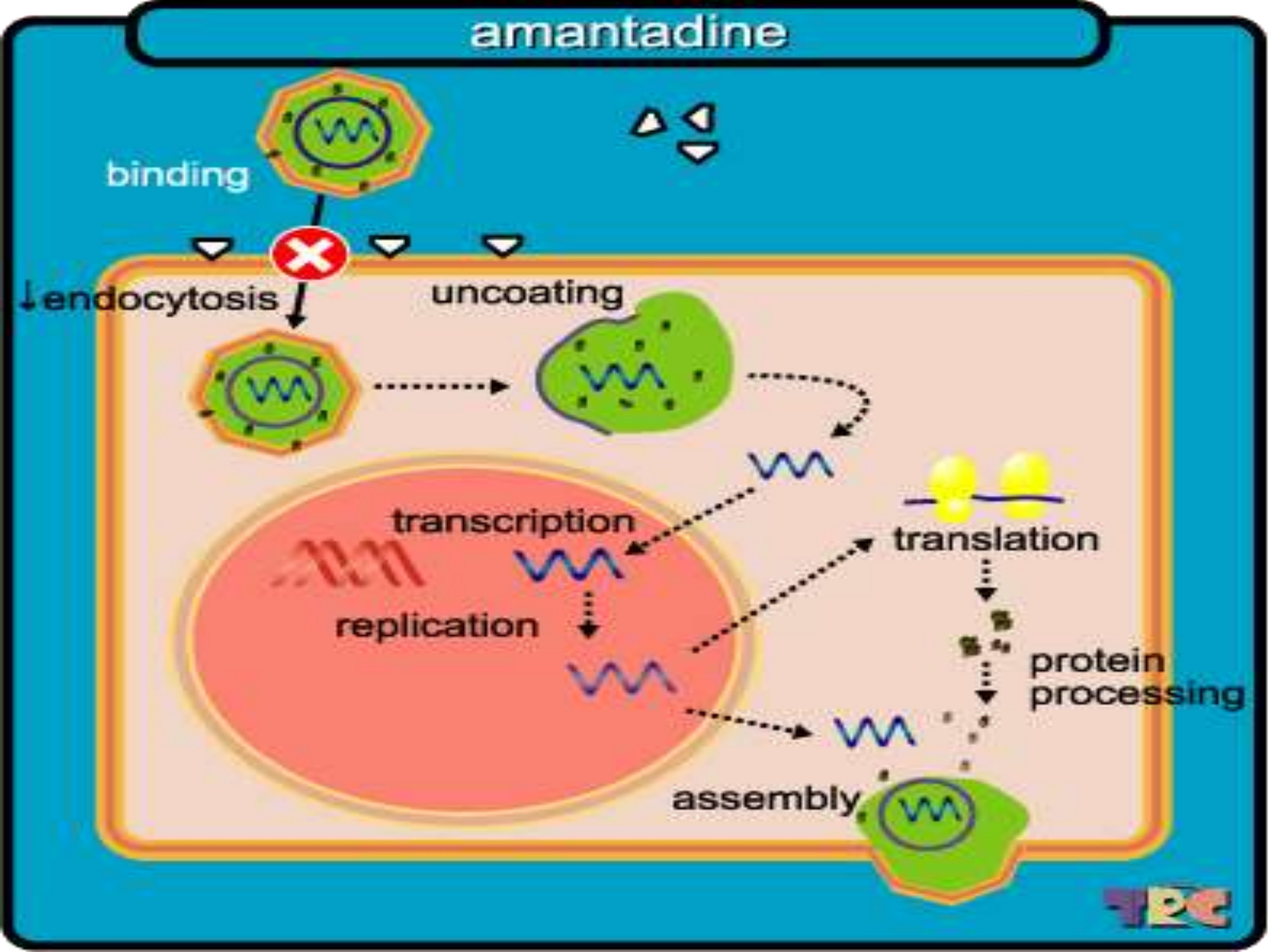
Neuraminidase inhibitors

- ***Oseltamivir*** = prodrug, relatif baru
- Inhibitor selektif pada neuraminidase (enzim dan glycoprotein pada permukaan virus influenza ➔ rangsang penetrasi virus dan pelepasan virus baru)
- Untuk prevensi dan terapi influenza A and B ??


neuraminidase inhibitors
inhibition of binding
binding
endocytosis
uncoating
transcription
translation
replication
protein processing
inhibition of assembly

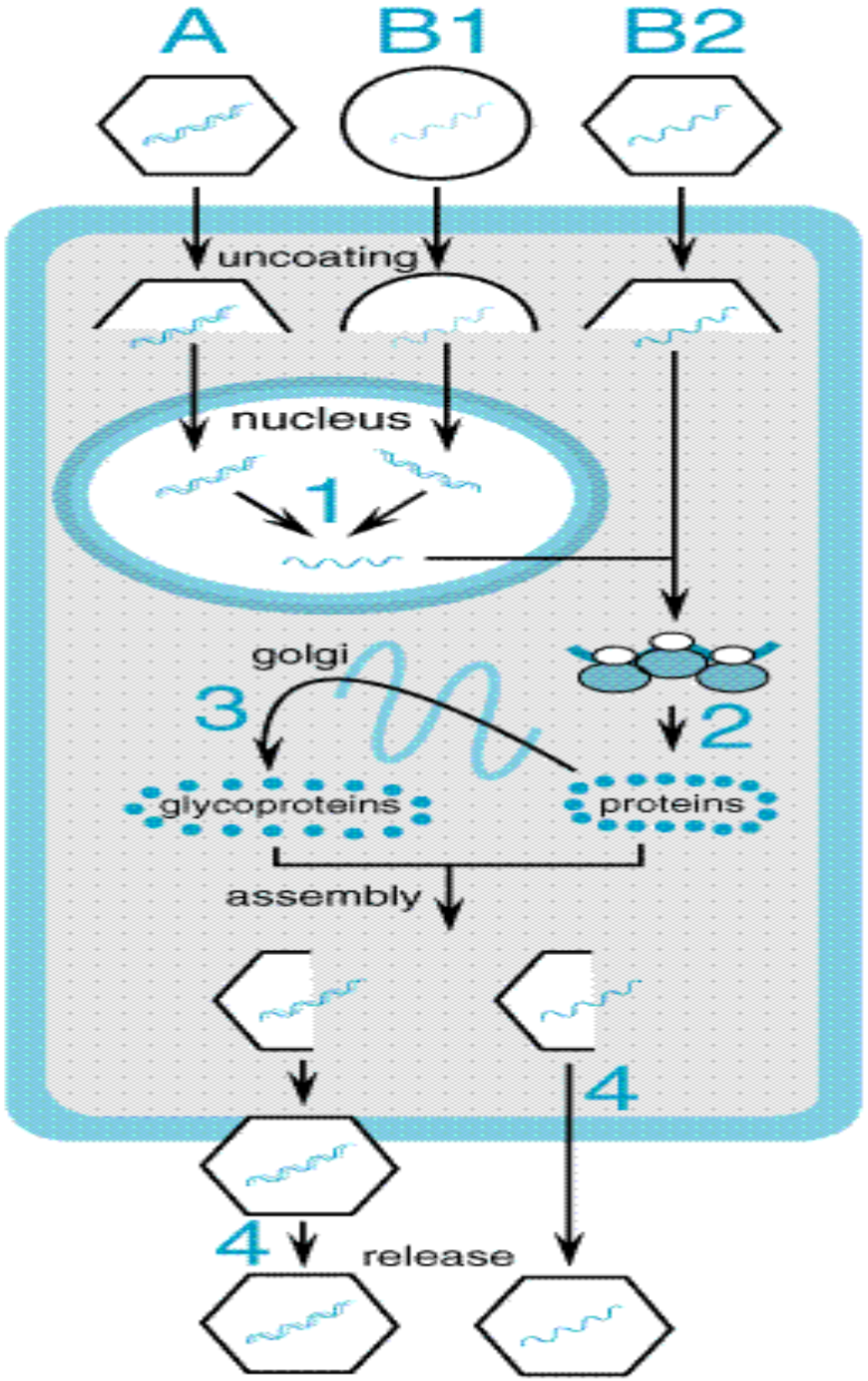
Amantadine

- **Mekanisme pasti belum jelas**
  - **Hambat tahap awal replikasi virus ➔ penetrasi**
  - **Hambat uncoating virus**
  - **Hambat viral assembly**
- **Absorbsi per-oral baik, distribusi luas**
- **ESO: gangguan gastrointestinal & SSP.**
- **Dosis tinggi ➔neurotoxic ➔ kejang ➔ koma**


amantadine
binding
endocytosis
uncoating
transcription
replication
translation
protein
processing
assembly

Interferons

- *Interferon* (***IFN-a 2a*** and ***IFN-a 2b***) ➔ sitokin dengan aktifitas antiviral dan immunomodulator.
- Interferons memberi tanda (marking) sel terinfeksi ➔ cegah replikasi virus dan aktifkan respons imun
- Pemberian via suntikan intramuscular, intravenous atau subcutaneous
- ESO: acute influenza-like symptoms
- Dosis tinggi ➔ myelosupresi.



Viruses

A. DNA

B. RNA

1. orthomyxoviruses and retroviruses
2. picornaviruses and most RNA viruses

IFN Effects

1. transcription inhibition

activates Mx protein
blocks mRNA synthesis

2. translation inhibition

activates methylase —>
blocks mRNA cap methylation

activates 2'5' oligoadenylate synthetase —> 2'5'A —> inhibits mRNA splicing and activates RNase L —> cleaves viral RNA

activates protein kinase P1 —> blocks eIF-2α function —> inhibits initiation of mRNA translation

activates phosphodiesterase —> blocks tRNA function

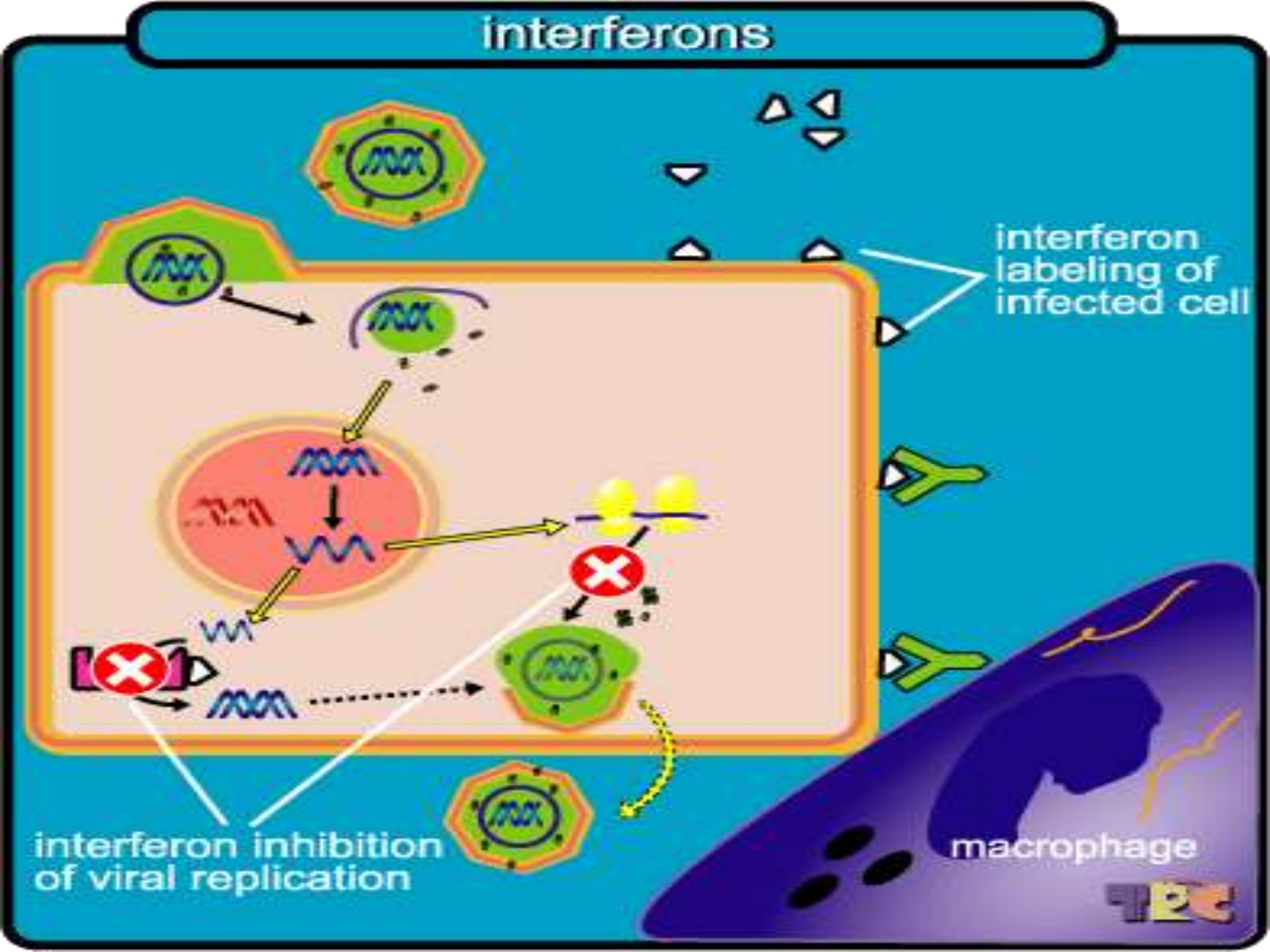
3. protein processing inhibition

glycosyltransferase —> blocks protein glycosylation

4. virus maturation inhibition

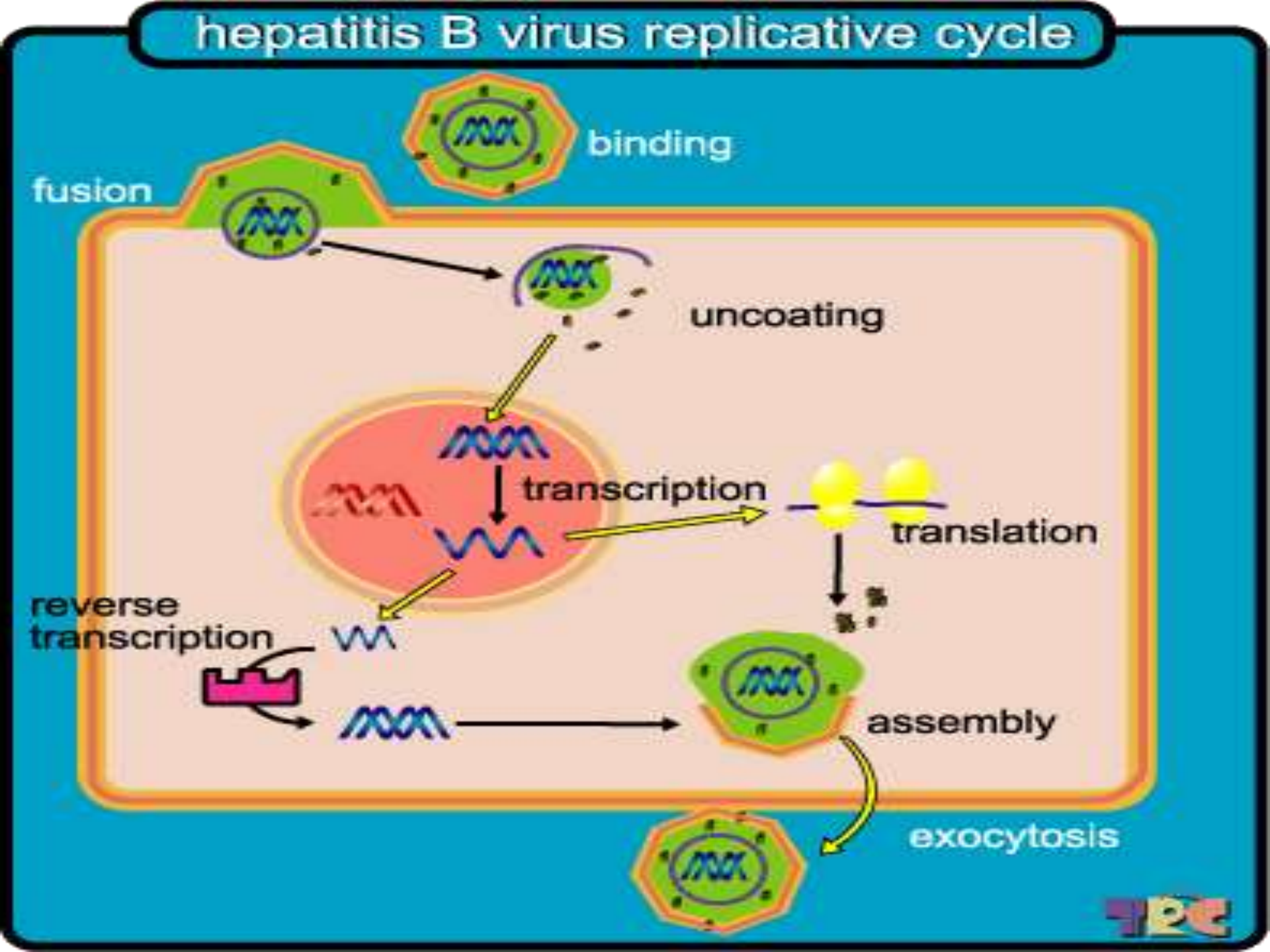
glycosyltransferase —>blocks glycoprotein maturation

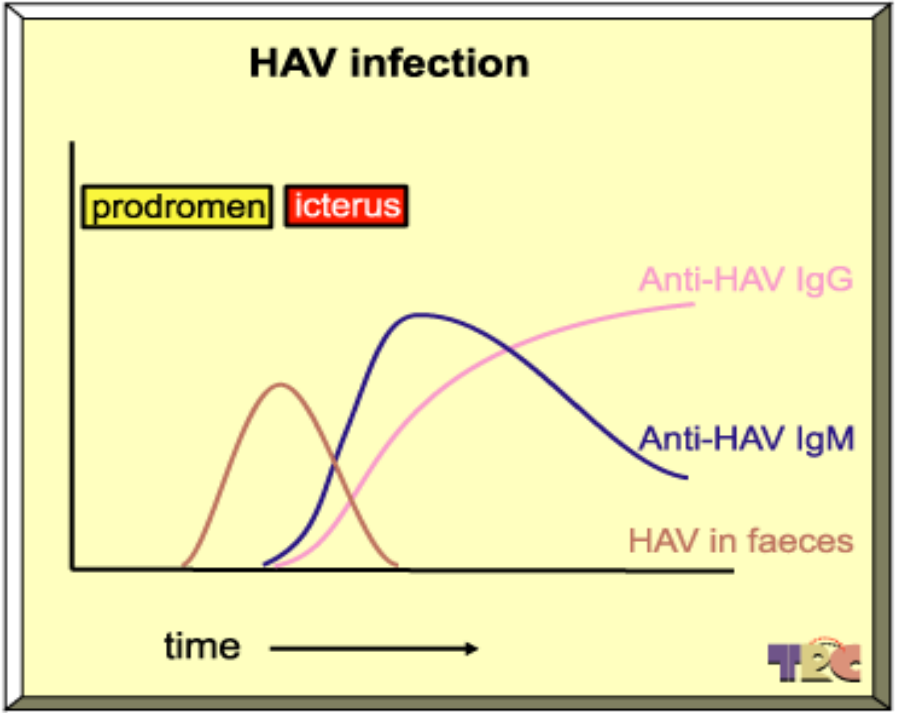
causes membrane changes —> blocks budding

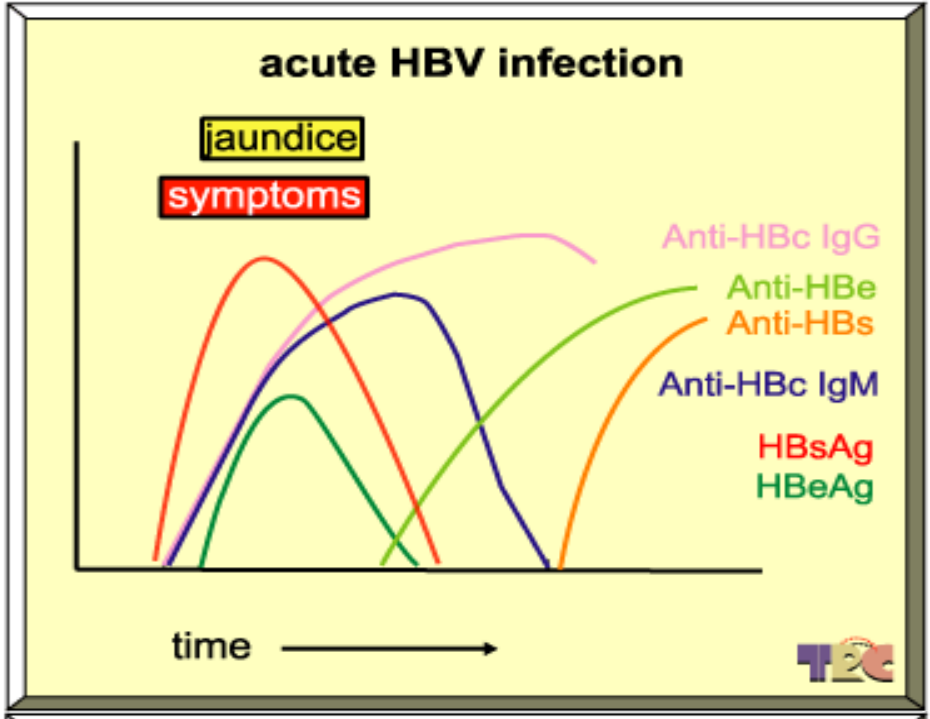

interferons
interferon
labeling of
infected cell
interferon inhibition
of viral replication
macrophage

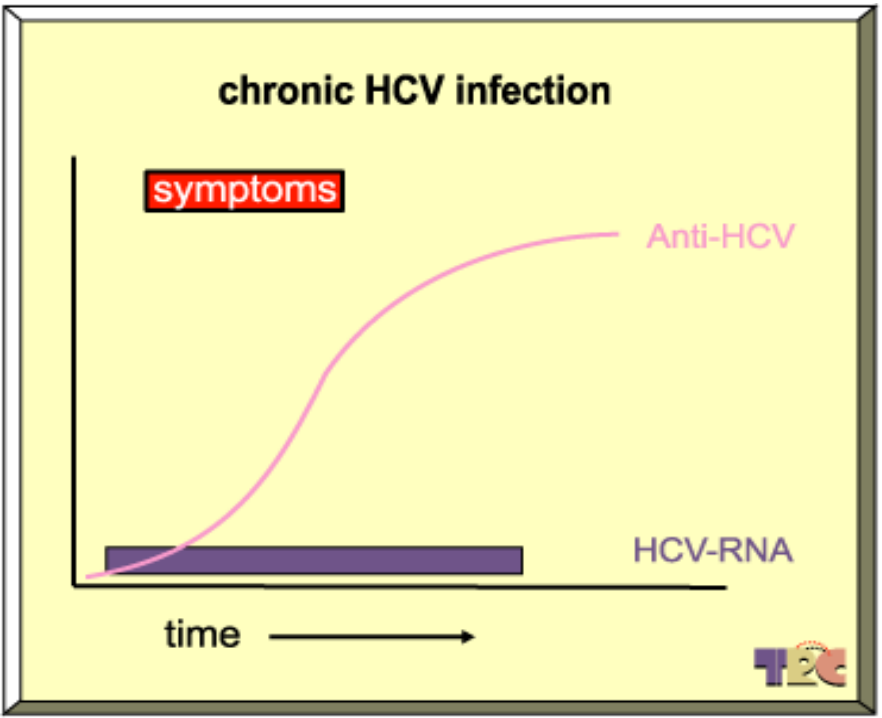
Hepatitis

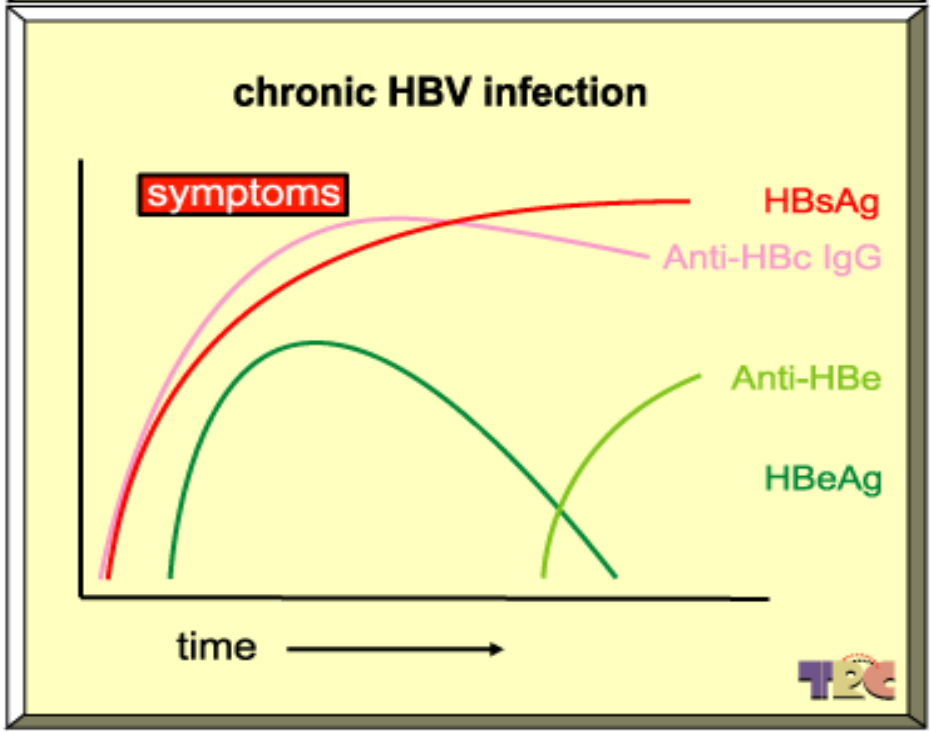
- After entry in the hepatocyte, the DNA of the hepatitis virus is uncoated and brought to the nucleus.
- There the DNA is transcribed and the resulting mRNA is transported to the cytoplasm.
- The viral genetic material is replicated by reverse transcriptase and viral proteins are synthesized.
- The viral DNA and proteins are assembled and enveloped before exocytosis.
- The resulting viremia can lead to either an acute viral hepatitis (with or without fulminant hepatic necrosis) or a chronic necro-inflammatory process.
- The individuals immune response determines the level injury from the viremia.


hepatitis B virus replicative cycle
binding
fusion
uncoating
transcription
translation
reverse
transcription
assembly
exocytosis


HAV infection
prodromen
icterus
Anti-HAV IgG
Anti-HAV IgM
HAV in faeces
time

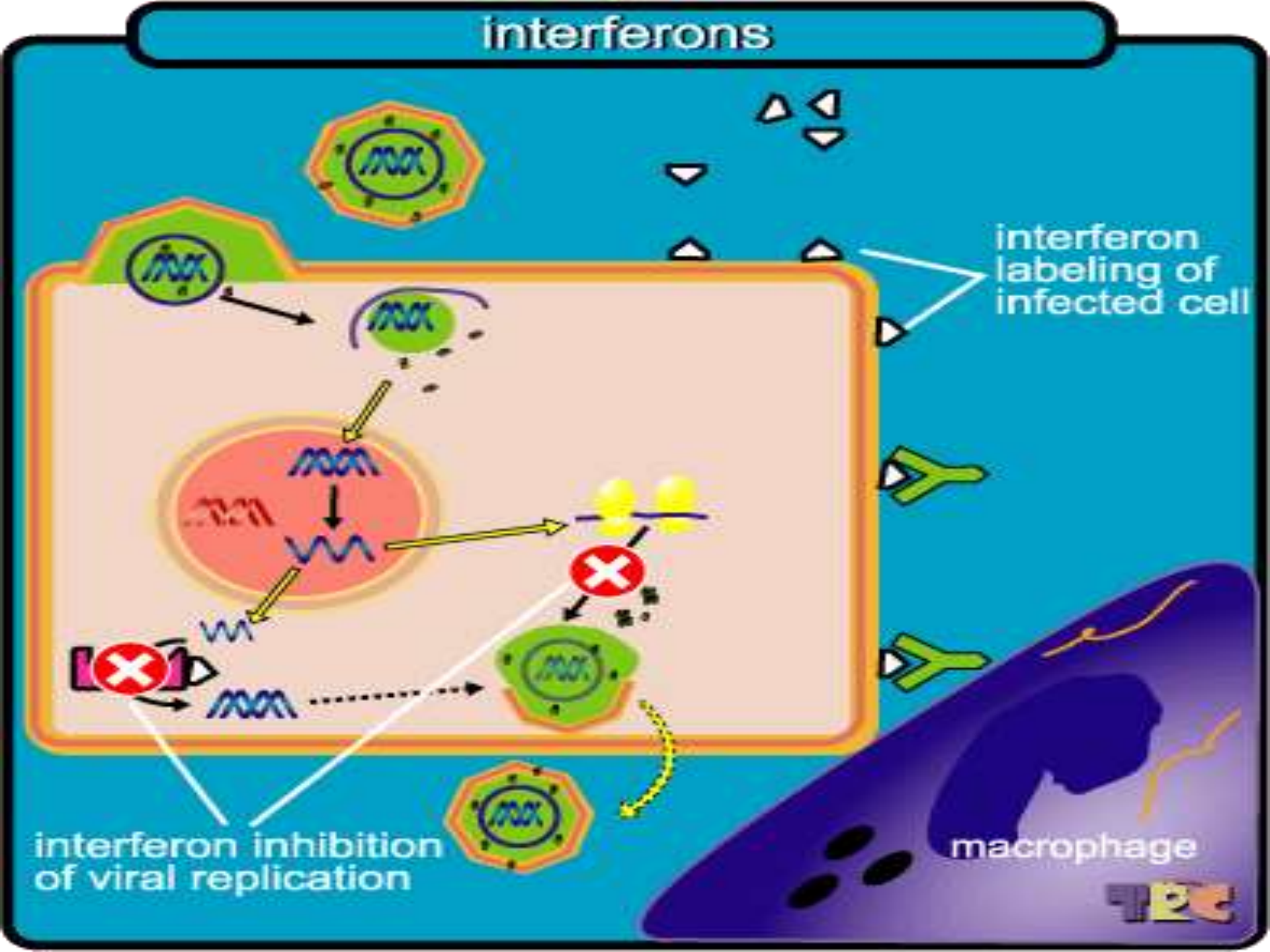

acute HBV infection
jaundice
symptoms
Anti-HBc IgG
Anti-HBe
Anti-HBs
Anti-HBc IgM
HBsAg
HBeAg
time


chronic HCV infection
symptoms
Anti-HCV
HCV-RNA
time


chronic HBV infection
symptoms
HBsAg
Anti-HBc IgG
Anti-HBe
HBeAg
time

Interferons

- Interferons (***IFN-a 2a*** and ***IFN-a 2b***) are compounds that are produced via recombinant DNA technologies in manipulated E. coli strains.
- **Interferons "mark" infected cells** by binding to receptors on the cell membrane of virus-infected cells ➔ initiate the synthesis of antiviral proteins that work via complex actions inside the cell to prevent viral replication and activate the immune system.
- The proportion of patients that will respond to interferon therapy seems to depend on which hepatitis infection is present (B, C, or D).
- Frequently patients will experience **fever, chills, headaches, and myalgias with the initiation of therapy**. ➔ paracetamol is often co-administered with interferon-a treatment.

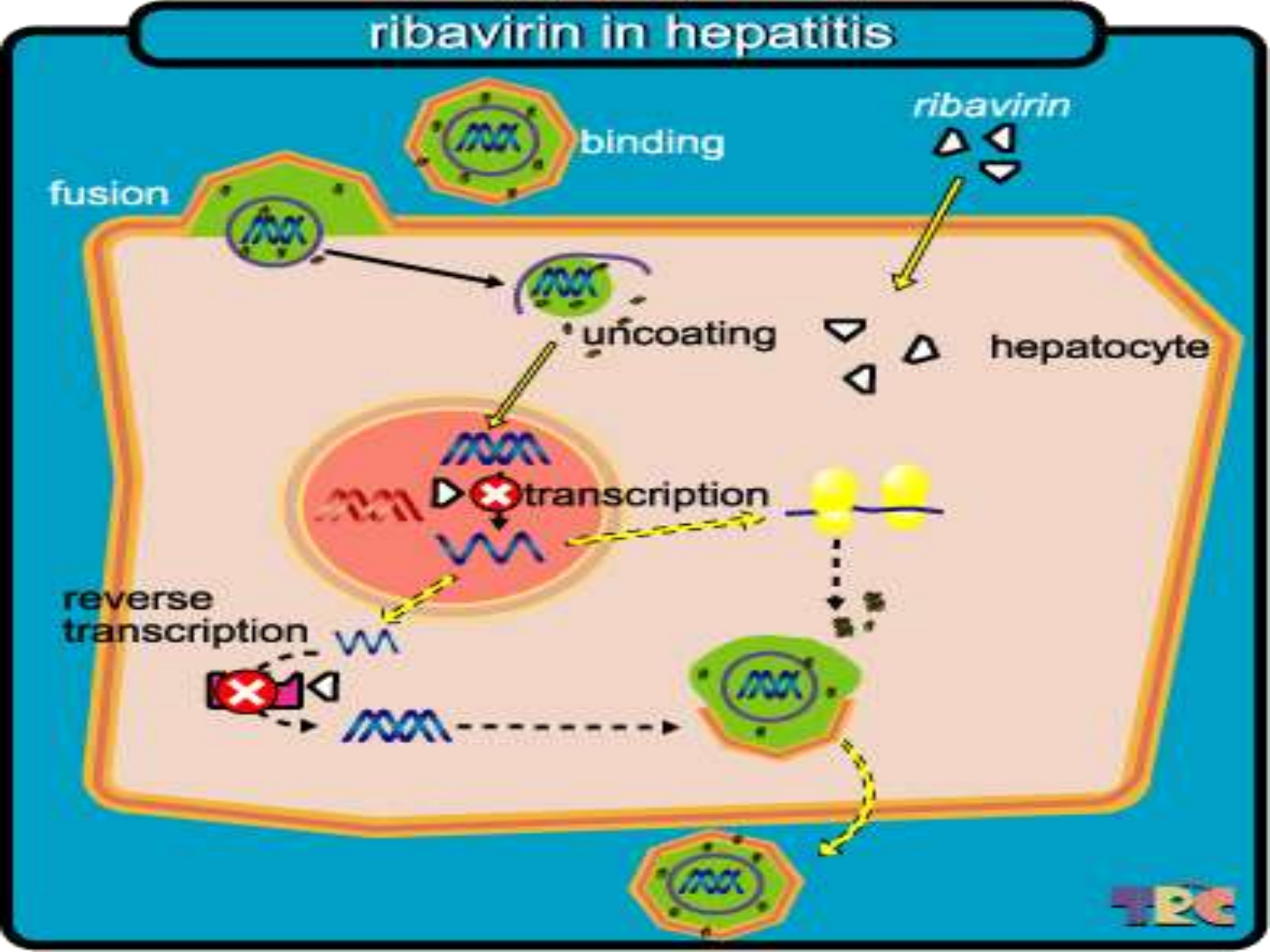

interferons
interferon
labeling of
infected cell
interferon inhibition
of viral replication
macrophage

Lamivudine for hepatitis B

- ***Lamivudine*** **is a drug with nucleoside reverse transcriptase inhibitor (NRTI)-like properties.**
- **It is an enantiomer of the NRTI drug *zalcitabine* (an anti-retroviral agent).**
- **1) competes for the reverse transcriptase activity with the normal substrate**
- **2) when incorporated in the viral DNA it terminates chain elongation.**
- **This effect has been shown clinically to have inhibitory activity against hepatitis B.**
- **The most frequently reported adverse effects are headache, fatigue, nausea, and insomnia. Dosages should be adjusted in patients with decreased renal function**

Ribavirin for hepatitis C

- ***Ribavirin*** is a small purine nucleoside analog that inhibits the replication of a variety of DNA and RNA viruses.
- the mechanism is not fully understood, it seems to inhibit nucleic acid syntheis, perhaps via inhibition of viral messanger RNA synthesis.
- chronic therapy is associated with dose related effects of anemia and bone marrow suppression
- Common side effects include headache, tiredness, muscle pain, fever and CNS disturbances such as depression, insomnia, and anxiety.


ribavirin in hepatitis
binding
ribavirin
fusion
uncoating
hepatocyte
transcription
reverse
transcription

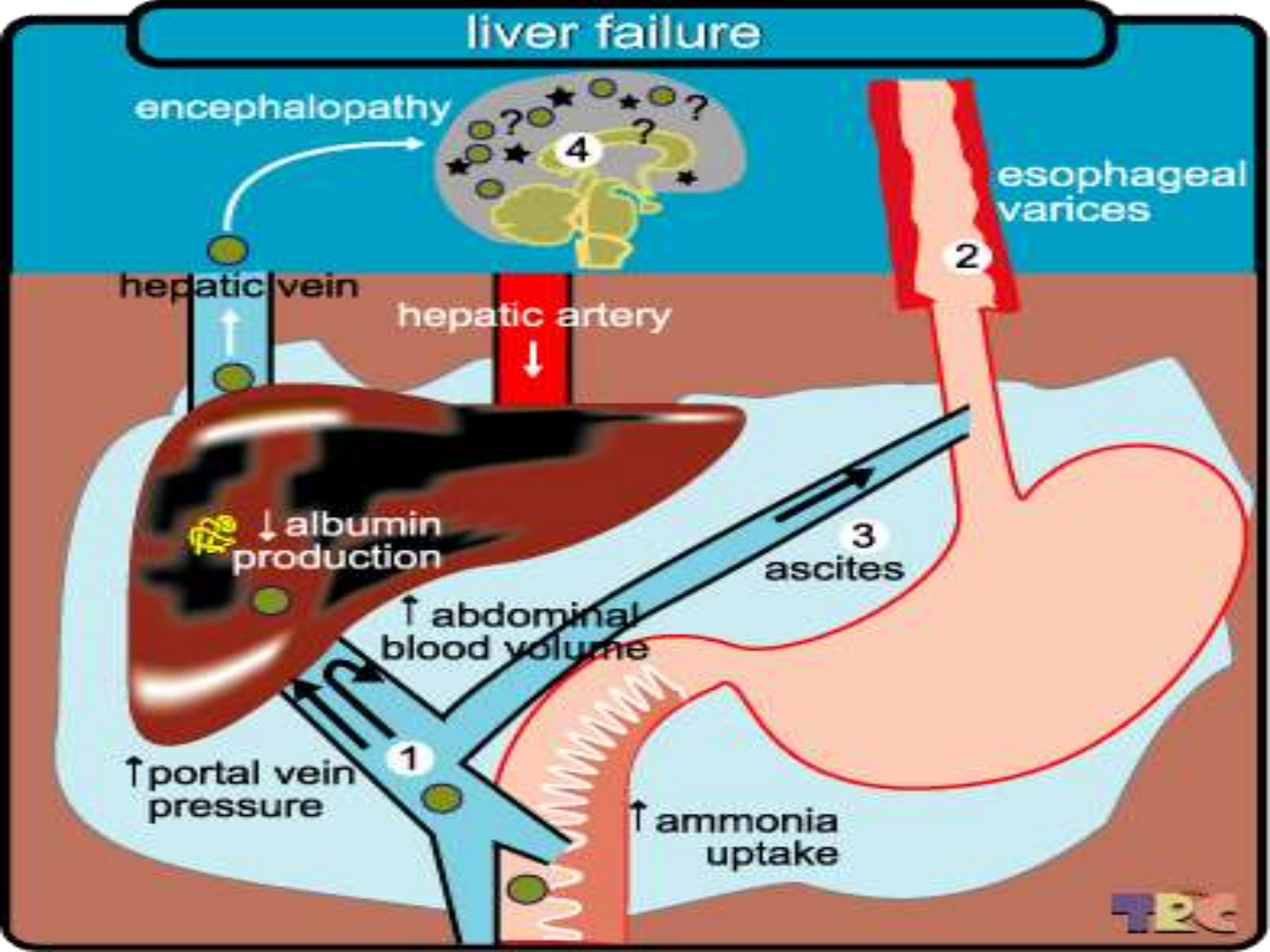
Liver Failure

Liver failure

- **The clinical presentation arise from many factors: hepatitis, alcoholic liver disease, etc.**
- **The end-result is cirrhosis and a fatty liver, which leads to intrahepatic obstruction and decreased liver function.**
- **Unfortunately there is no other treatment of liver failure than transplantation. Instead, most patients receive treatment for complications that arise as a result of liver disease.**

The complications of liver failure:

- **1. Increased pressure in the portal vein**
- **2. Oesophageal varices.**
- **3. Ascites ➔ portal hypertension, decrease in production of albumin in the liver, decreased clearance by the liver and hyperaldosteronism.**
- **4. Encephalopathy: high circulating levels of ammonia result from an increased ammonia uptake in the GI tract and decreased conversion of ammonia in the liver**


liver failure
encephalopathy
4
esophageal varices
2
hepatic vein
hepatic artery
↓albumin production
3
ascites
↑abdominal blood volume
1
↑portal vein pressure
↑ammonia uptake

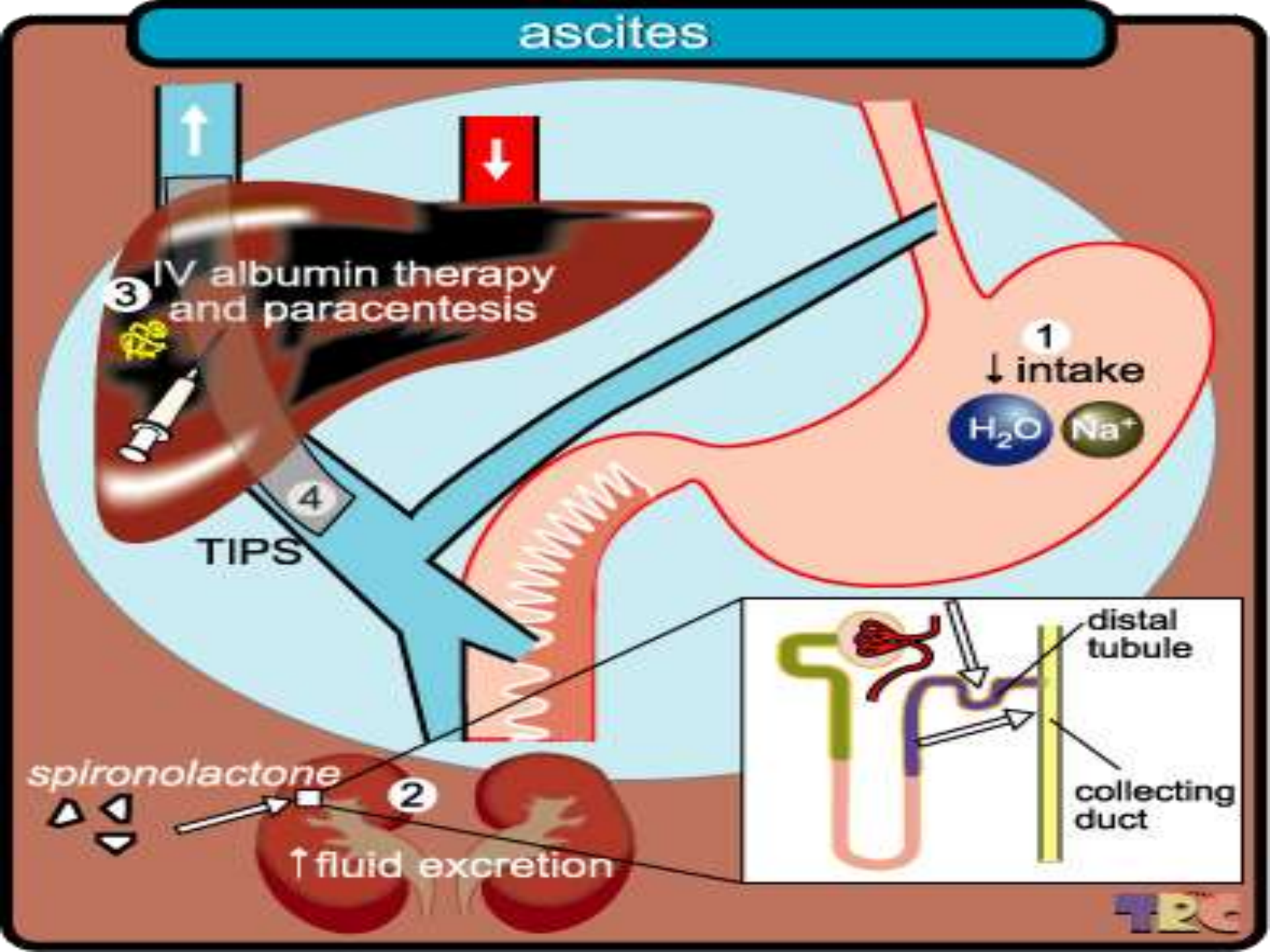
Ascites and treatment

Ascites is an abnormal accumulation of fluid in the abdominal cavity.

The treatment :

- **1. Decreasing water and salt intake**
- **2. Increasing the water and salt excretion by the kidneys with the diuretic *spironolactone***
- **3. Paracentesis and albumin therapy.**
- **4. Bypassing liver obstruction by placing a TIPS (transjugular intrahepatic portosystemic shunt), ➔ decreasing portal hypertension**

ascites

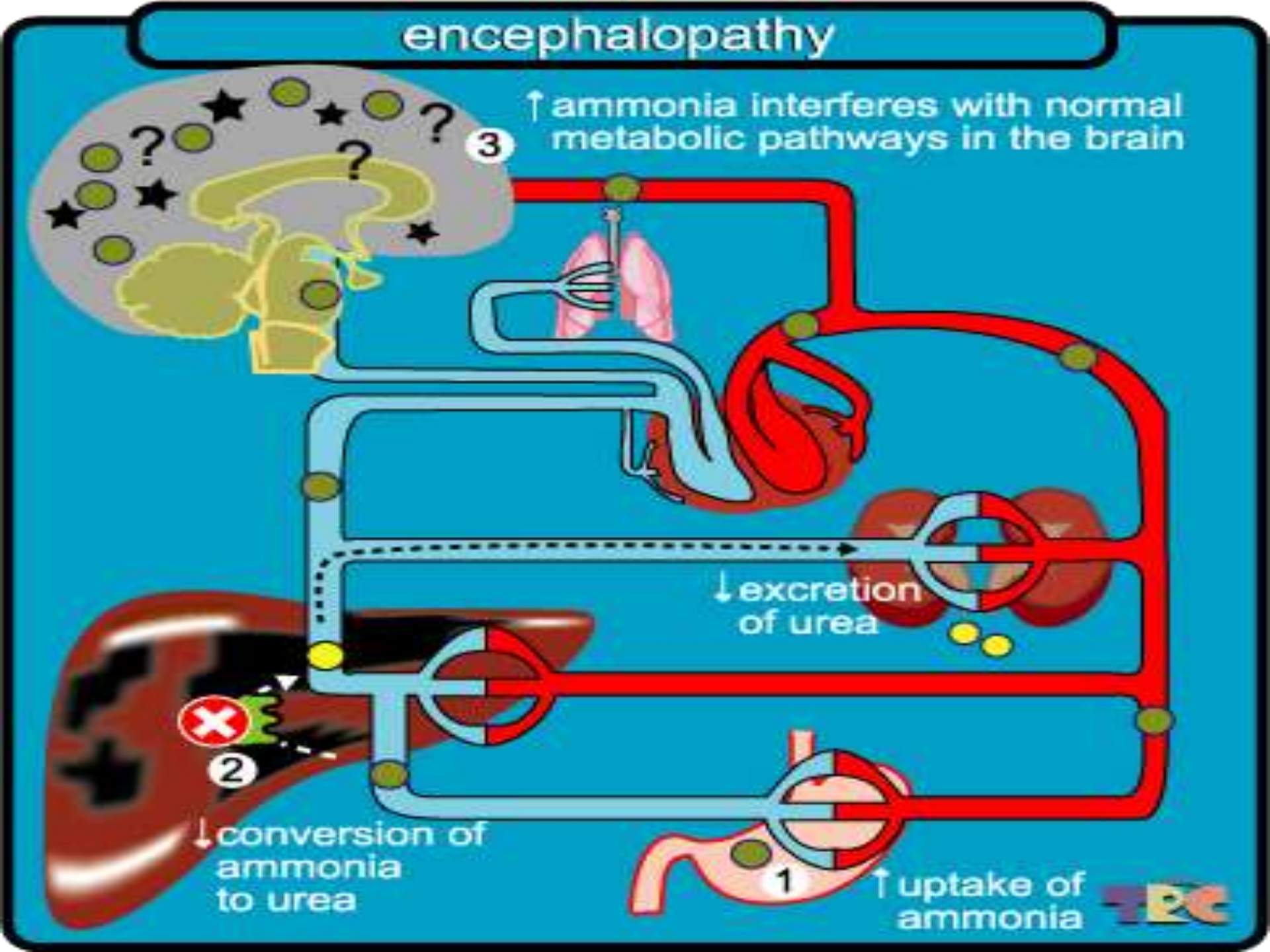

3
IV albumin therapy
and paracentesis
1
↓ intake
H_2O
Na^+
4
TIPS
distal
tubule
collecting
duct
spironolactone
2
↑ fluid excretion

Encephalopathy

- **metabolic disorder arising in the CNS in patients with liver failure.**
- **associated with increased circulating levels of ammonia (NH3)**
- **Patients present with altered mental status, asterixis with flapping tremor, confusion, disturbed day-night rhythm and decreased motor ability.**

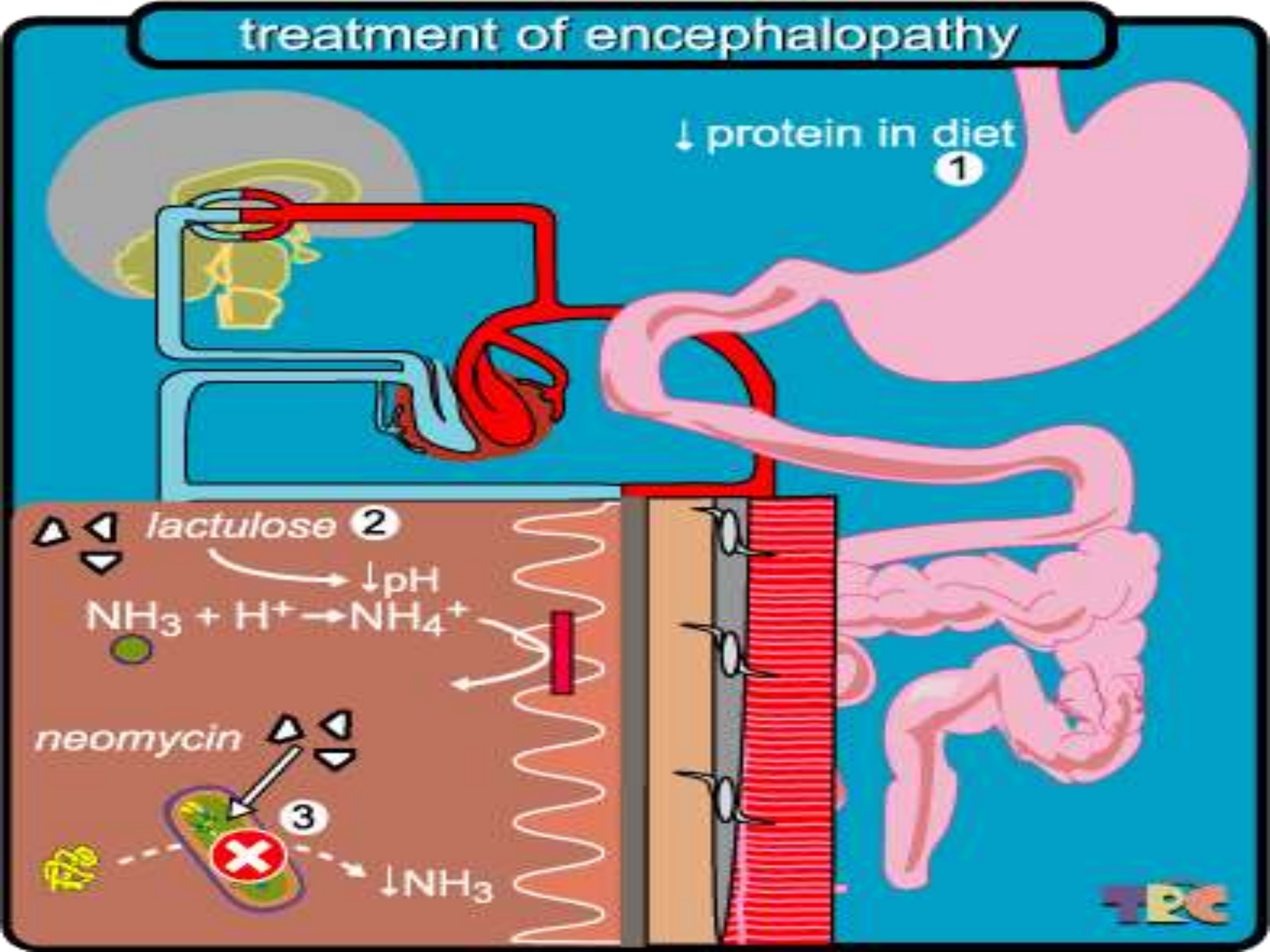
The cause of hepatic encephalopathy is not known but is probably multifactorial:

1. **Increased uptake of ammonia from the GI tract.**
   - **a. Increased dietary protein intake**
   - **b. Resulting from absorption of blood from bleeding oesophageal varices**
2. **Decreased conversion of ammonia into urea in the liver. Normally, ammonia is converted into urea by the liver and then excreted by the kidneys.**
3. **High circulating ammonia levels interfere in the CNS with normal metabolic pathways resulting in encephalopathy**


encephalopathy
↑ammonia interferes with normal metabolic pathways in the brain
3
↓excretion of urea
2
↓conversion of ammonia to urea
1
↑uptake of ammonia

Treatment of encephalopathy

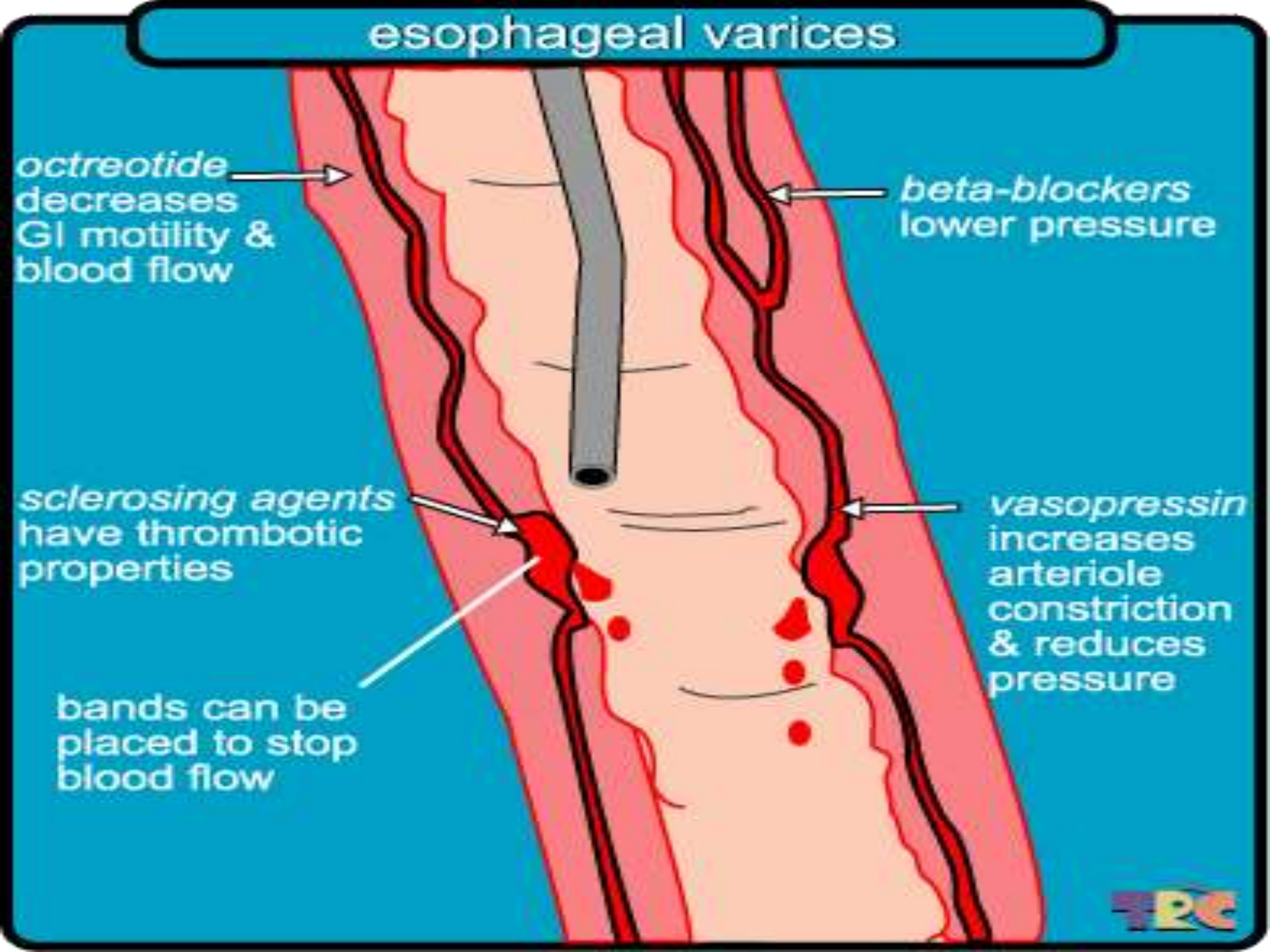
- Treatment is aimed at decreasing the intake and uptake of ammonia.
- Different opportunities:
  1. Lowering ammonia uptake by decreasing the protein intake via the diet. (less meat, cheese etc.)
  2. The laxative **lactulose** is broken down in the GI lumen to form lactic and acetic acids, thereby decreasing the pH in the colonic lumen. The resulting increased presence of hydrogen ions binds the ammonia and forms NH4+, which is not absorbed from the colonic lumen.
  $NH_3 + H^+ = NH_4^+$
  3. *Neomycin* is an **aminoglycoside** antibiotic, which is not broken down and barely absorbed by the GI tract. Neomycin will eradicate the bacteria in the gastric lumen that break down proteins to produce ammonia.


treatment of encephalopathy
↓ protein in diet
1
lactulose
2
↓pH
NH3 + H+ → NH4+
neomycin
3
↓NH3

Esophageal varices

- Therapy: 1. treatment of acute variceal bleeding, 2. prevention of recurrent bleeding.
- The acute treatment requires restoration of the systemic circulation (if impaired), use of drugs that reduce variceal pressure and flow (*vasopressin, somatostatin, octreotide*) and endoscopic sclerotherapy.
- Preventing recurrent bleeding can be obtained by repeated endoscopic sclerotherapy or band ligation and/or the treatment with *beta-blockers* that will reduce portal vein pressure.

esophageal varices

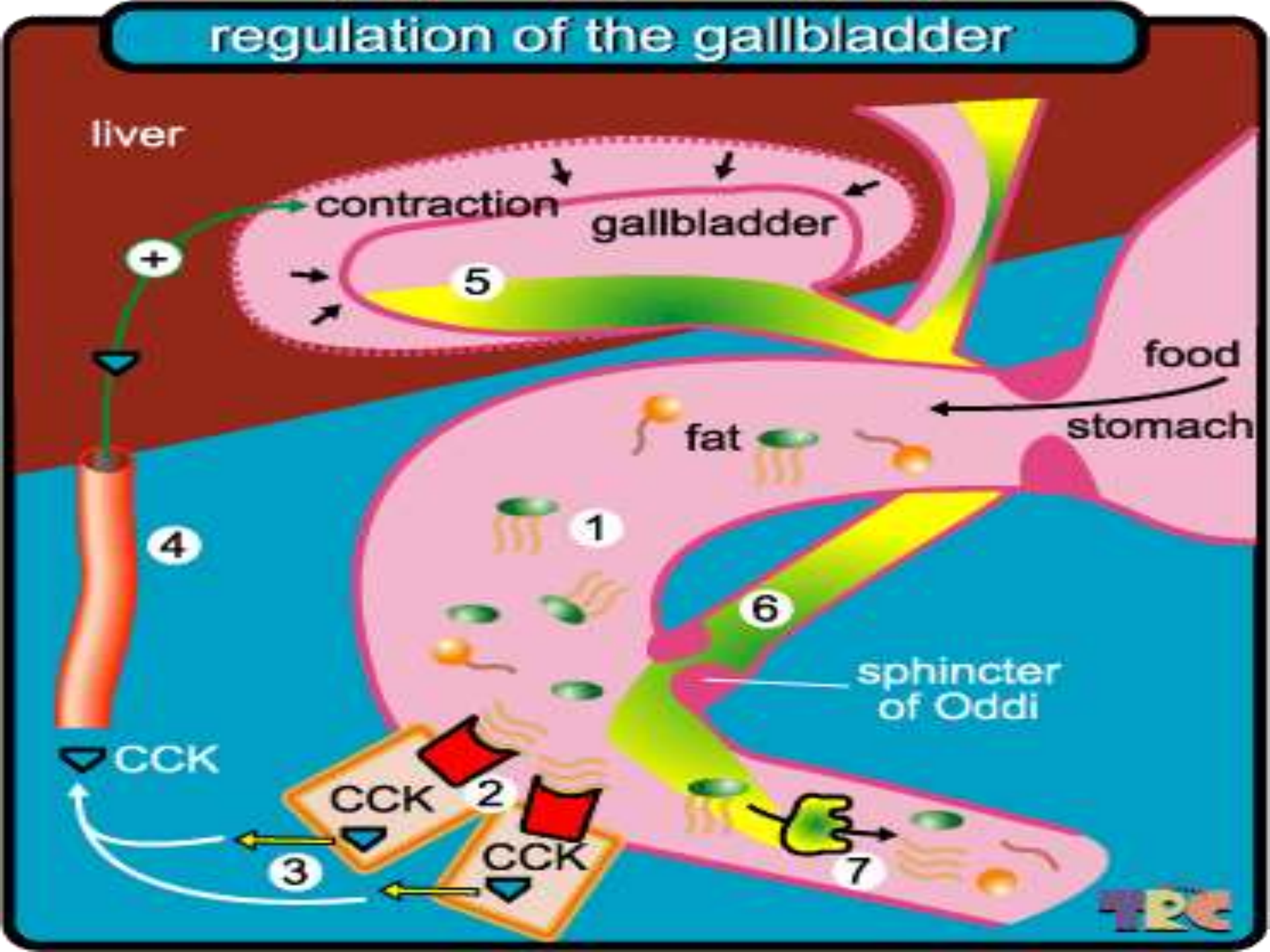


Gallbladder

2 major functions:

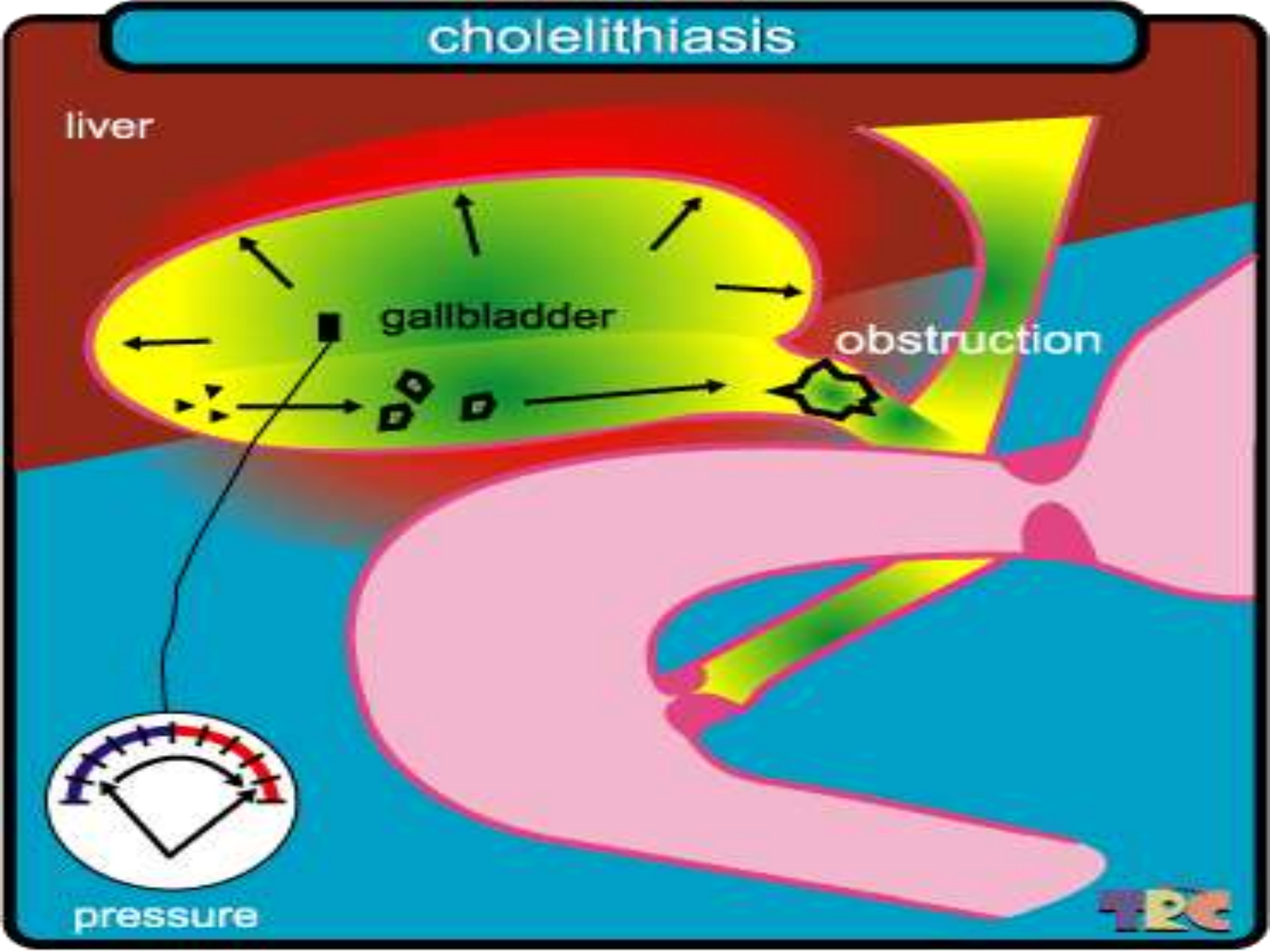
- **bile storage**
- **bile modification.**

- **The bile produced by the liver is concentrated and stored in the bladder.**
- **Without food in the stomach the sphincter of Oddi is closed and the bile remains in the gallbladder.**
- **Upon arrival of food (containing lipids) in the duodenum (1), the cells in the wall of the duodenum release cholecystokinin (CCK) (2,3). Via the circulation (4) CCK reaches the gallbladder and stimulates contraction of the bladder (5). CCK also relaxes the sphincter of Oddi (6), which results in secretion of bile in the duodenum.**
- **Bile salts break fat droplets; this is called emulsification (7)**


regulation of the gallbladder
liver
contraction
gallbladder
+
5
food
stomach
fat
1
4
6
sphincter
of Oddi
CCK
CCK
2
CCK
3
7

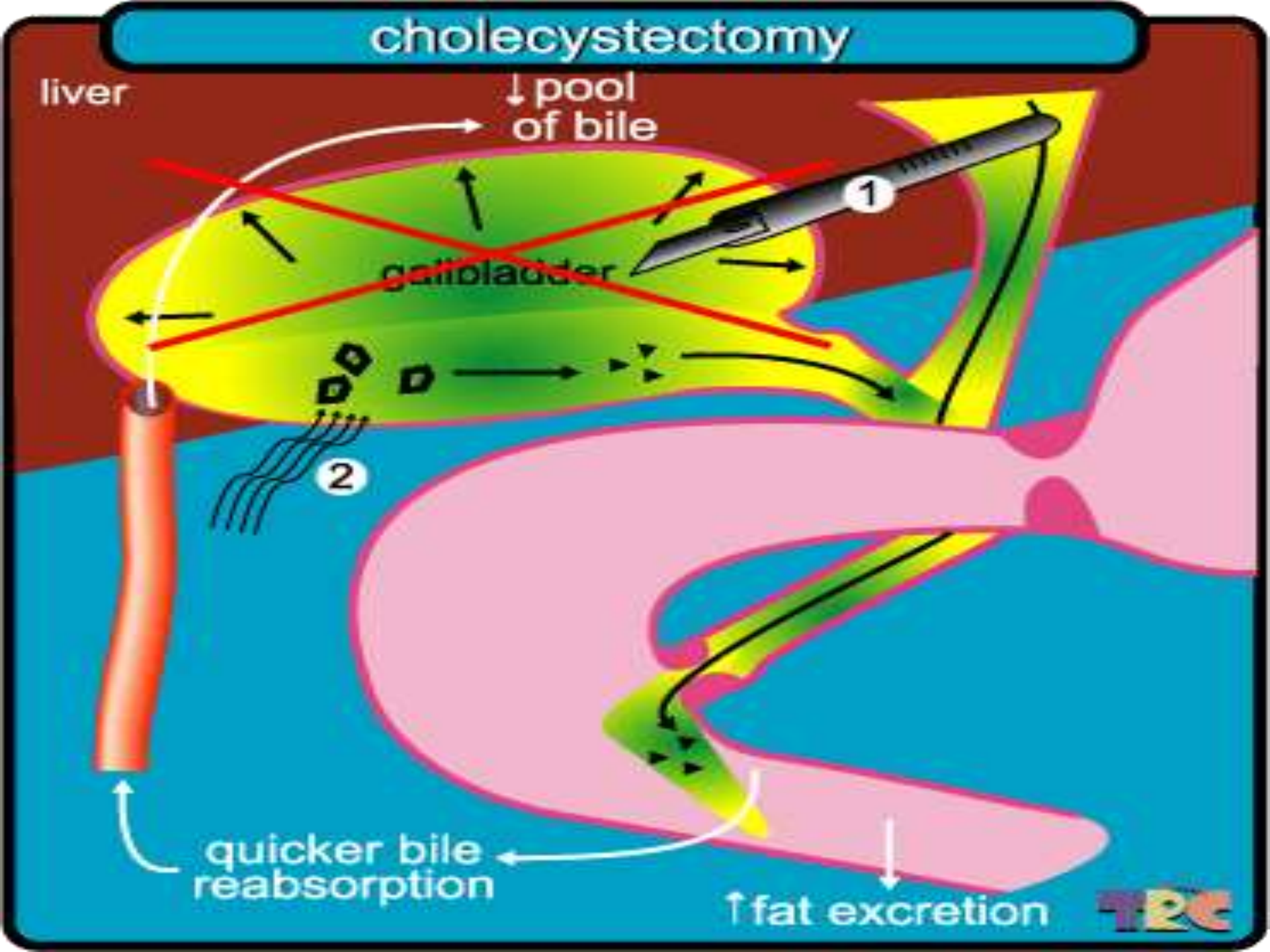
Cholelithiasis

- When bile becomes too concentrated, crystals can be formed.
- Bile salts and phospholipids keep cholesterol in a micelle solution.
- shortage of bile salts or a surplus of cholesterol, gall stones can be formed.
- In cholelithiasis the crystals/stones are small enough to pass through the bile duct.
- If the crystals and stones become too large, they can damage the wall of the gallbladder and block the bile duct.


cholelithiasis
liver
gallbladder
obstruction
pressure

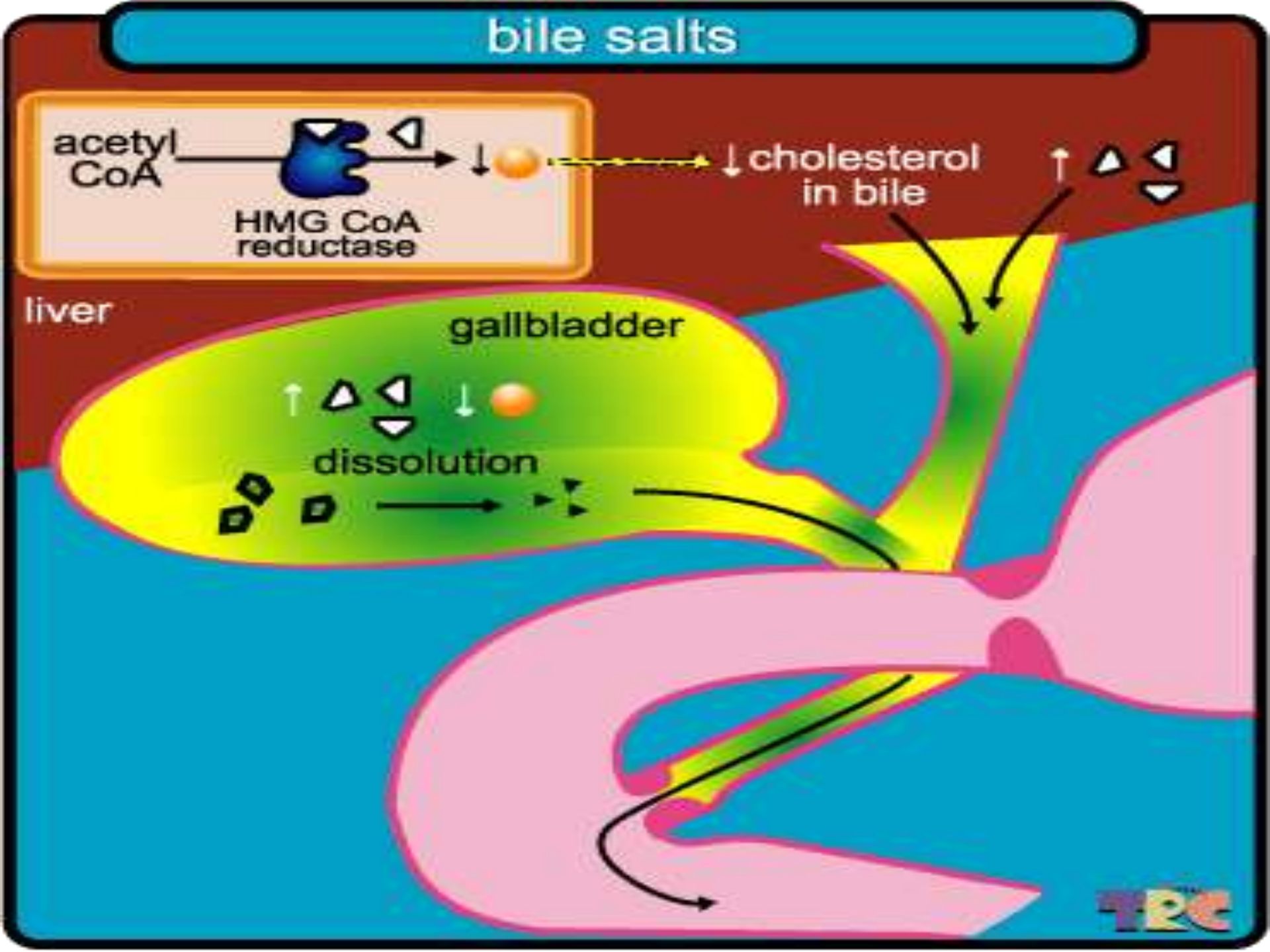
Cholecystectomy

- **Surgical treatment is the best option in case of severe damage or inflammation of the gallbladder by gallstones.**
- **Surgical removal of the gallbladder (1, cholecystectomy by laparoscopy) has no severe impact on the digestive process. Bile production continues, however, it is no longer concentrated and its release in the duodenum is not closely tied to food arrival in the stomach. The circulation of bile salts is quicker and more fat is excreted via the digestive tract.**
- **Another non-pharmacological option to treat gallstones is the non-invasive method lithotripsy (2). In this case the gallstones are shattered by focused sound waves.**


cholecystectomy
liver
↓pool
of bile
gallbladder
1
2
quicker bile
reabsorption
↑fat excretion

Bile salts

- **In people with a functioning gallbladder, bile salts (which act by desaturating cholesterol in the bile) taken by mouth may dissolve gallstones containing cholesterol. However, the process may take 2 years or longer, and stones may return after the therapy is ended**
- **Medical dissolution, using *urodeoxycholic acid* is successful in 40% of cases. This bile salt is used for the dissolution of gall stones and for various liver disorders. It suppresses hepatic cholesterol synthesis and secretion.**
- **For the treatment of liver disorders other properties of urodeoxycholic acid are useful: it reduces the toxic bile acids in bile, and it has immunomodulating effects on the hepatocellular membranes.**


bile salts
acetyl CoA
HMG CoA reductase
cholesterol in bile
liver
gallbladder
dissolution