بسم الله الرحمن الرحيم

Pharmacology

﴿ وَقُل رَّبِّ أَدْخِلْنِي مُدْخَلَ صِدْقٍ وَأَخْرِجْنِي مُخْرَجَ صِدْقٍ وَاجْعَل لِّي مِن لَّدُنكَ سُلْطَانًا نَّصِيرًا ﴾

ربنا آتنا من لدنك رحمة وهيئ لنا من أمرنا رشدًا

FINAL | Lecture 9

Antimalarial Drugs

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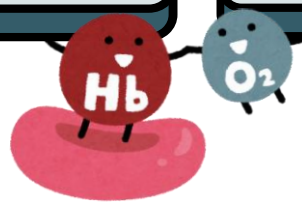
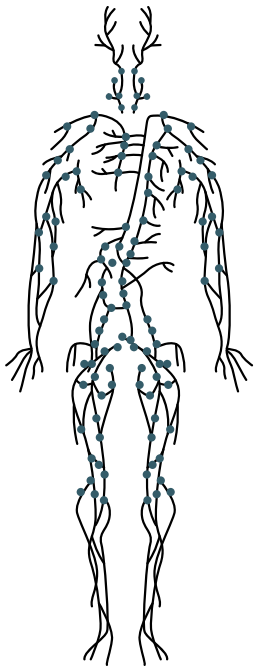
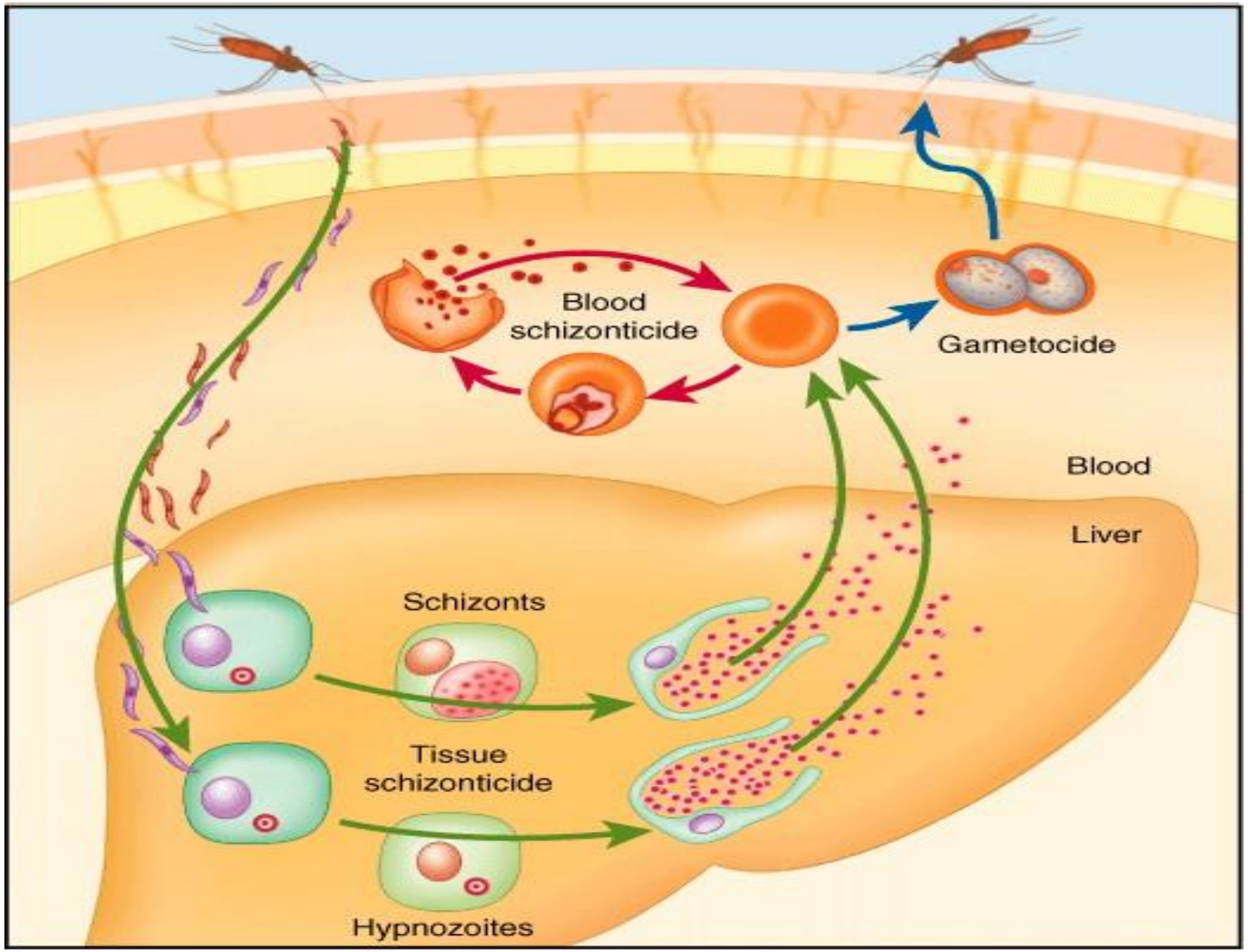




Malaria — Read this slide on your own

- It is a **mosquito-born** disease causing about 3 million deaths a year world-wide. Many are children under the age of 5.
- The parasite is transmitted by bites from the **female** anopheles mosquito.
- Currently, there are over 300 million new infections annually.
- The disease is caused by several species of the Plasmodium parasite. The two most important are **P. falciparum** and **P. vivax**.
- **P. falciparum** causes “**malignant** tertian malaria”. “Malignant” because it is the most severe form of malaria and can be fatal. “Tertian” because it is said to produce fever every third day.
- **P. vivax** produces “**benign** tertian malaria”. “Benign” because it is less severe than falciparum and is seldom fatal.



This parasite has **three developmental phases** inside the human body:

1. **Tissue schizonts** *(in the liver)*
2. **Blood schizonts** *(in red blood cells)*
3. **Gametocytes** *(sexual forms ready for transmission to another mosquito)*

Some species, such as **P. vivax** and **P. ovale**, can form **hypnozoites**, which remain dormant in the liver and may **reactivate after a period of latency**.

Life Cycle

- Two Interdependent Life Cycles:
  - **Sexual** cycle: in the **mosquito**
  - **Asexual** cycle: in the **human**
- Knowledge of the life cycles is essential for understanding antimalarial drug treatment.
- Drugs are **only** effective during the **asexual** cycle.
- The **Asexual** cycle has **two phases**
  - **Exo**erythrocytic phase: occurs "**outside**" the erythrocyte
  - Erythrocytic phase: occurs "**inside**" the erythrocyte

Erythrocytes = RBCs

Anti-Malarial Agents

- Drugs that eliminate developing or dormant **liver** forms are called **tissue schizonticides**;
- Those that act on **erythrocytic** parasites are **blood schizonticides**;
- Those that kill **sexual** stages and prevent transmission to mosquitoes are **gametocides**.
- **No single available agent** can reliably achieve a radical cure, i.e., eliminate **both** hepatic and erythrocytic stages.
- It is important to understand all these drug types because **no single agent can target every developmental form simultaneously**.

Chloroquine — Overview

- It is an **old** drug.
- It is a potent **blood schizonticidal** drug which is effective against **all four types** of clinically important plasmodium species.
- Its mechanism of action is complex and not fully understood. (Two proposed mechanisms; the second is more likely.)
  - It accumulates in parasite lysosomes. Chloroquine **inhibits digestion of hemoglobin** by the parasite and thus helps **reduce its supply of amino acids**.
  - It also inhibits heme polymerase – the enzyme that polymerizes toxic **free heme** to the innocuous **hemozoin**.
    - Free heme is toxic to the parasite.

Underlined word is hyperlinked.

Chloroquine — Clinical Uses & Resistance

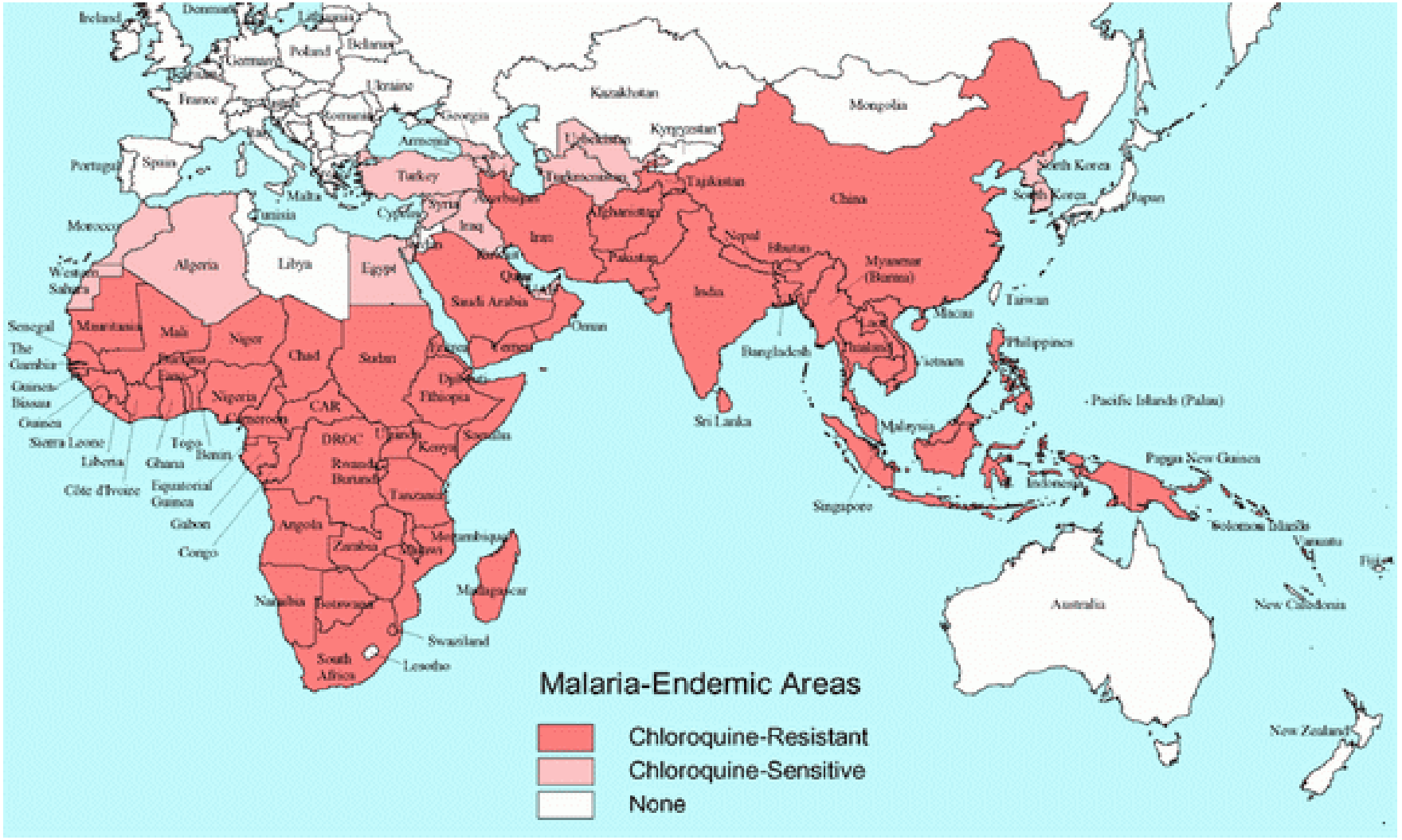
- **Drug of choice** for erythrocytic ***P. falciparum*** malaria, except in resistant strains.
- Chloroquine is **less effective** against ***P. vivax*** malaria.
- It is also effective in the treatment of **extraintestinal amebiasis** *(irrelevant in HLS).*
- It is used for the treatment of malaria in pregnancy (safe, not teratogenic).
- Used in **malaria prophylaxis** (in endemic, non-resistant areas)
- **Resistance** is a major issue.

Chloroquine — Adverse Effects & Contraindications

- At **high doses** toxic effects occur:
  - Gastrointestinal upset, pruritus, headaches, and visual disturbances (an ophthalmological examination should be routinely performed).
- Parenteral administration: may cause hypotension, cardiac arrhythmias and convulsions.
- Contraindications: **psoriasis** or **porphyria**

Underlined word is hyperlinked.

Choloroquine resistance is a world-wide problem; take a look at all these red countries.



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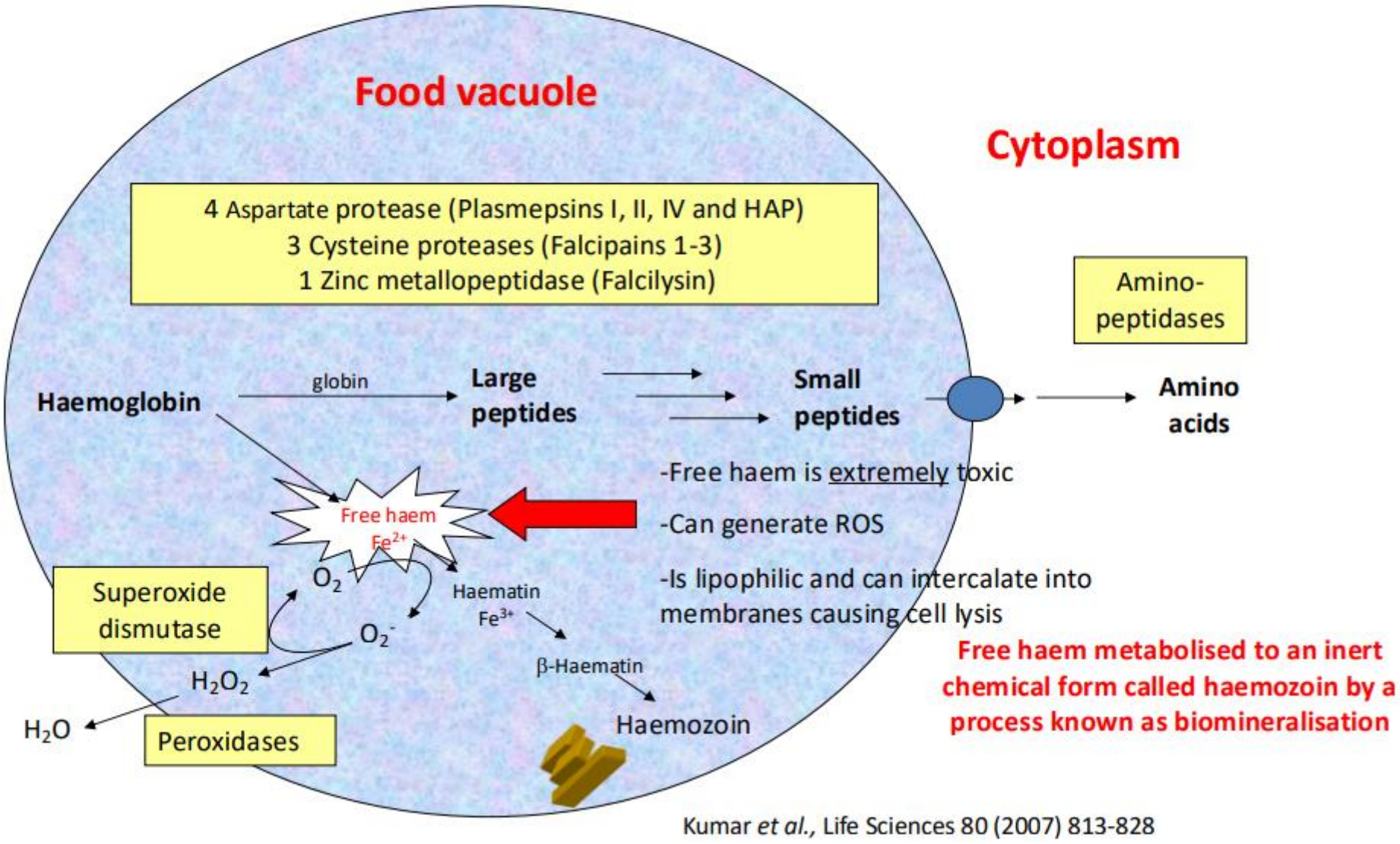
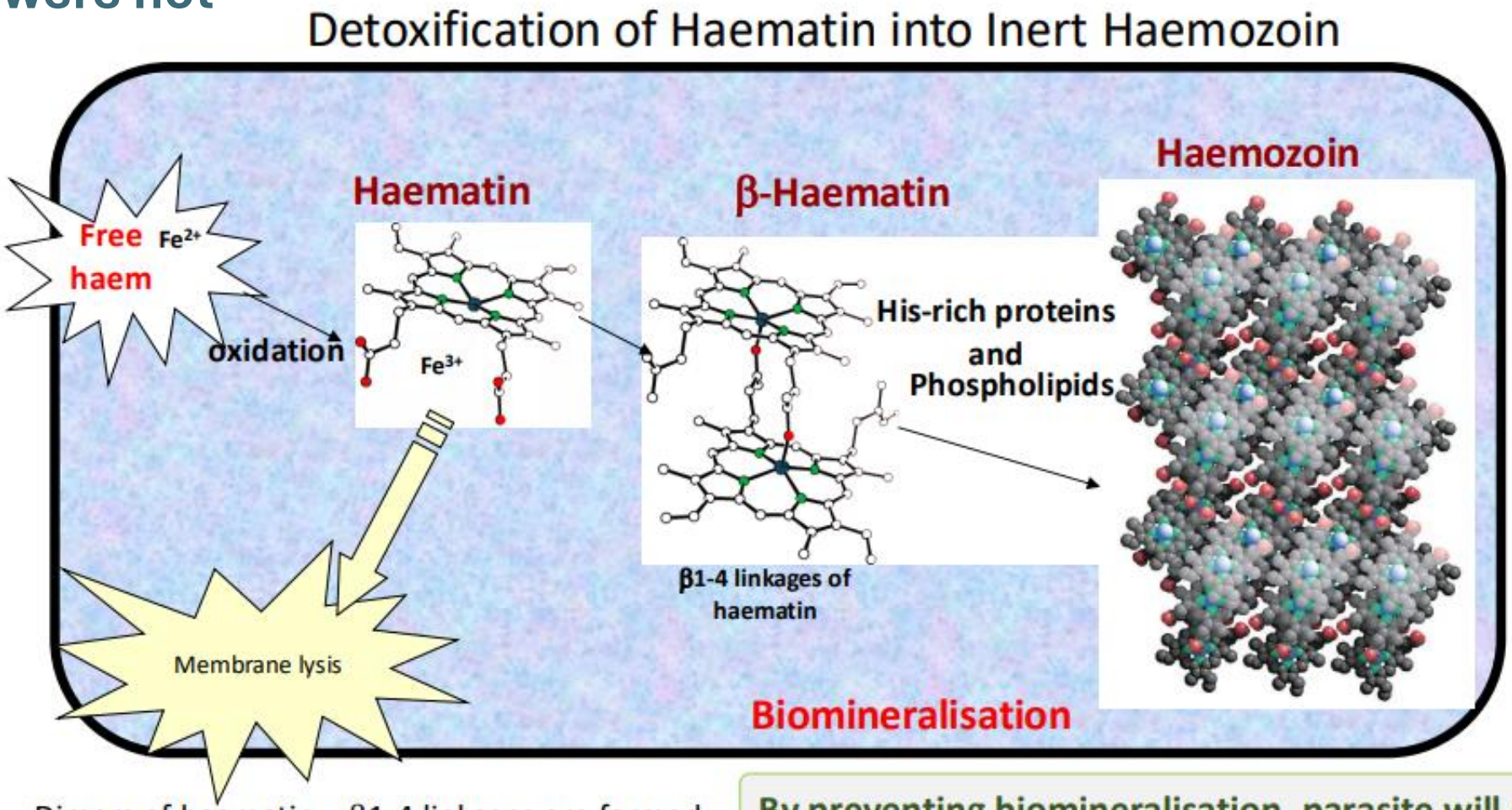


Kumar *et al.*, Life Sciences 80 (2007) 813-828

Details of the figure were not explained.

Must know: The parasite is **killed** when the **formation of hemozoin** (also called **biomineralization of heme**) is **inhibited.**



Dimers of haematin – β1-4 linkages are formed

By preventing biomineralisation, parasite will die.

Dimers then begin to crystallise in a process known as biomineralisation to generate haemozoin

Process not fully understood but is thought to be promoted by several factors including – the low pH of the food vacuole, association of haematin with histidine-rich proteins and phospholipids

Ultimately haemozoin crystals are formed which are chemically inert and a safe storage mechanism for the parasite

Quinine and Quinidine — Mechanism and Use

- Is a rapid-acting, highly effective **blood schizonticide** against the four species of human malaria parasites. They are **older** than chloroquine.
- The drug is **gametocidal** against ***P. vivax*** and ***P. ovale*** but not ***P. falciparum***. It is **not** active against liver stage parasites.
- Quinine and quinidine remain **first-line** therapies for falciparum malaria—especially **severe** disease—although toxicity may complicate therapy.
- Quinine is **more** toxic and **less** effective than chloroquine against malarial parasites susceptible to both drugs.
- Used as **substitute** for chloroquine in **severe & resistant** malaria, although they are **more** toxic.

Quinine and Quinidine — Toxicity and Adverse Effects

- **Therapeutic** dosages of quinine and quinidine commonly cause tinnitus, headache, nausea, dizziness, flushing, and visual disturbances, a collection of symptoms termed **cinchonism**.
- Therapeutic doses may cause **hypoglycaemia** through stimulation of insulin release (especially in **pregnant** patients).
- Quinine can **raise** plasma levels of warfarin and digoxin; by inhibiting their metabolism by **cytochrome P450** enzymes.

❖ Note: Quinine, quinidine, and chloroquine **do not target tissue schizonts**.

❖ Quinidine is a **myelosuppressive** drug.

Proguanil (Chloroguanide)

- **slow-acting erythrocytic schizonticide**, also inhibits the preerythrocytic stage of ***P. falciparum***.
- Mechanism of action:
  - It is cyclized in the body to cycloguanil which inhibits plasmodial **DHFRase** in preference to the mammalian enzyme.
- Current use of proguanil is **restricted** to prophylaxis of malaria **in combination** with chloroquine in areas of low-level chloroquine resistance among P. falciparum.
- **Safe** during pregnancy.

DHFRase: Dihydrofolate Reductase

Mefloquine

- Mefloquine is effective therapy for many chloroquine-resistant strains of *P. falciparum* and against other species. Thus, it is used **instead** of chloroquine in case of resistance.
- Although **toxicity** is a concern, **mefloquine** is one of the recommended chemoprophylactic drugs for use in most malaria-endemic regions with chloroquine-resistant strains.
- Its mechanism of action appears to be associated with **inhibition** of the haem polymerase.
- Adverse effects: **Weekly** dosing with mefloquine for chemoprophylaxis may cause nausea, vomiting, dizziness, sleep and behavioral disturbances, epigastric pain, diarrhea, abdominal pain, headache, rash, and dizziness.
  - Unlike other drugs, mefloquine does **not** cause visual disturbances.
- Neuropsychiatric toxicities??? (it is questionable)
- It is contraindicated in cases of neural and cardiac disturbances, such as in a patient with a history of epilepsy, psychiatric disorders, arrhythmia, cardiac conduction defects.

Primaquine — Mechanism and Use

- Destroys primary and latent **hepatic, tissue schizonts,** stages (*hypnozoites*) of ***P. vivax*** and *P.* ***ovale*****.**
- Thus, has great clinical value for preventing relapses of *P. vivax* or *P. ovale* malaria after latency (standard therapy).
- Exerts a marked **gametocidal** effect against all **four** species of *Plasmodium* that infect humans, especially ***P. falciparum***.
- Because of its lack of activity against the **erythrocytic schizonts**, primaquine is often used in **conjunction** with a **blood schizonticide**.

Primaquine — Toxicity and Adverse Effects

- **Due to the interaction of the drug with cytochrome P450 in both humans and parasites, notice the following:**
  - Induced **hemolytic anemia** in patients with genetically **low** levels of **glucose-6-phosphate dehydrogenase (G6PD)**.
  - Patients should be tested for G6PD deficiency before primaquine is prescribed.
- Causes nausea, epigastric pain, abdominal cramps, and headache; these symptoms are more common with **higher** dosages and when the drug is taken on an **empty** stomach.
- Primaquine should be avoided in patients with a history of **granulocytopenia** or **methemoglobinemia**, or in those receiving potentially **myelosuppressive** drugs (e.g., quinidine).
- **Avoided** in pregnancy & G6PD deficiency.

Artemisinin Derivatives

- They are new drugs, plant-derived and include: Artemether / Arteether / **Artesunate** (most commonly used)
- It is a potent and rapidly acting **blood schizonticide** and has a peroxide configuration — responsible for its action.
- Combination therapy. Used **only in combination.**
- Duration of action: **short**, with a possibility of **recurrence.**
- **Recrudescence** (recurrence) rate is high when used alone in short courses.
- **The mechanism of action of artemisinin** depends on its ability to **induce peroxidation**, leading to **free radical formation**, and to **form adducts** that contribute to cellular damage.
- The term “adducts” refers to compounds formed when reactive species bind to cellular components (like proteins or DNA). Artemisinin can form adducts with biomolecules, contributing further to parasite damage and disrupting its vital functions.

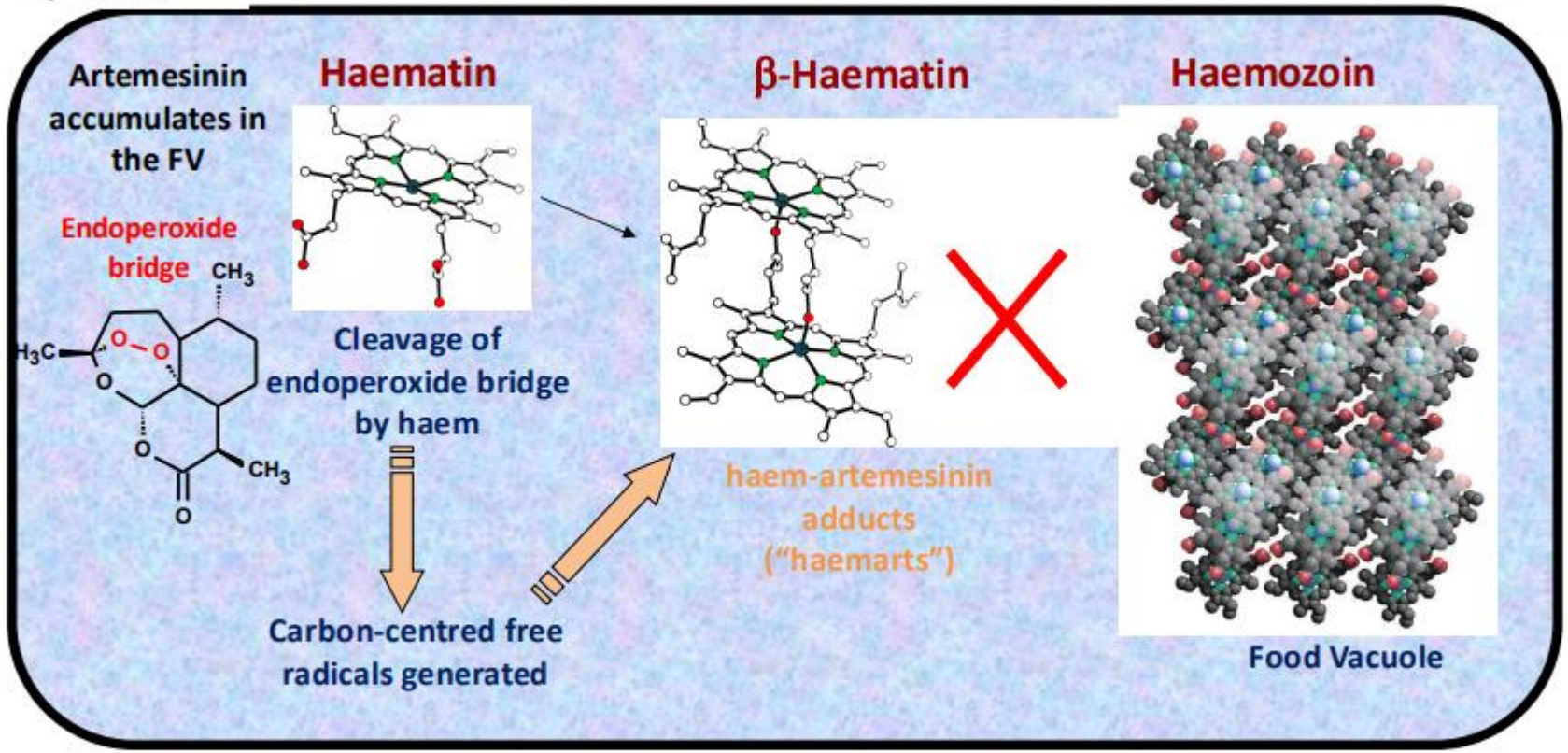
Artemisinin Combination Therapy (ACT)
Current frontline therapy

- Artemisinins reduce parasite burden **rapidly**.
- Used in combination with other drugs to prevent the emergence of resistance to the partner drug (ACT).

Artemisia annua – sweet wormwood

Youyou Tu
Nobel Prize – Medicine 2015

Haem and Mode of Action of Artemisinins



Possible targets of artemisinin free radicals:
TCTP (translationally controlled tumour protein homolog)
SERCA (sarco/endoplasmic reticulum Ca^{2+} ATPase)
Cysteine proteases

- Relevant details are written down (in congenial).

- Artemisinin **accumulates in the parasite's food vacuole (FV).**
- It could form endoperoxide bridge. Do your own research
- Artemisinin forms **heme-artemisinin adducts** that **inhibit the polymerization of heme into hemozoin**, ultimately leading to **parasite death**.

Pyrimethamine–sulphonamide & Antibiotics

- Historically, **antibiotics** were also used to treat malaria. They may still be used nowadays.
- These drugs are **NOT** required.
- **Pyrimethamine** inhibits *plasmodial dihydrofolate reductase* at much lower concentrations than those that inhibit the mammalian enzyme. It is often combined with a sulfonamide (e.g., sulfadoxine).
- Tetracycline and doxycycline are active against erythrocytic schizonts of all human malaria parasites. They are **not active against liver stages.**
- Doxycycline is used in the treatment of *falciparum* malaria in conjunction with quinine, allowing a shorter and better-tolerated course of that drug.

This slide is **NOT** required.

~~Drugs > Treatment of Malaria > Chemoprophylaxis & Treatment >~~

Drug	Use2	Adult Dosage3
Chloroquine	Areas without resistant P falciparum	500 mg weekly
Atovaquone - proguanil (Malarone)	Areas with chloroquine-resistant P falciparum	1 tablet (250 mg atovaquone/100 mg proguanil) daily
Mefloquine	Areas with chloroquine-resistant P falciparum	250 mg weekly
Doxycycline	Areas with multidrug-resistant P falciparum	100 mg daily
Primaquine4	Terminal prophylaxis of P vivax and P ovale infections; alternative for primary prevention	52.6 mg (30 mg base) daily for 14 days after travel; for primary prevention 52.6 mg (30 mg base) daily

PHARMACOLOGY QUIZ

LECTURE 9

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			