Malaria

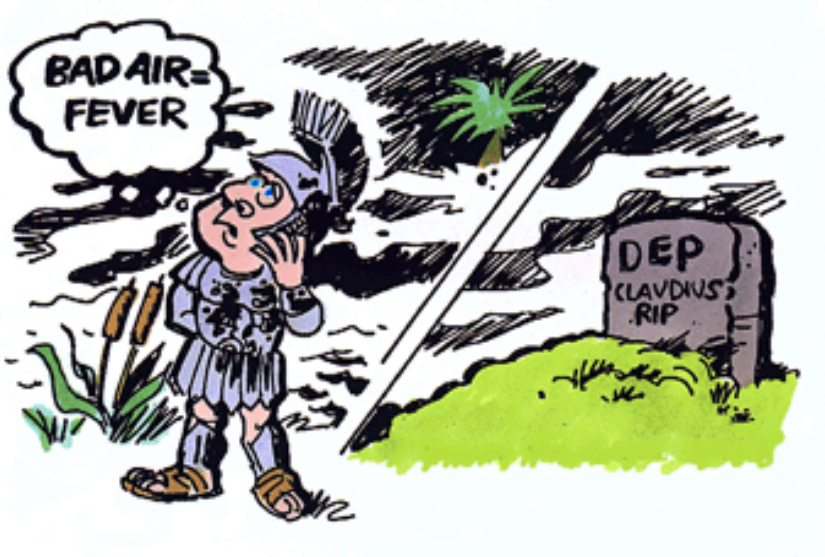
Jarmila Kliescikova, MD, Department of Tropical Medicine, 1st Faculty of Medicine, UK

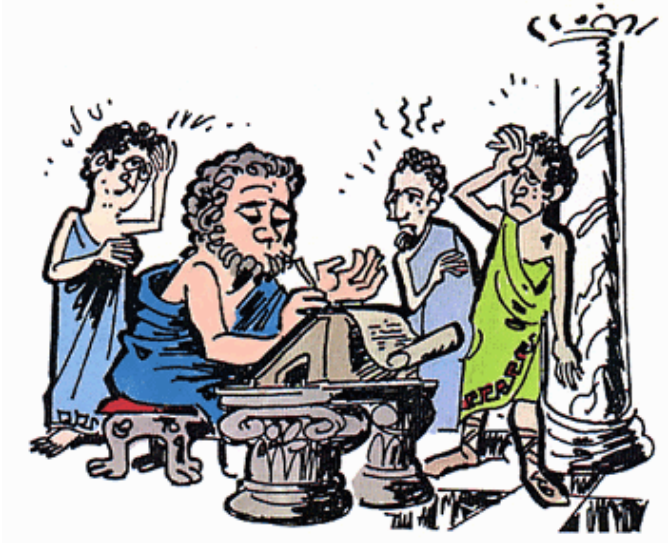
300-500 mil cases each year

(1-3 millions of deaths – children in subsahar Africa)

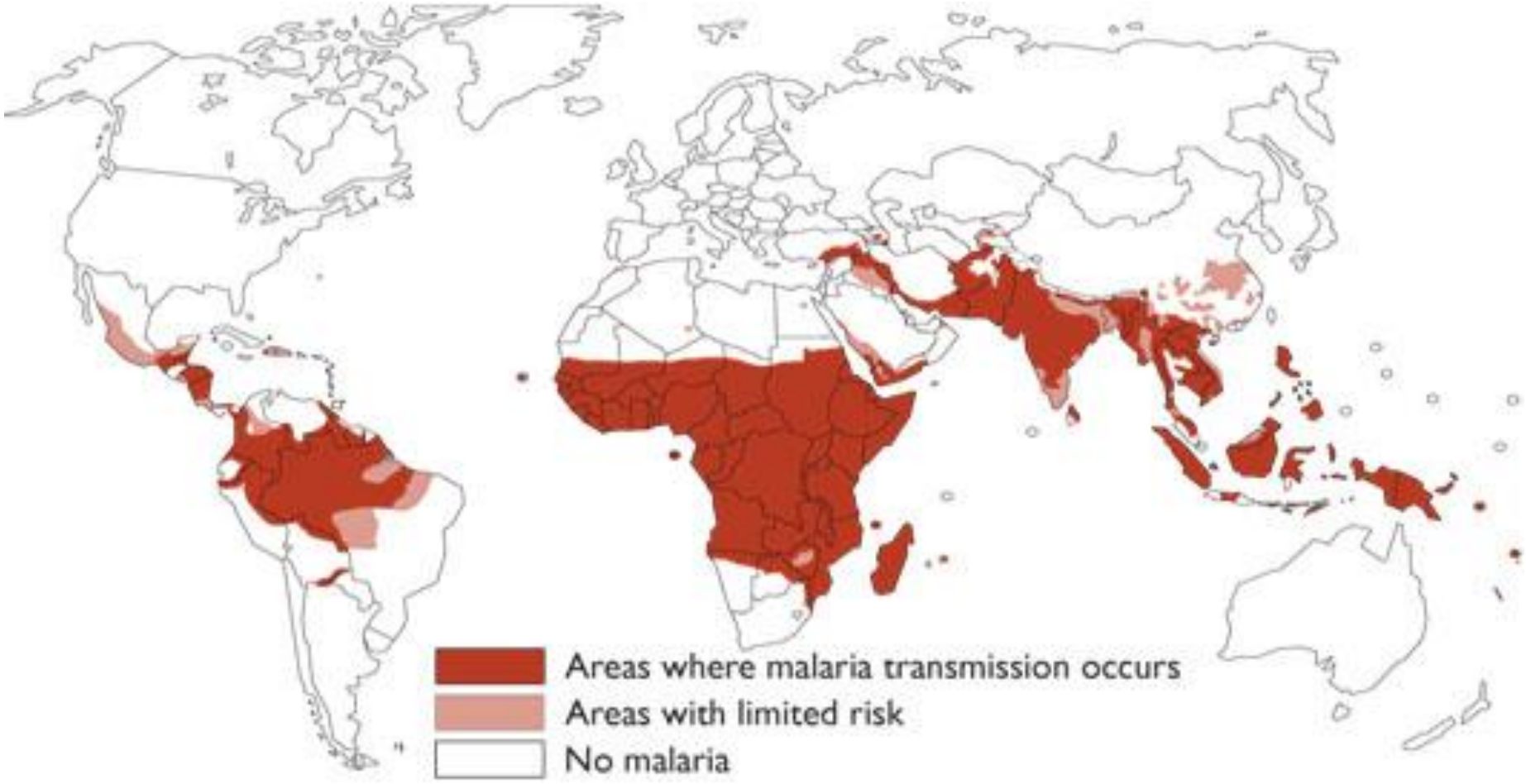
25-30 millions of people travelling each year to tropical countries;

10 – 30 thousands of travellers infected by malaria



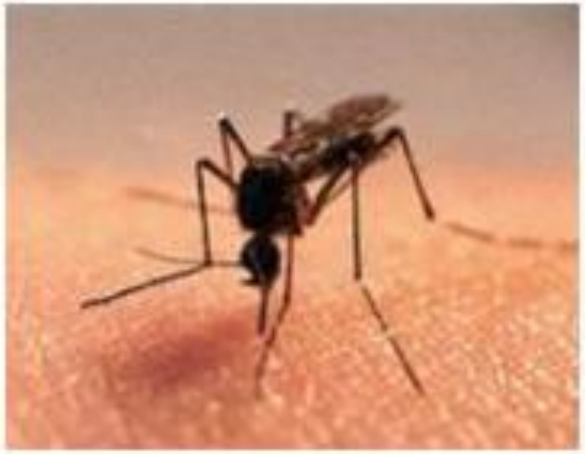


Distribution of malaria, 2005

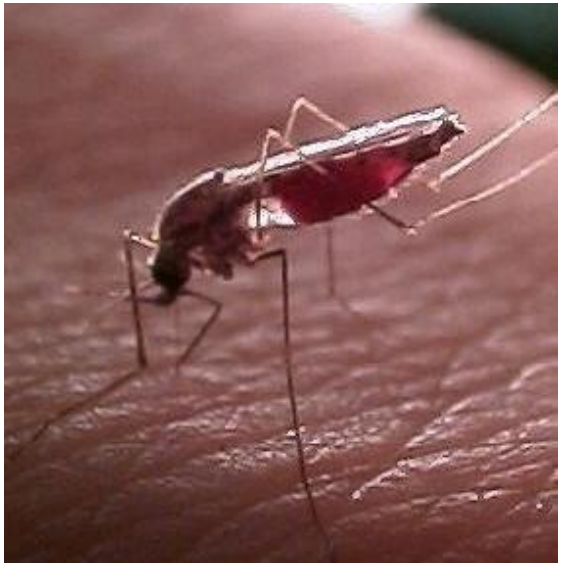


Malaria

Plasmodium falciparum
Plasmodium ovale
Plasmodium vivax
Plasmodium malariae



Anopheles

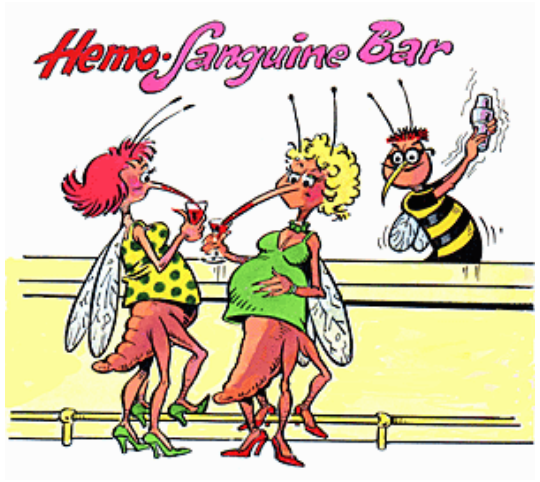


Vector: mosquito –

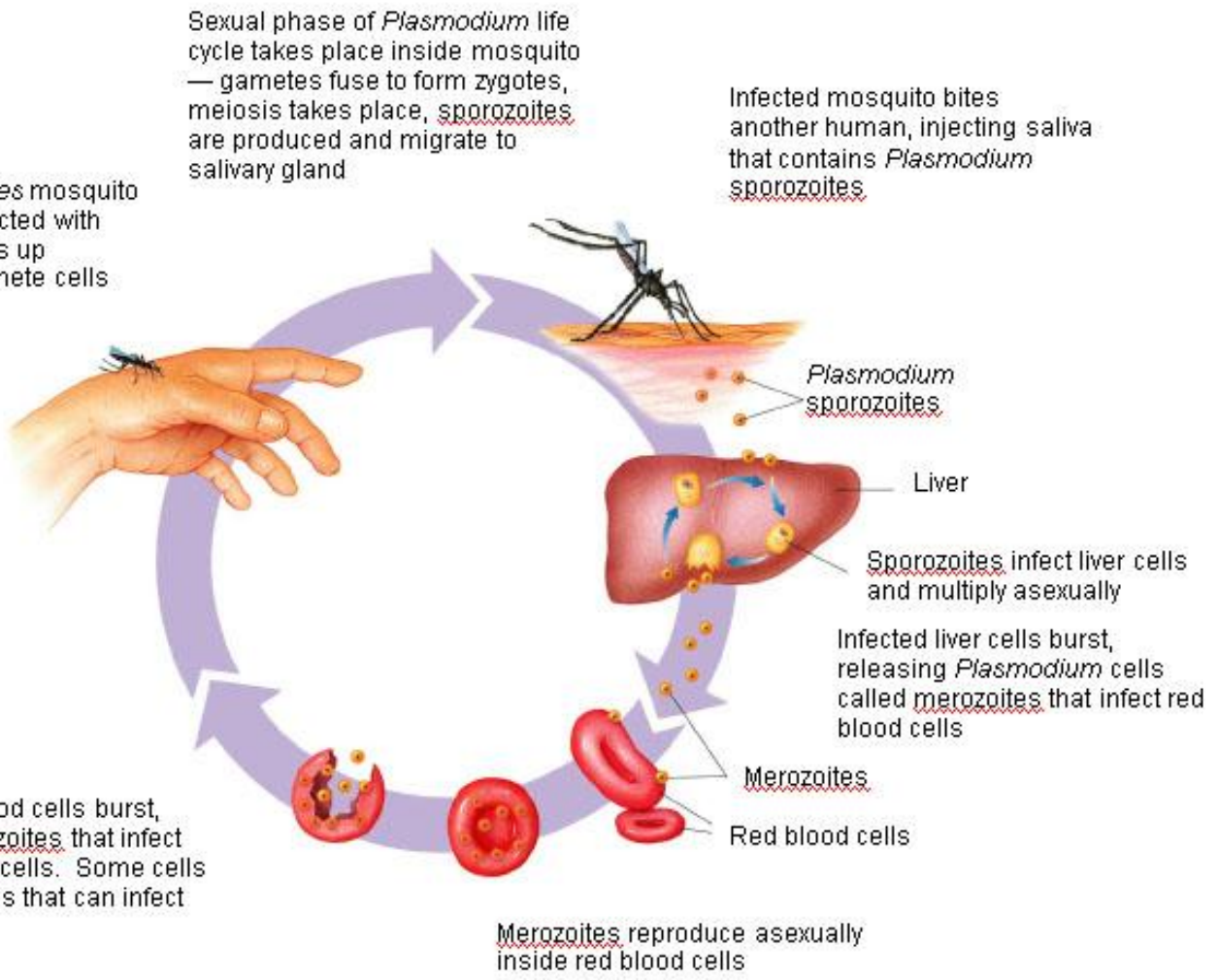
Anopheles spp.

Anopheles spp.

- Female
- Biting at dawn and during night
- Like lowland areas with clean water (swamps, paddyfields, rain puddles)
- Appropriate temperature for development of plasmodium 16-33°C
- Salivary glands



Life cycle of plasmodia



Stages of life cycle

Sporozoityes

(mosquito) infectious for human

Asexual replication in hepar

H Y P N O Z O I T E S!!!

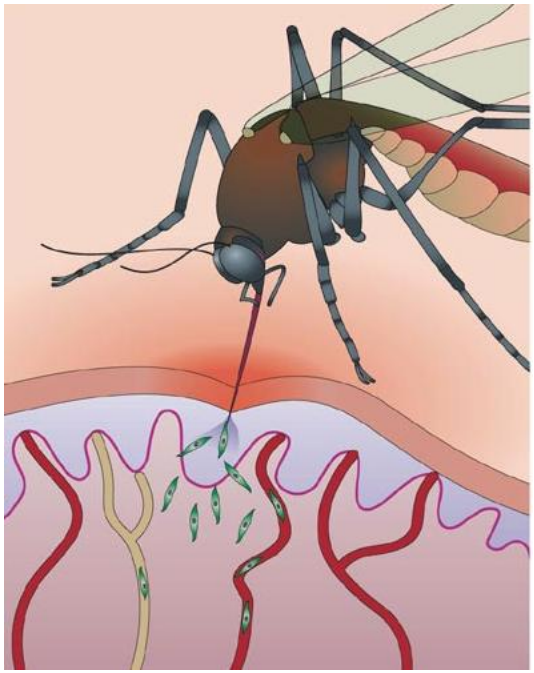
(*P. vivax, P.ovale*)

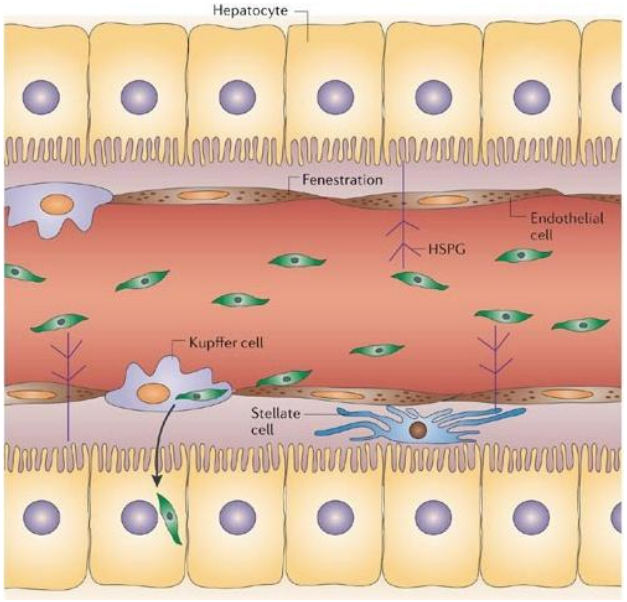
Merozoites

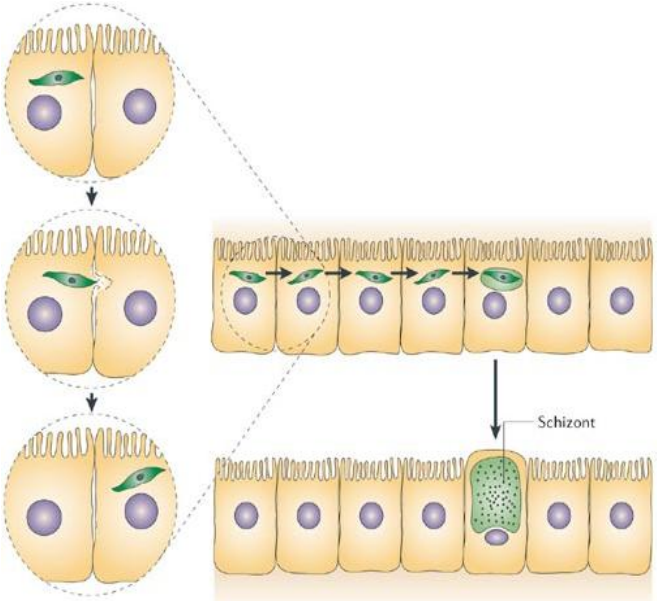
(infectious for erythrocytes)

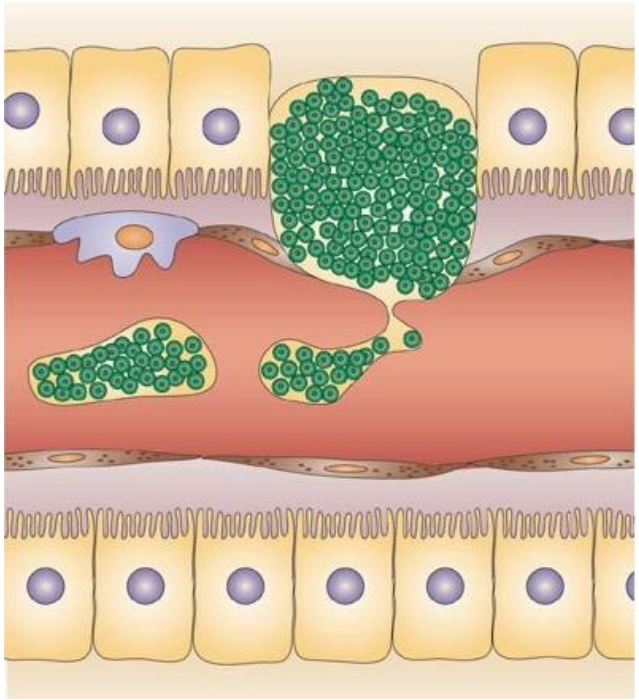
Gametocytes

(infectious for the mosquito)




Hepatocyte
Fenestration
Endothelial cell
HSPG
Kupffer cell
Stellate cell

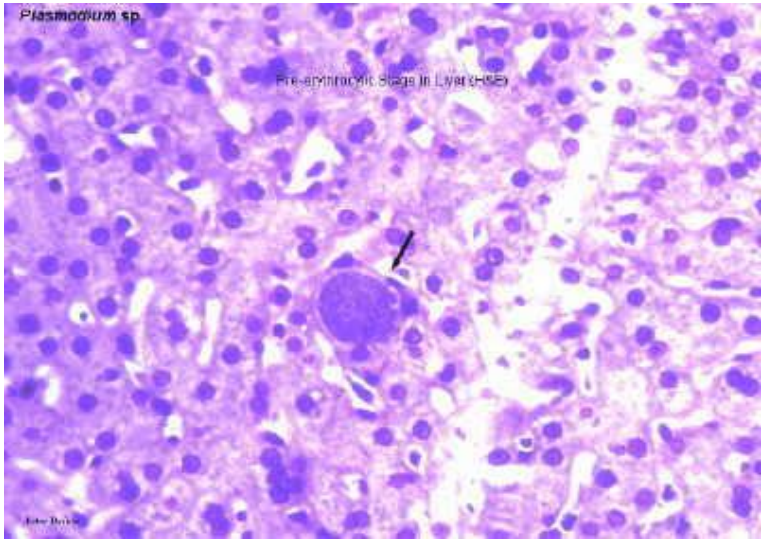

Schizont

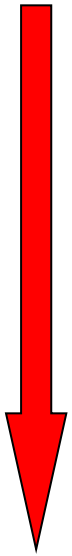


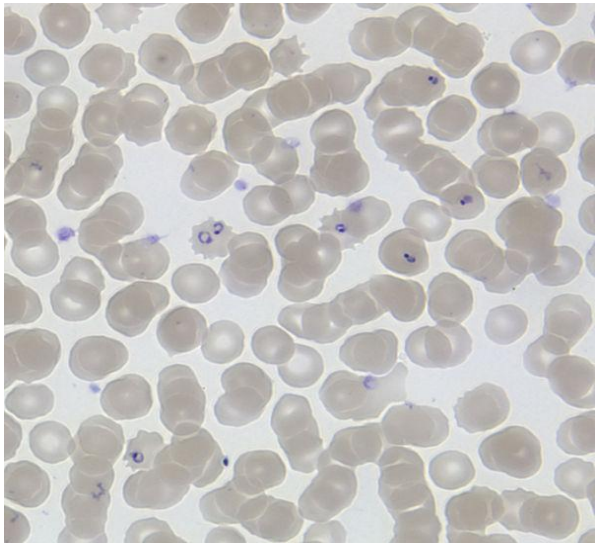
Intrahepatic development (exoerythrocytic) ⇒ asymptomatic

(circulation in blood before the entering into hepatocyte: 15-60 min)

Development in the hepatocyte: *Pl. Falciparum*: 5.5 days, *Pl. Malariae*: 15 days







Intraerythrocytic development ⇒ malaria

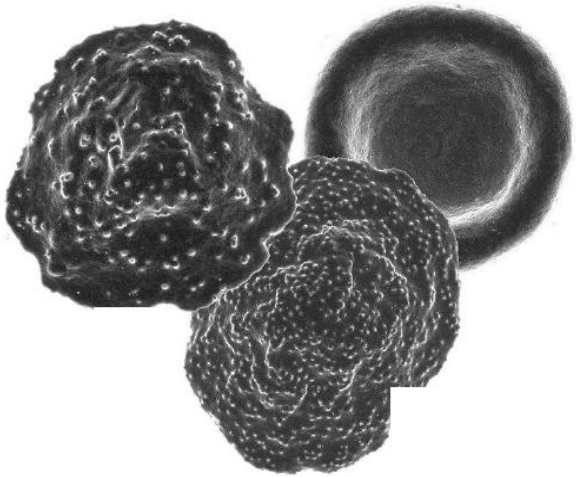
development in ery: *Pl. Falciparum, vivax, ovale* - 48 hrs; *Pl. Malariae: 72 hrs*

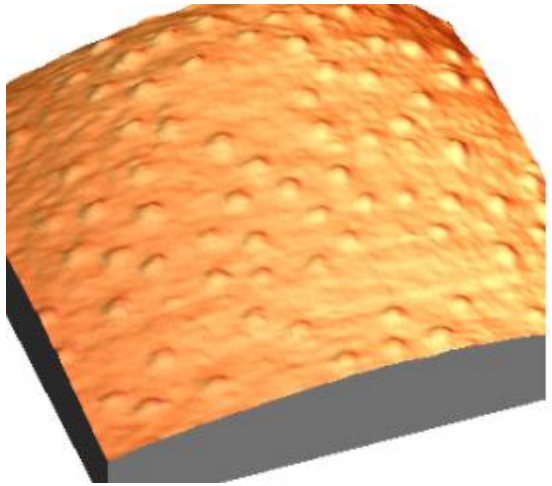
Infected ery:

Shape changes ➡ reduced flexibility

Membrane knobs

(Pl. falciparum, malariae)





„Glueing“ to the endothelium

(Pl. falciparum) tzv. knobs – sequestration

Rosetting

Adherence between erythrocytes

(infected and non-infected)

malfunction of the microcirculation

Sequestration

Adherence to venules of vital organs

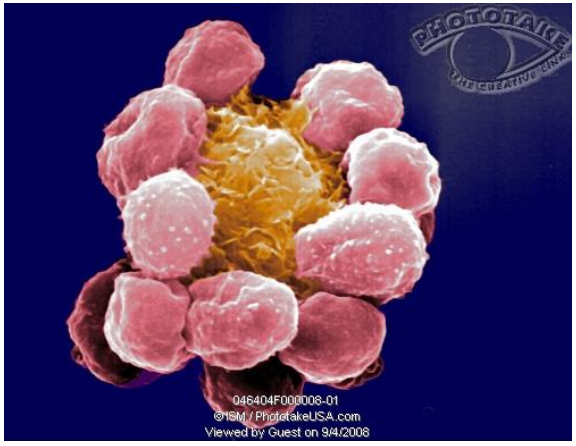
(HRP, sequestrin/CD36, ICAM)

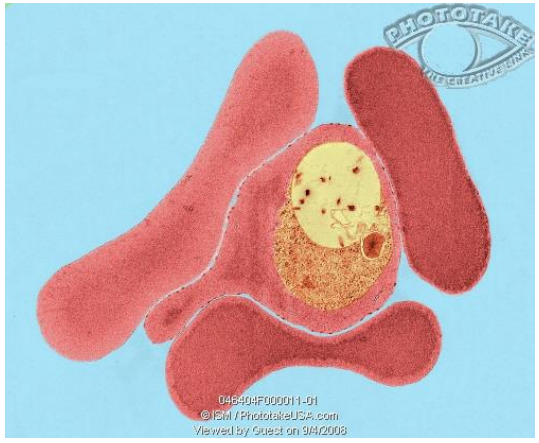
(brain, heart, hepar, ren, intestine)

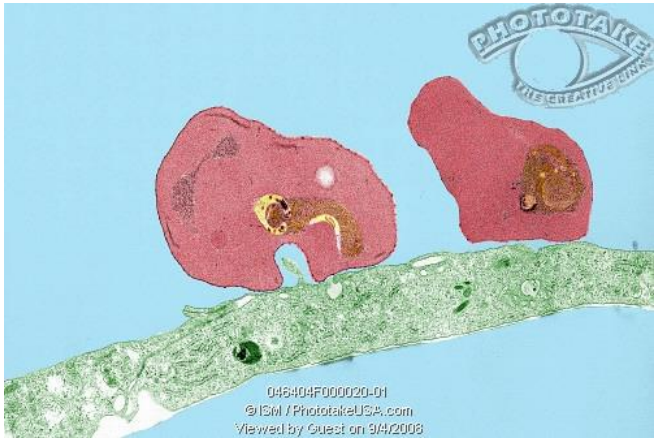
malfunction of the microcirculation

Cerebral malaria

anaerobic glykolysis, lactate acidosis







Plasmodia

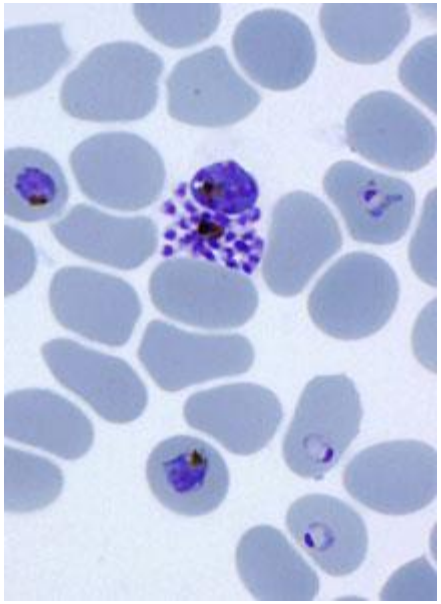
degradate Hb in affected ery (production of hemozoine), utilise glucose, produce of lactate

Preference of ery:

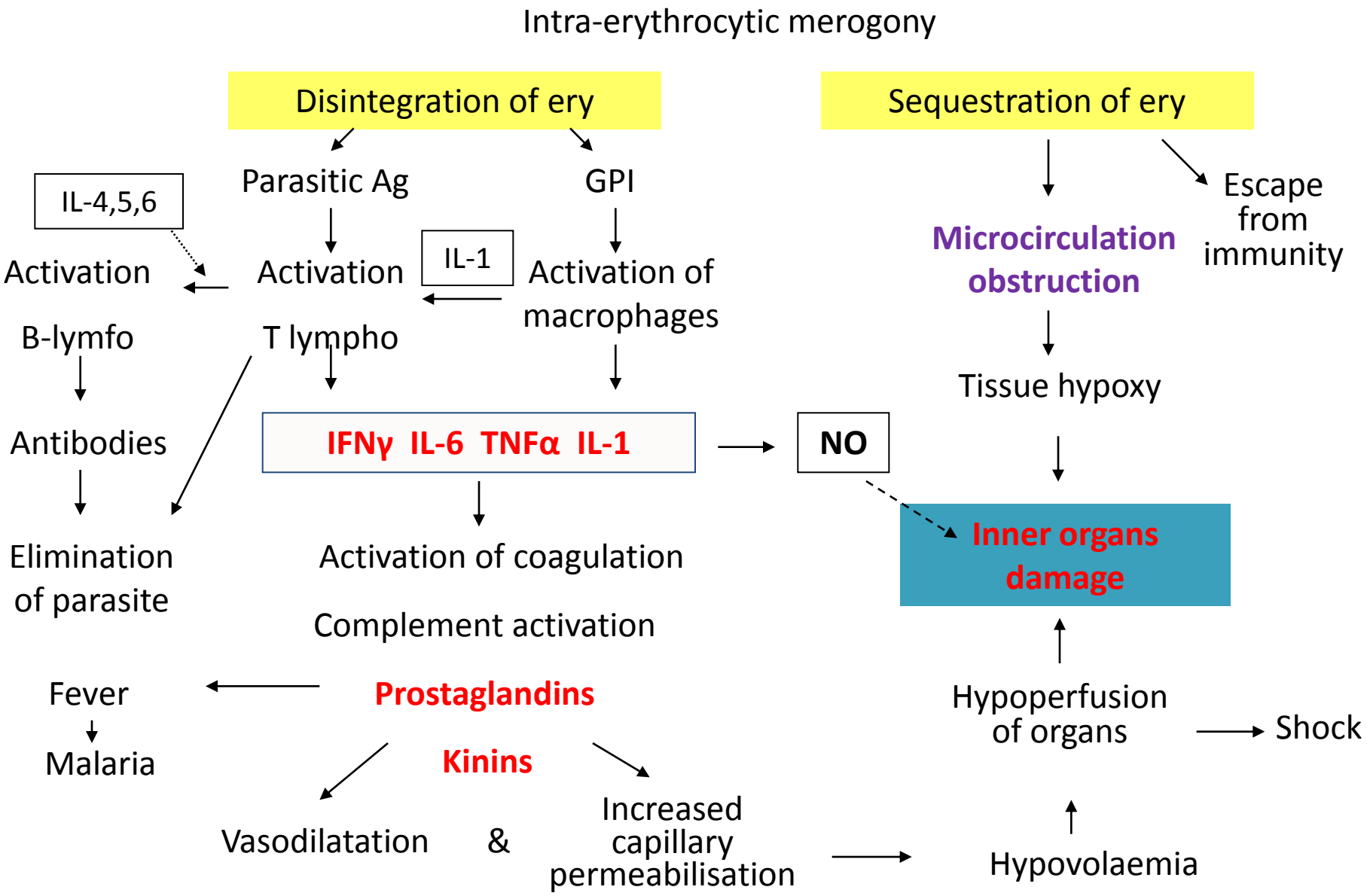
P. falciparum: no preference

P.vivax: young ery (Duffy+)

P. malariae: old ery



PATHOGENESIS OF TROPICAL MALARIA



Malaria aethiology

Species	Disease	Development	Distribution	Relapses
P. falciparum	Tropical malaria, malignant tertian	24-48 hrs	Africa, SE Asia, India, S and Str. Amerika	No
P. vivax	Benignant tertian vivax	48 hrs	Tropics, subtropics	Yes
P. ovale	Tertian, ovale	48 hrs	Tropical western Africa	Yes
P. malariae	Quartan	72 hrs	Tropics, subtropics – some parts	No

Symptomatology

prodromal symptoms

nausea, anorexia, headaches, myalgia

- Adults:
  - Fever – typical malaria paroxisms
  - Anaemia – lack of reticulocytosis = supression of bone marrow
  - Splenomegaly – very early sign
  - Icterus – absent or very mild, elevation of HE

  Children:
  - Fever, cought, vomiting, diarrhoea, anaemia
  - Faster progression (1-2 days)
  - Pulmonary oedema
  - Renal failure very rare

Course of the disease

Incubation period: malignant tertian: 11 days

tertian: 12 days

quartan: 13-28 days

FEVER: 3 phases: chills (temperature increase) myalgia and headache 10-30 min

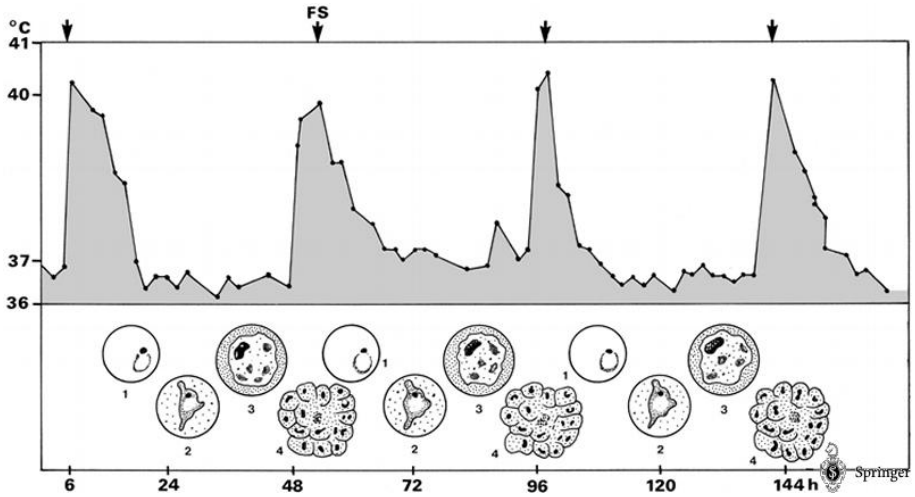
fever

sweating

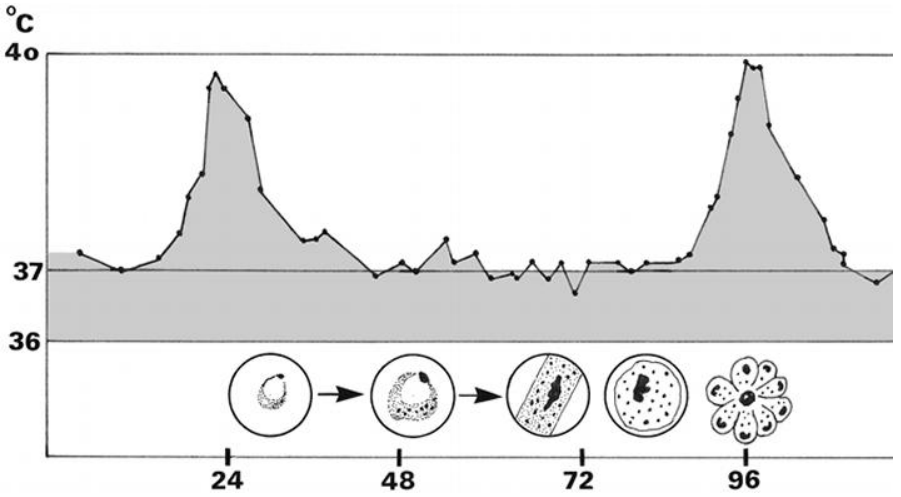
(vasodilatation, ortostatic hypotension – 4-8 hrs)

Temperature curves:

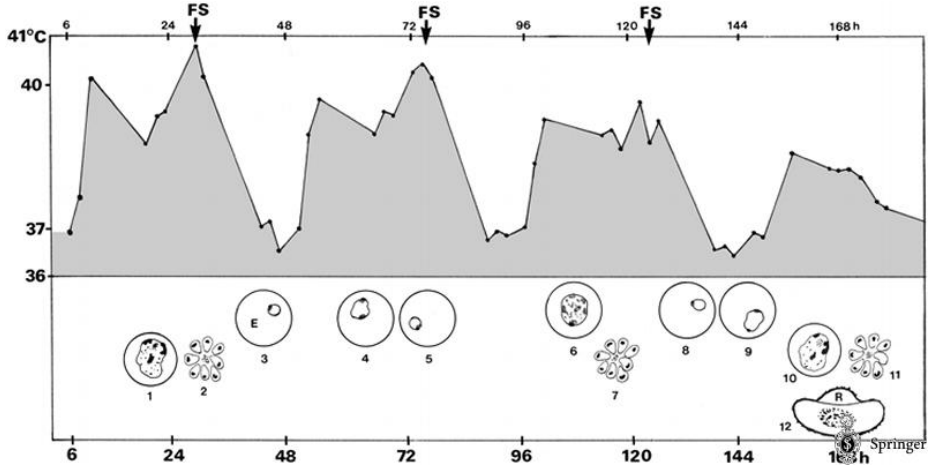
Tertian

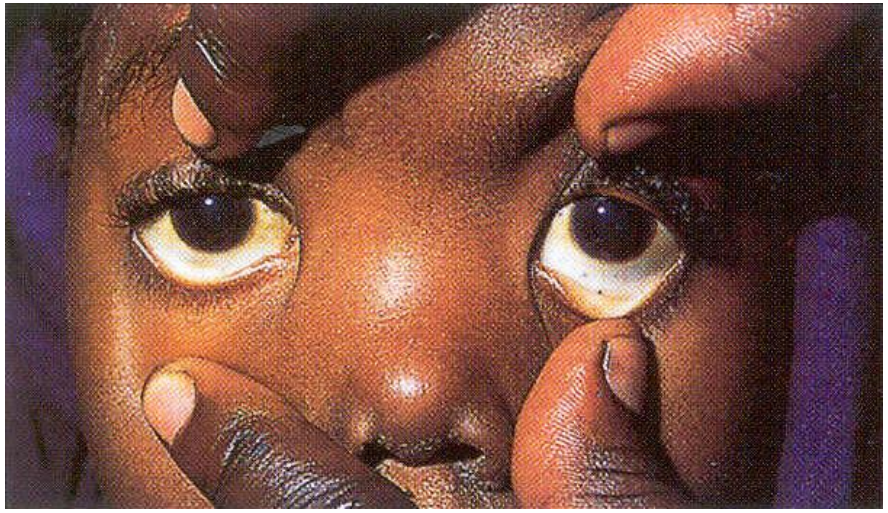


Quartan

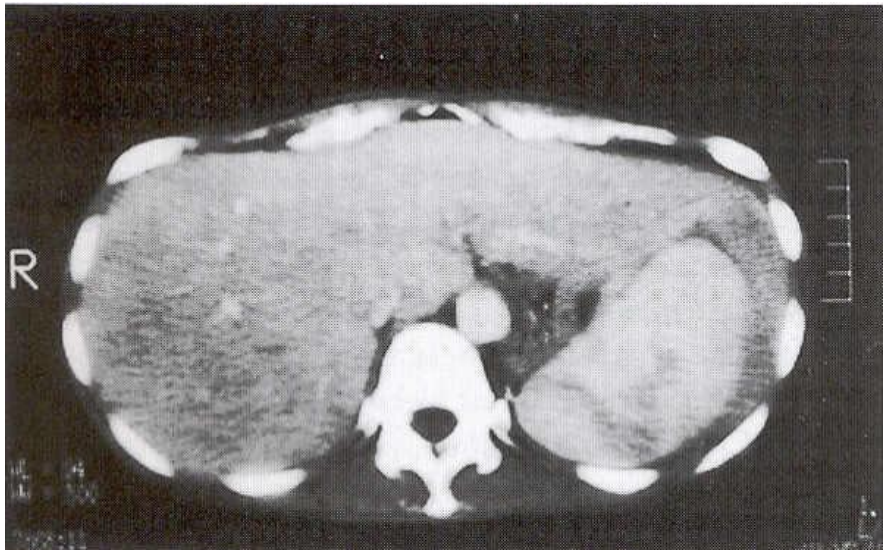


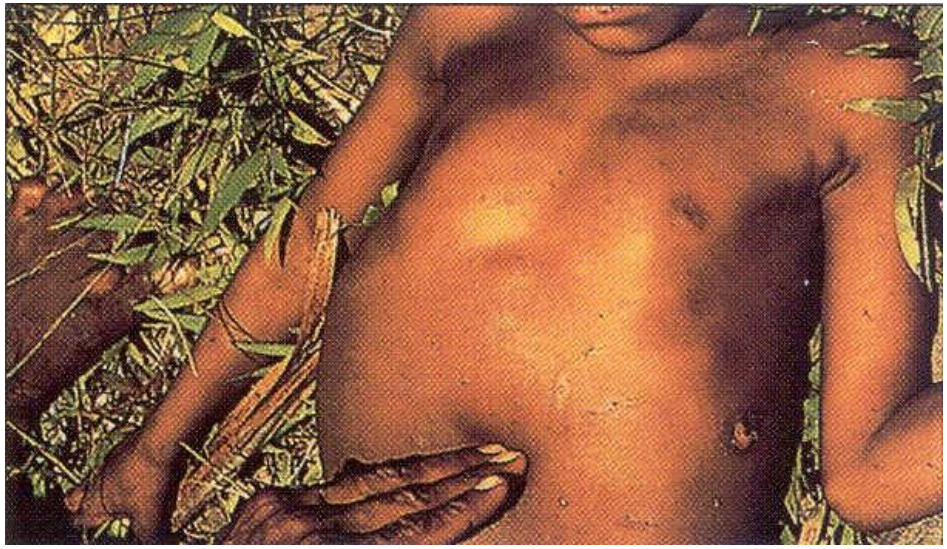
Malignant malaria





Anaemia





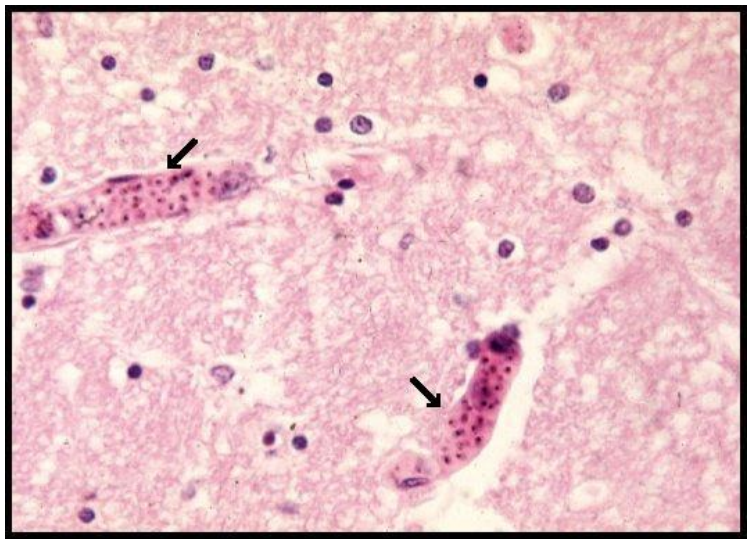
Hepatosplenomegaly

MALARIA

Species	Disease	Parasitaemia	IP (days)	Compl.
P. falciparum	Tropical malaria/ Malignat tertian	- 30%	7-14	Malignant malaria
P. vivax	Benign tertian	- 2%	12-17	Anaemia, splenome-galy
P. ovale	Tertian ovale	- 1-(2)%	15-18	Anaemia, splenome-galy
P. malariae	Quartan	- 1%	18-40	Glomerulo-nephritis, nephrotic sy

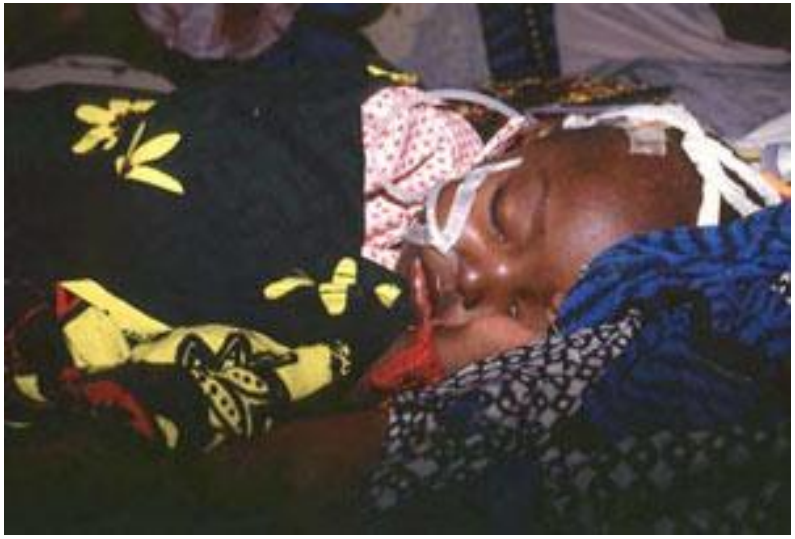
COMPLICATIONS OF MALIGNANT MALARIA

- **Cerebral malaria**
- **Renal failure**
- **Pulmonary oedema**
- Bleeding disorders
- Hepatic failure
- GIT complications
- Circulation colapsus – algid malaria
- Hypoglycaemia, ion dysbalance

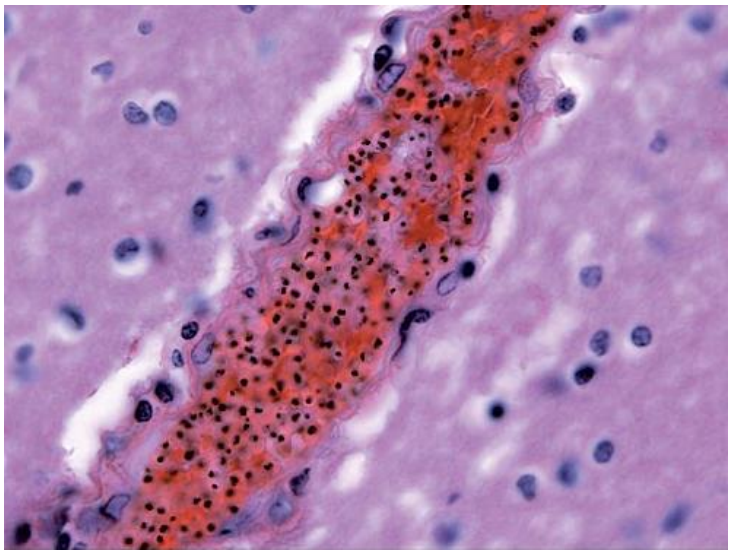


CEREBRAL MALARIA

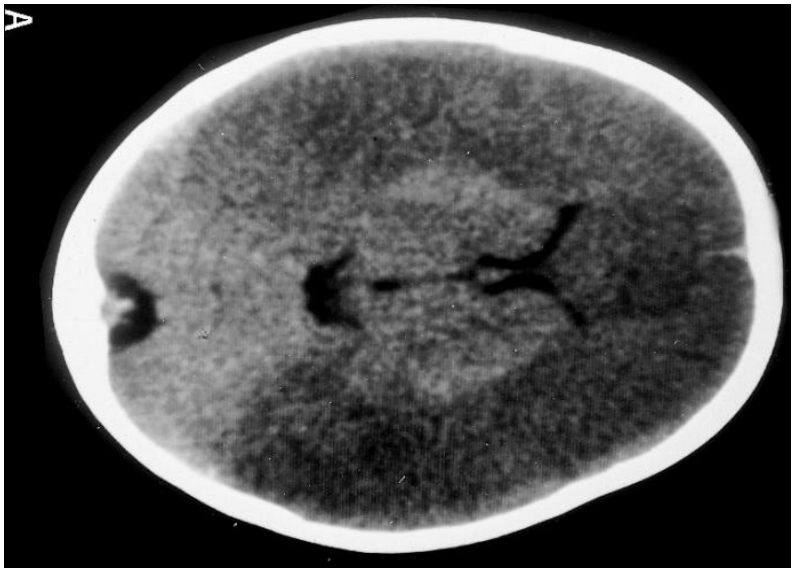
- **Severe conciousness disorder, unconciousness, coma**
- Focal neurologic deficiency uncommon
- In children - **seizures**, paresis of oculomotoric nerves
- Meningeal irritation signs usually negative
- 30-50 % mortality
- **CT normal**
- Oedema of the brain - terminally
- Pathogenesis not completely understood: NO and lactate production, malfunction of microcirculation



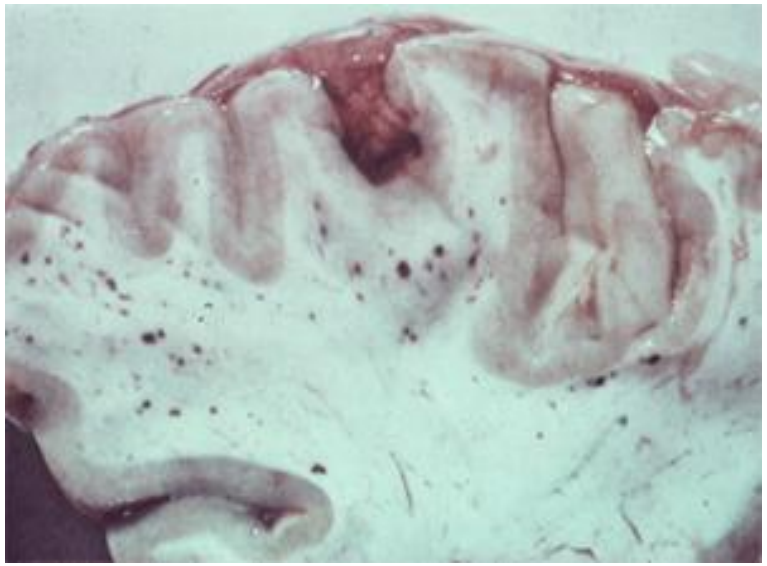
unconciousness, cerebral malaria



Cerebral malaria



Oedema of brain, cerebral malaria

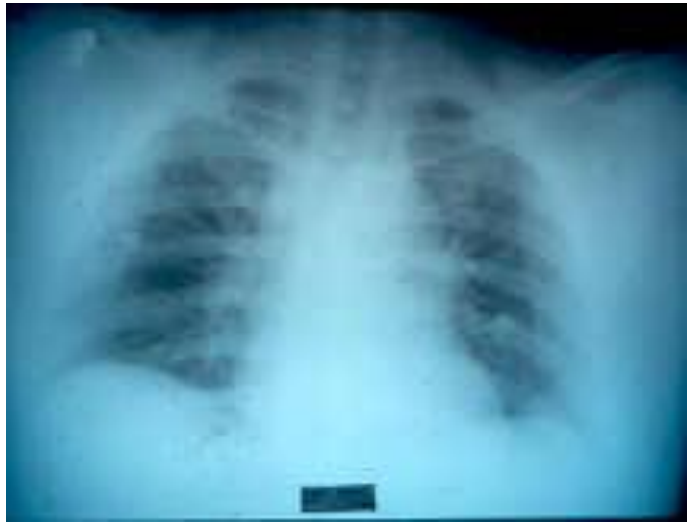


Multiple petechias, cerebral malaria

Pulmonary oedema- ARDS

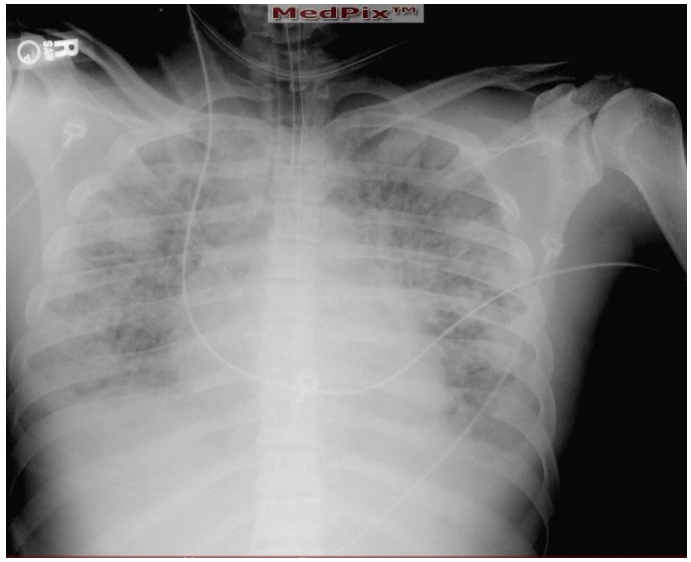
Adherence of neutrophils to the endothelium of pulmonary capillaries

Activation of neutrophils and macrophages



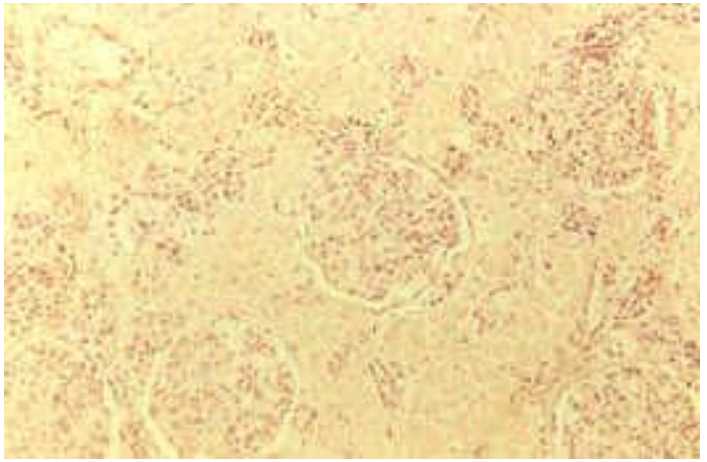
Increased permeability of pulmonary cappilaries

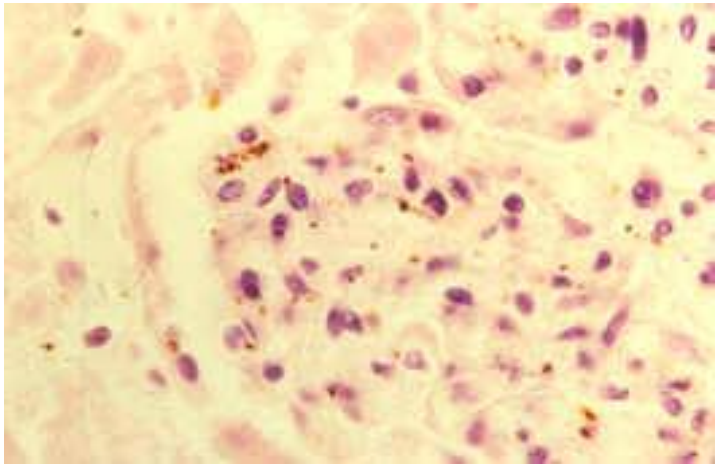
- Oedema of endothelium and interstitium, hyalinous membranes formation
- Increased hydratation of patient



RENAL FAILURE

- Malfunction of **microcirculation**
- Hypovolemy and hypoperfusion of ren
- Acute tubular necrosis
- Anuria, asotaemia and ureamia
- Hemoglobinuric fevor
- Formation of haemoglobin cylinders

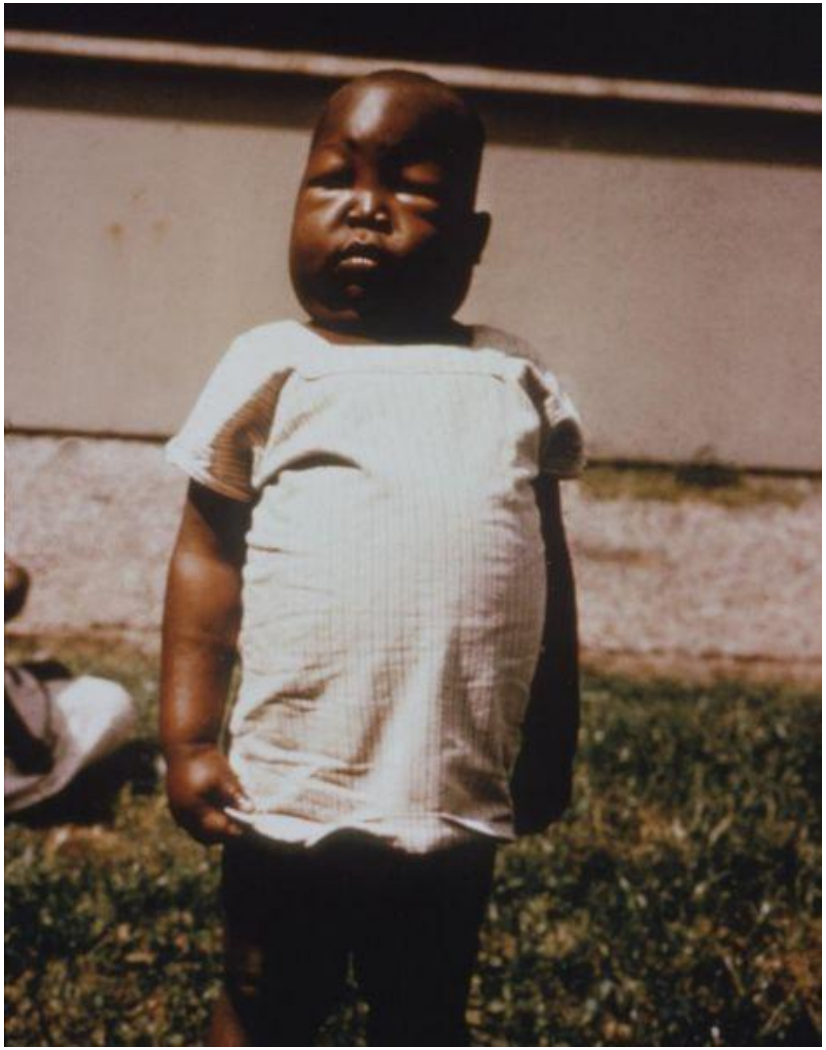


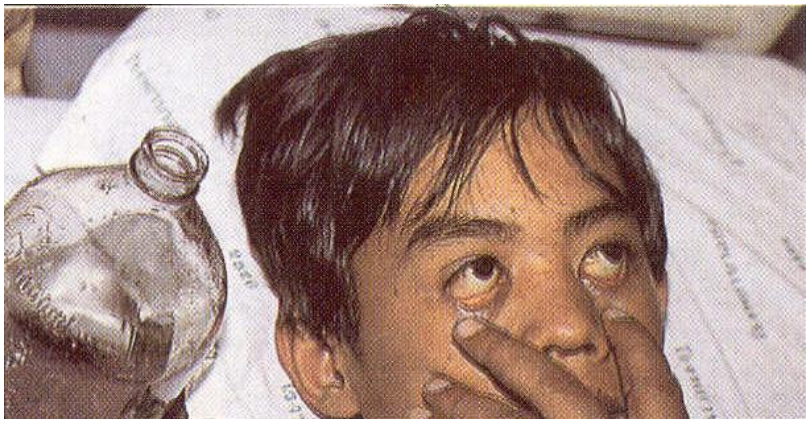


Nephrotic sy/Blackwater fever

- ***Pl. Malariae;***
  imunocomplex format.

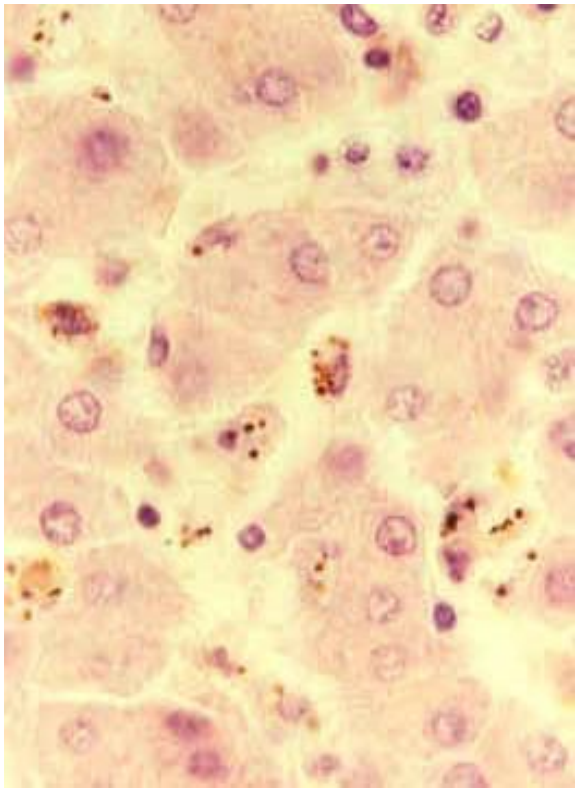
- Deficiency of G6PD
- Quinine
- Urine of Coca-cola colour





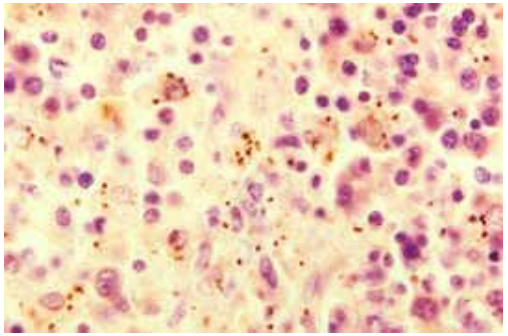
Hepatic failure

- **Uncommon** in malaria
- Hyperbilirubinaemia, elevation HE
- Defect of glukoneogenesis and glycogenolysis
- Defect in utilisation of lactate
- Hypoalbuminemy
- Decreased synthesis of lipoproteins

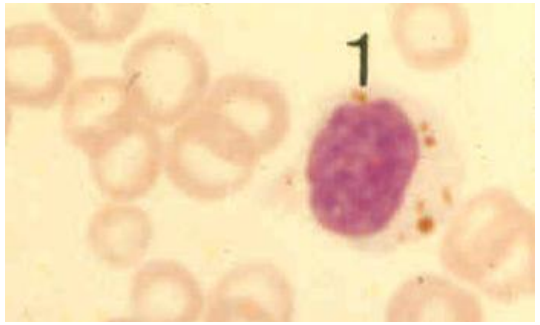


PANCYTOPENY

- Anaemia
  - Defect of erythropoesis in bone marrow
  - Intravascular hemolysis, hypersplenism
- Thrombocytopeny
  - Decreased production and survival of thrombocytes
- Leucopeny



Malaric pigment in lien



Malaric pigment in monocyte

Defects in the inner environment

Hypoglycaemia

- Increased utilisation of glucose – hyperparasitaemia
- Defect of gluconeogenesis
- Hyperinsulinemia

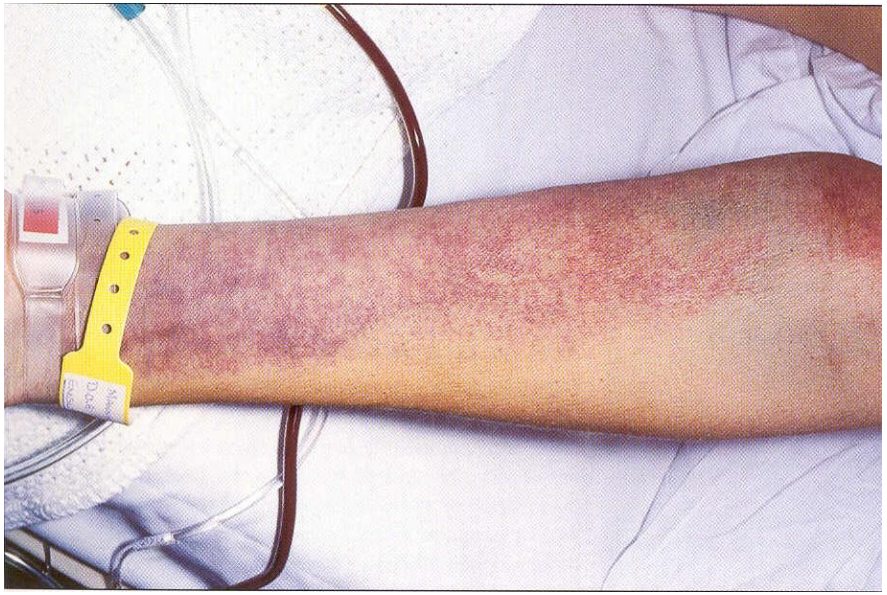
Lactate acidosis

- Tissue hypoxia
- Defect of hepatic function

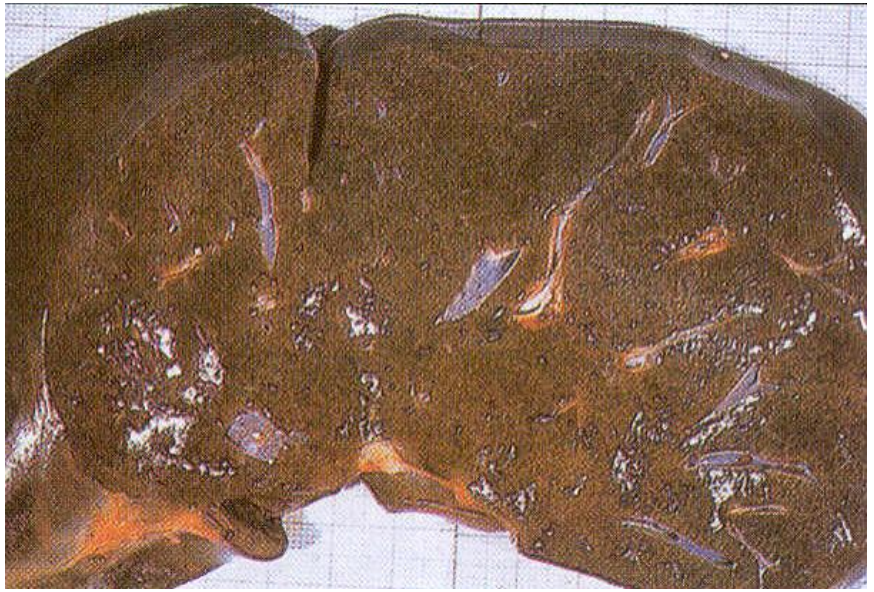
Increased Kalium, Decreased Natrium and Chlorides

Clinical criteria of the malignant tropical malaria

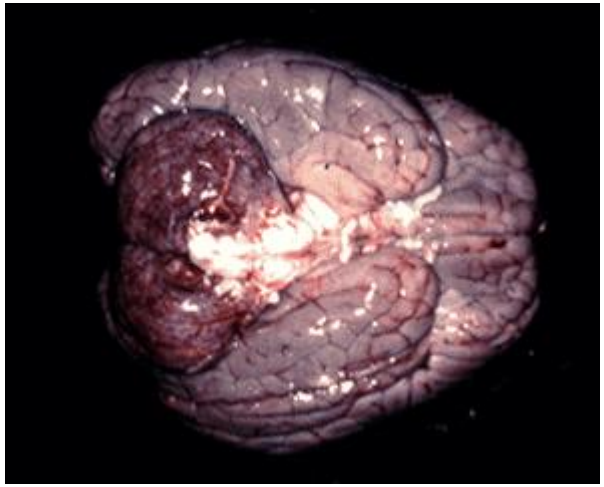
- **Hyperpyrexia > 24 hrs**
- **Cerebral malaria**: unconciousness – coma, seizures, focal neurological deficiency
- **Oliguria** (< 400 ml/24 hrs.)
- Macroscopic haematuria
- **Pulmonary oedema**
- Shock, hypotension
- Fast progressing icterus
- Fast progressing anaemia
- Hemorrhagia, DIC
- Very severe vomiting



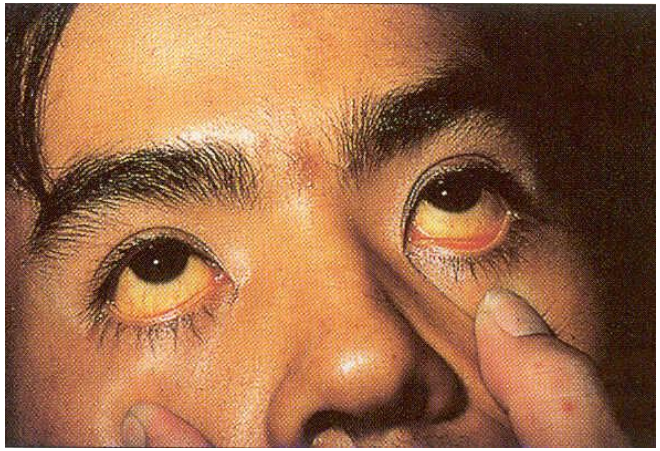
DIC, malignat tertian



Hepatic failure, hemozoin

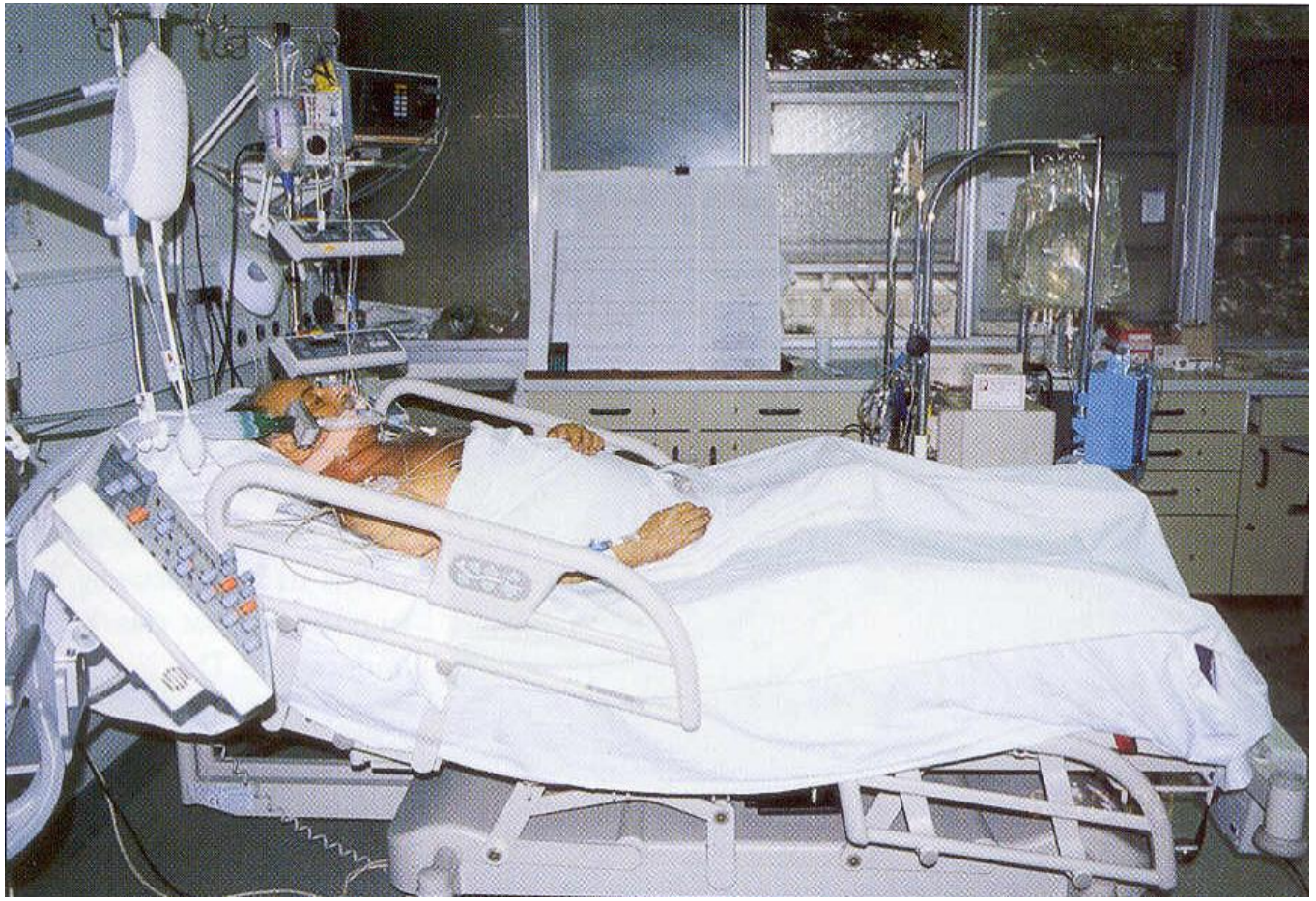


Cerebral malaria, hemozoin



Icterus

Malignant malaria should be treated in the **ICU**



Laboratory criteria of malignant tropical malaria

Serum concentration of creatinin < 265 µmol/l (3 mg/dl)

Bilirubin > 50 µmol/l

Hematocrit < 20 %

Haemoglobin < 75 g/l

Severe thrombocytopenia (< 20 000/µl)

Haemoglobinuria

Acidosis (bikarbonate < 15 mmol/l)

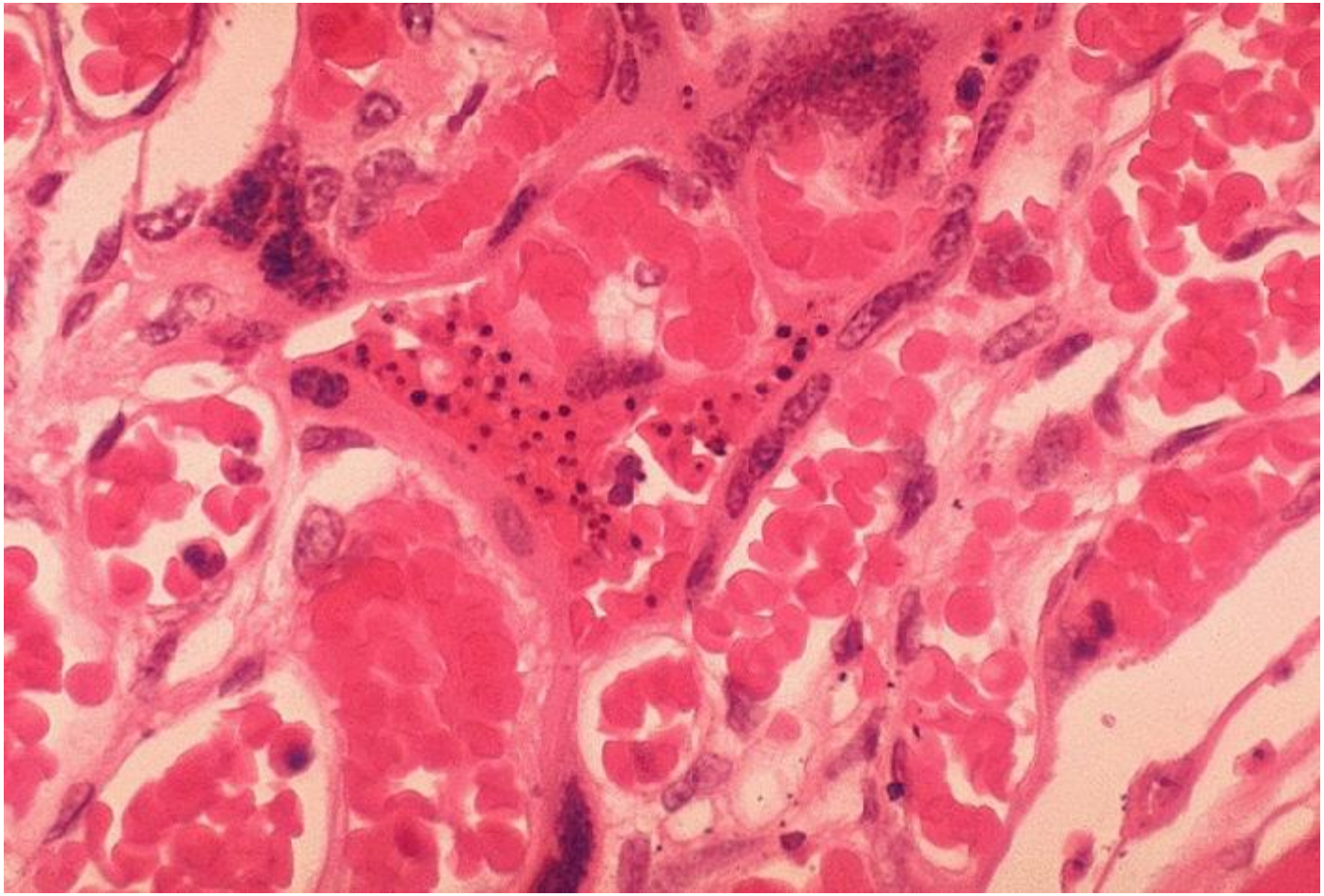
Hypoglycaemia (< 2,2 mmol/l)

Parasitaemia before treatment initiation > 5%

MALARIA in pregnancy

- Increased risk of abortion, premature birth, decreased birth weight and neonatal mortality, **hypoglycaemia!!!!!**
- Increased maternal morbidity and mortality
  - Parasitaemia higher and anaemia more severe
  - Increased risk of hypoglycaemia and pulmonary oedema
- Congenital transmission very rare, more common in non-immune and infections with *P. vivax, P. malariae*

Infiltration of placenta, sequestration of ery



Relapses

P. vivax; P. ovale

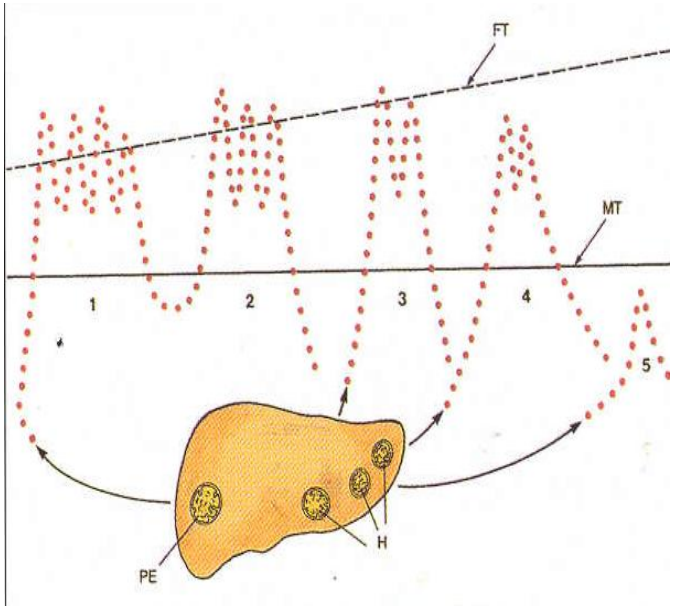
Hypnozoites in hepar

- Time periods longer in subtropical (*vivax*) than in tropical relapses (*ovale*)

Onset of the disease faster,

Paroxyzmys synchronised from the start

- Primachin destroys about 80% of present hypnozoites



MALARIA : important

- Incubation period- **min 8 days**
- **No lymphadenopathy**
- **No exantema**
- **Hepatosplenomegaly;** mild elevation of HE
- **Relative lymphocytosis and thrombocytopaenia,** anaemia not present in acute phase
- Fatal complication of the disease can occur within first 48 hours
- **NO protective immunity!!!!**

MALARIA AND IMMUNITY

- Newborns protected first 6 months
- Repeated exposition: immunita in 5 years = **nonsterile immunity**
- Partial immunity disappears after five years of no exposition

Natural partial resistence against malaria

Disorders in the shape of ery

(sicle cell anaemia, thalassemia, ovalocytosis)

Enzymatic defects: deficiency of G6PD

Variability of surface ery antigens

(Duffy in *P. vivax*)

Variability in imune system (HLA)

MALARIA IN CR

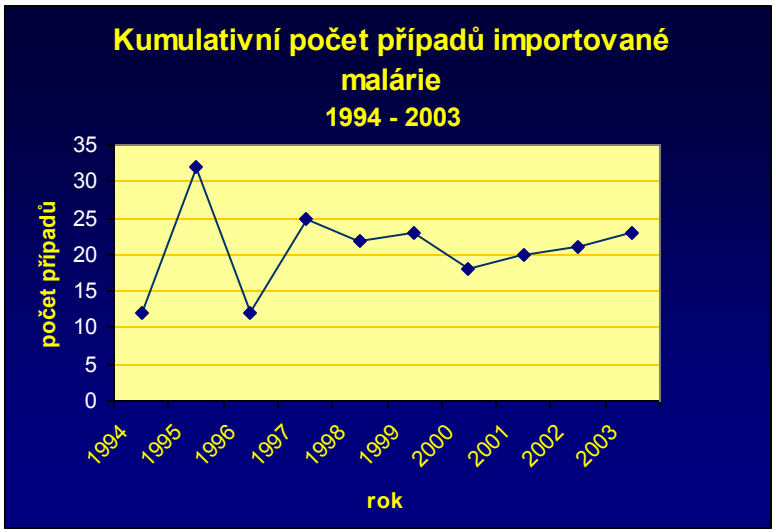
NRL for diagnostics of tropical parasitic infections – Dr. Nohýnková

1994 – 2004: IMPORTED MALARIA

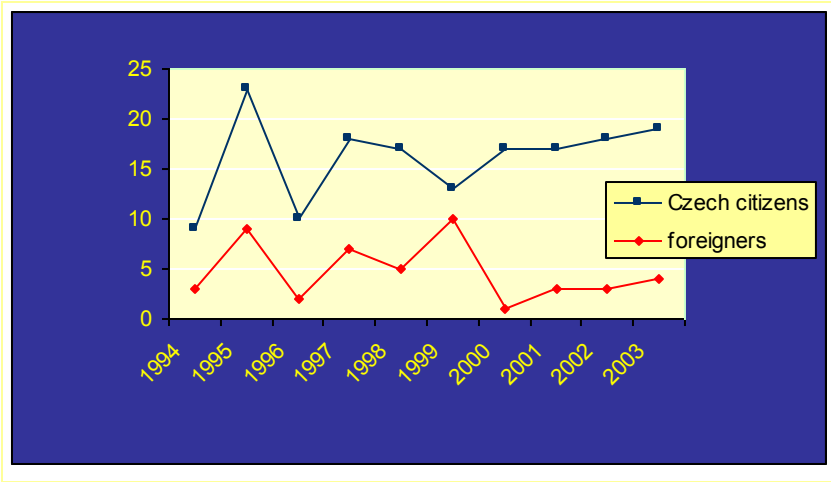
Together : 216 cases

170 citizens of CR 3 deaths (2%): 1996, 1998, 2003

46 foreigners



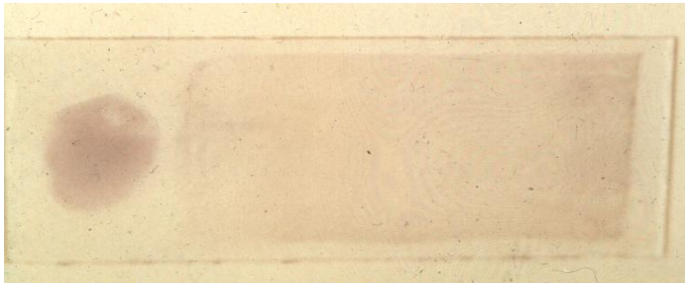
- import from1997 stabil (!)
- ~ 20-25 cases treated in CR/year



Foreigners since.2000 low number of cases

Diagnostics of the malaria

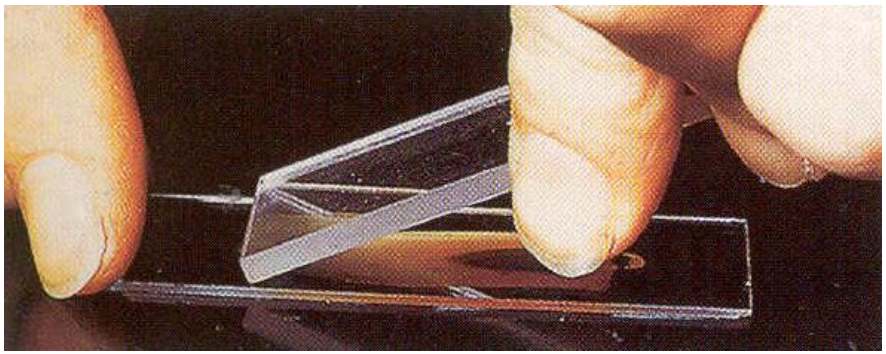
- Thick and thin blood smear –„golden standard“ of the diagnostics
- Smears of the periferal blood, repeat in specific time intervals (after 12 – 24 hrs.); also in the case of afebrilia
- Always important to know the parasitaemia – response to the treatment
- Sensitivity of the thick blood smear: 50/µl ~ 0,001% parasitaemia

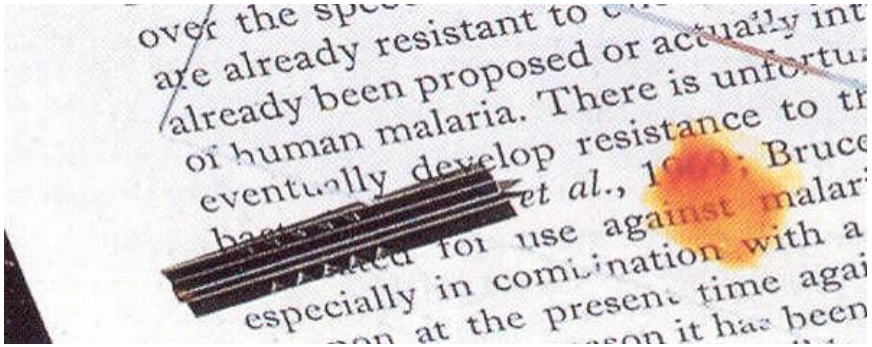


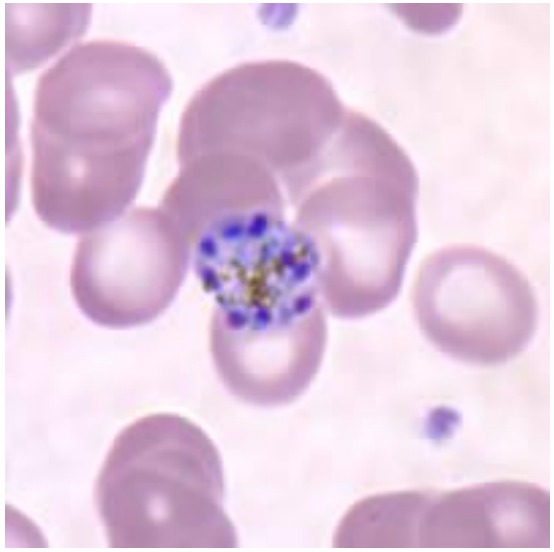
Thick and thin blood smear, stained with Giemsa

Diagnostics of the malaria

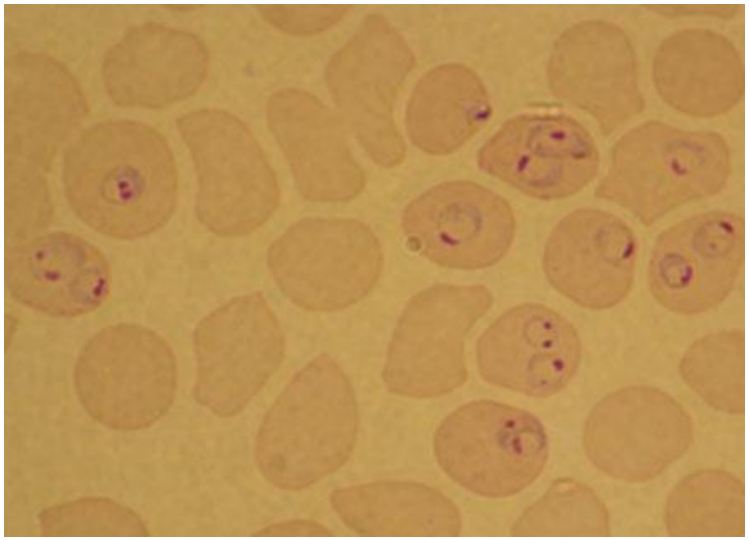
Thick and thin blood smear/film



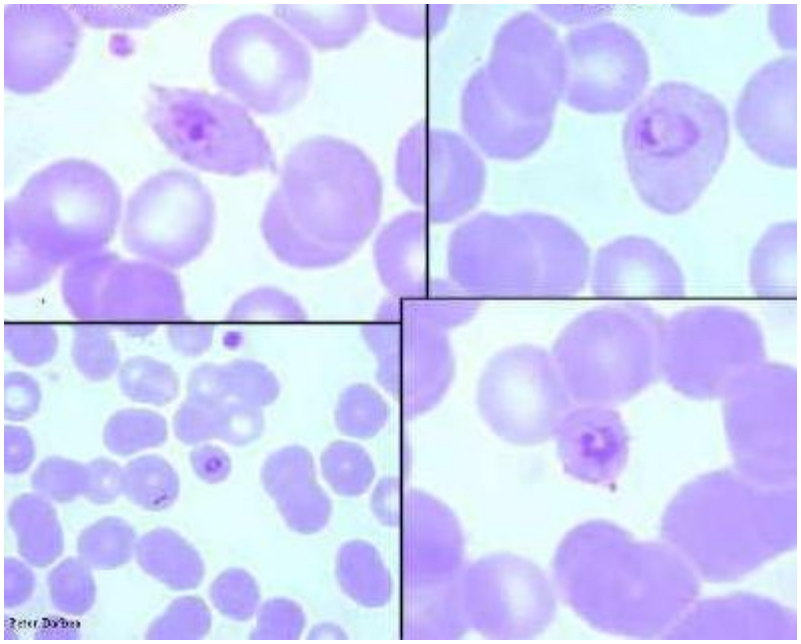




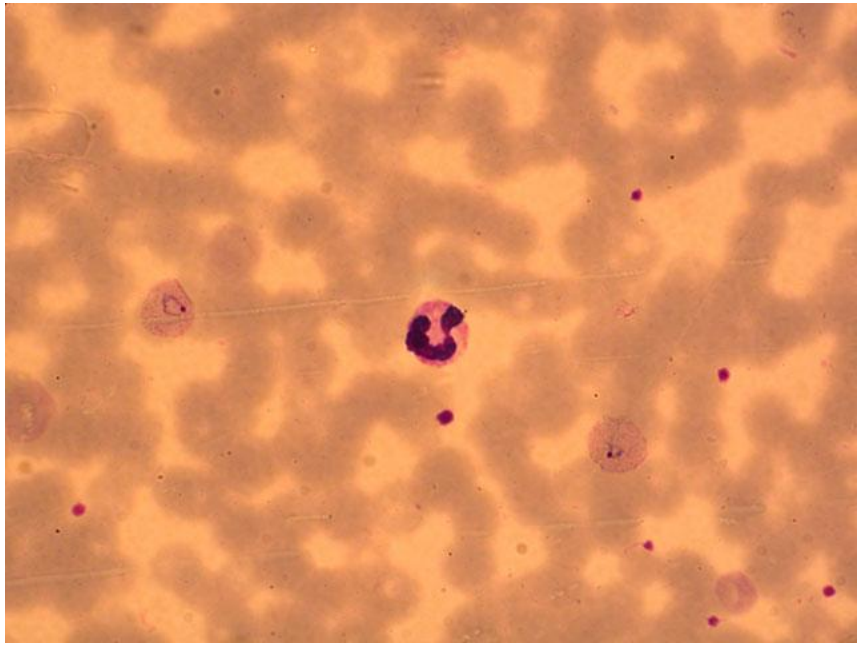
Pl. Malariae



Pl. Falciparum

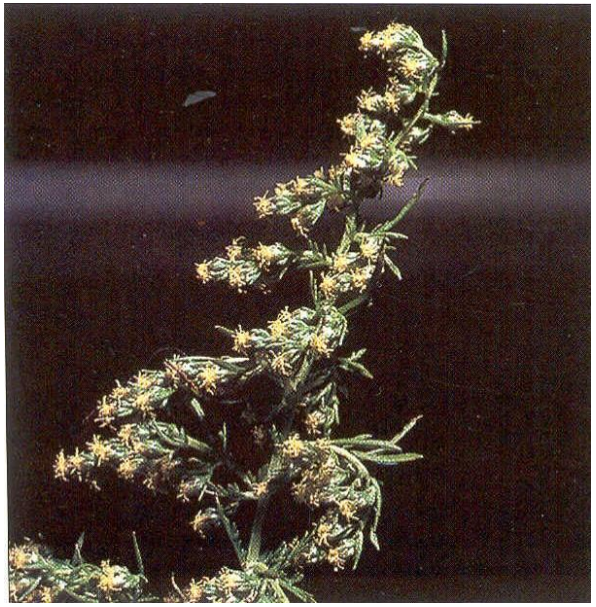


Pl. Ovale



Pl. vivax

Therapy of malaria

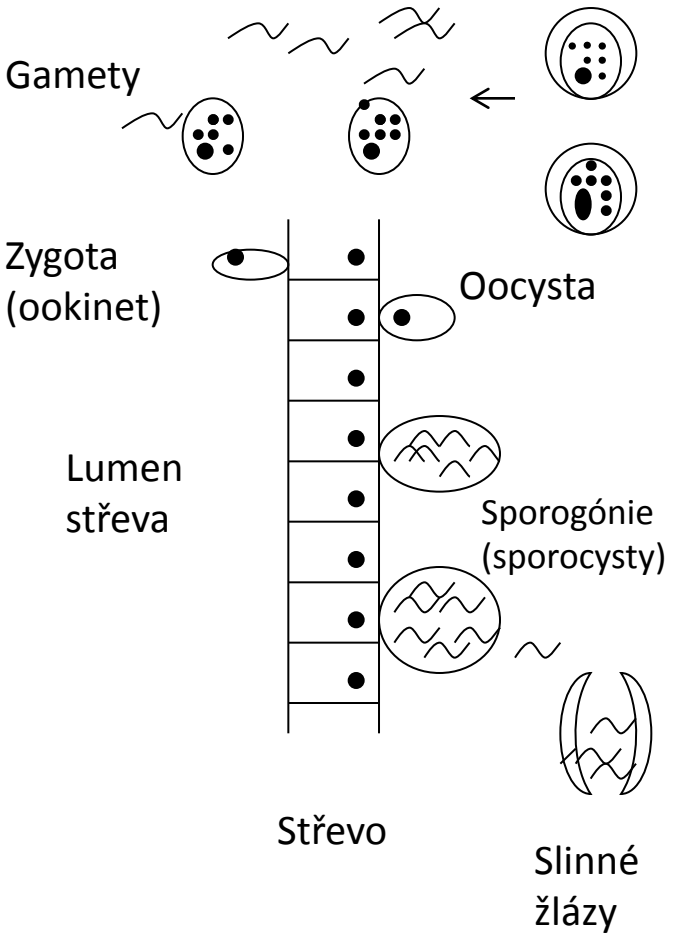


LIFE CYCLE AND ANTIMALARIALS

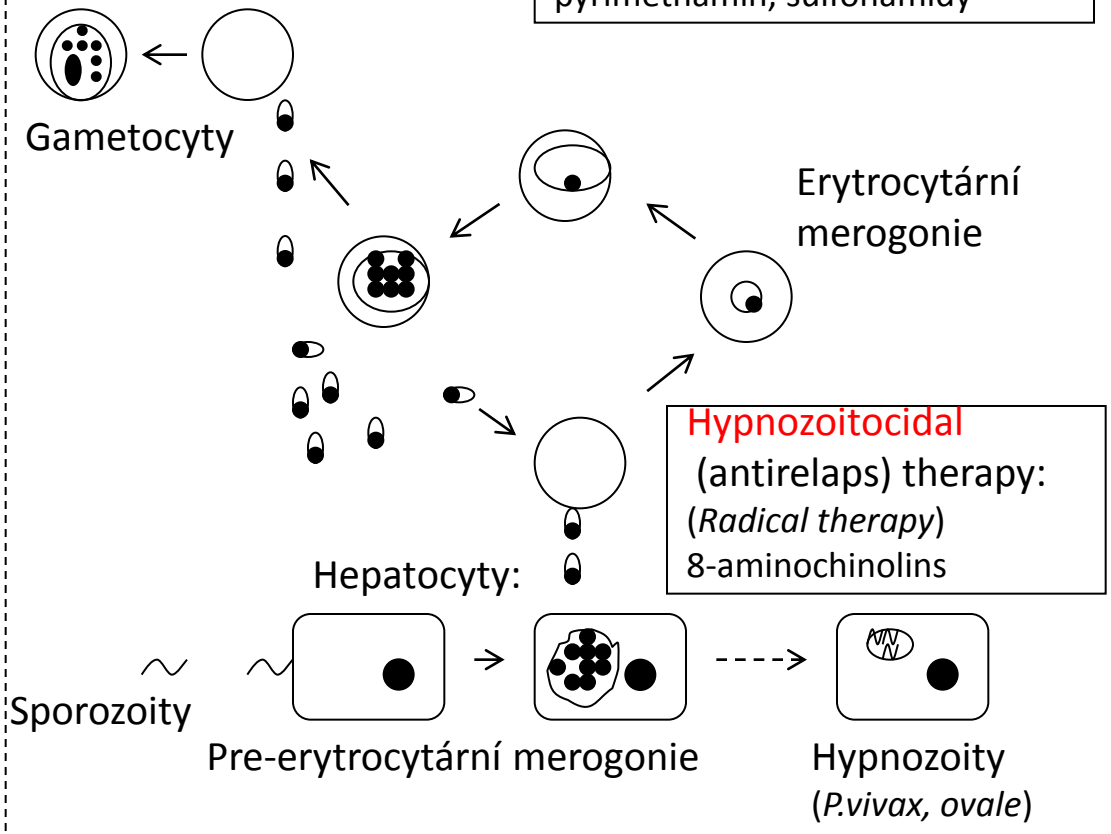
Sporontocidal:
(*Radical prophylaxis*)
Proguanil, pyrimethamin, atovachon

Gametocidal:
(*Radical prophylaxis*)
8-aminochinolins.
Chinin, meflochin, chlorochin -
No effect against P.falciparum

Blooíd schizontocidal:
(*Supresive therapy*)
Chlorochin, chinin, meflochin, artemisinin, atovachon, tetracykliny, klindamycin, pyrimethamin, sulfonamidy



Anopheles



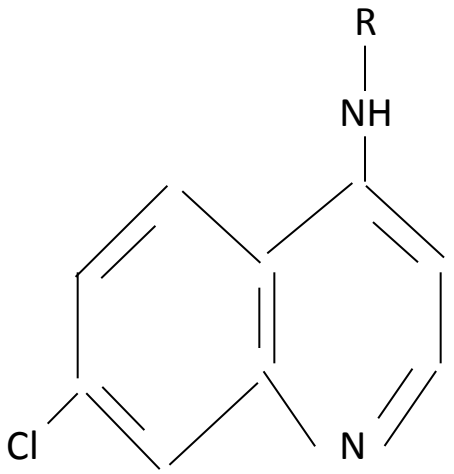
Hypnozoitocidal
(antirelaps) therapy:
(*Radical therapy*)
8-aminochinolins

Human

Tissue schizontocidnal:
(*Causal prophylaxis*)
8-aminochinoliny, proguanyl, atovachon
Tetracykliny, azitromycin

4-AMINOCHINOLINS

- Chlorochin = 4-(4-diethylamino-1-methylbutylamino)-7-chlorchinolin
  (DELAGIL, tbl. 150 mg báze)
- Hydroxychlorochin (PLAQUENIL)
- Amodiachin

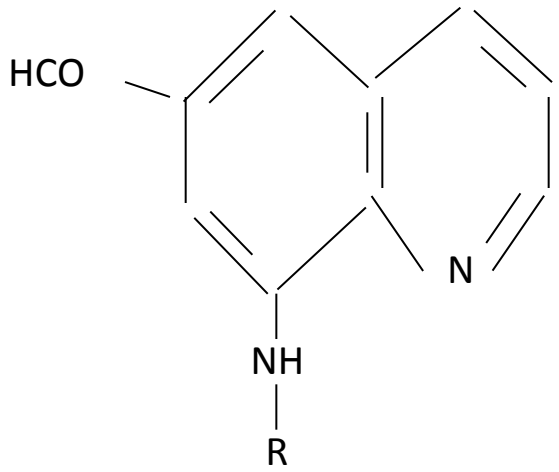


4-AMINOCHINOLINES

- Mechnism of effect: interference with detoxification of free hem while degrading Hb
- Indications
  - *Plasmodium sp.*: schizontocide, gametocide(*Pl. vivax, ovale, malariae*), prophylaxix of malaria
  - Extraintestinal amebiasis
- Side effects: pruritus, headache, GIT problems, exfoliative dermatitis; retinopathy and keratopathy in high doses
- Contraindication: severe malfunction of hepar and ren, neurologic disorders (epilepsy), retinopathy, porphyria, careful with psoriasis
- Drug interaction: increasing the plasma levels of digoxin and methotrexate; inhibitors of MAO increase the toxicity

8-AMINOCHINOLINY

- Primachin = 8-(4-amino-1-methylbutylamino)-6-methoxychinolin (PRIMAQUINE, tbl. 7,5 mg báze)
- Pamachin
- Tafenochin



8-AMINOCHINOLINES - PRIMACHIN

- Mechanism of effect: activation to form toxic aminocholins, interference with redox reactions
- Fast absorbation from GIT, $T_{1/2}$ = 5 hrs.
- Indication: gametocide in all plasmodia, antirelaps treatment of *Pl. vivax* and *ovale* (destroys hepatic hypnozoites)
- Side effects: GIT (anorexia, nausea, abdominal pain), methemoglobinaemia, leucopenia; haemolytic anaemia in patients with G-6-P DH deficiency
- Contraindications: defects of haemopoiesis, pregnancy, lactation
- Drug interactions: increase in plasma levels of meflochin
- Doses: 0,25 (0,33) mg/kg/day, 14 days

Effective substances from plants

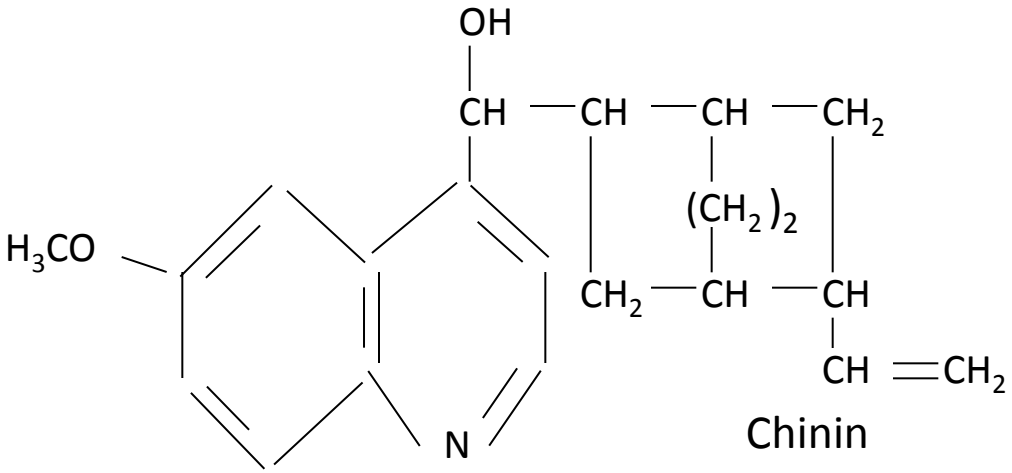
- Mostly alkaloides
- One of the most effective antiinfectious drugs from plants
  - Extrakt from qing hao (*Artemisia annua*) – was used in China for fever treatment since 430 AC („Handbook of Prescriptions for Emergency Treatments“)
  - Cinchona was used by Indians as antimalarial and antipyretic treatment in Peru

Effective substances from plants

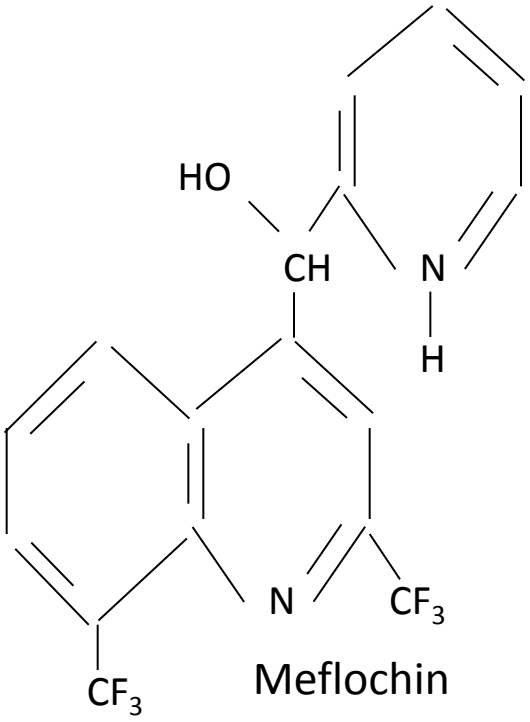
- Quinine – alcaloid of (*Cinchona succirubra*) isolated by Pelletier at the beginning of 19th century (1820 n. 1834)
- Artemisinin = qinghaosu – qing hao (*Artemisia annua*)
- Emetin – alcaloid from (*Cephaelis ipecacuanha*) used for treatment of amebiasis
  - **Less toxic derivate dehydroemetin is still used**
- Konesin – alcaloid from *Holarrhena antidysenterica* was used in India for treatment of *Entamoeba histolytica* a *Trichomonas vaginalis*

DERIVATES OF QUININE

- Quinine = 8-(4-amino-1-methylbutylamino)-6-methoxychinolin
- Quinidine = D-isomer of quinine
- Meflochin = 4-chinolinemethanol (LARIAM, MEPHAQUIN, tbl. 250 mg báze)



Chinin



Meflochin

MEFLOCHIN

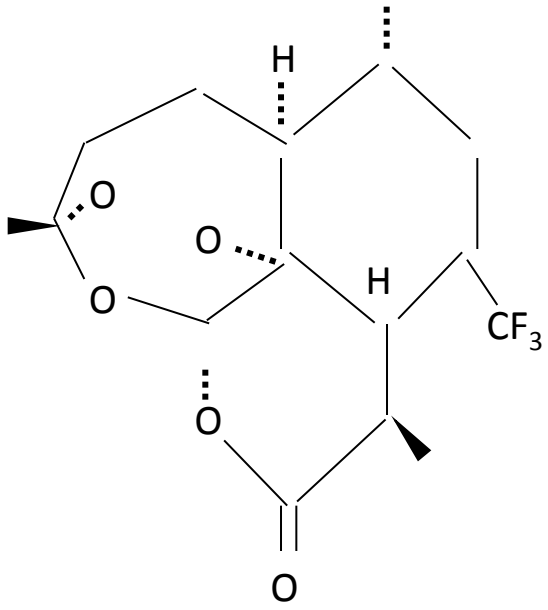
- Mechanism of effect: inhibition of Hb detoxification in a food vacuole
- Fast absorbtion from GIT, 98% binds to plasma proteins, $T_{1/2}$ = 21 days, elimination by bile
- Indication: *Plasmodium sp.*: schizontocide (uncomplicated malignant malaria resistent to chloroquine), gametocide (*Pl. vivax, ovale, malariae*), prophylaxis of malaria
- Side effects: GIT (nausea, vomiting, diarrhoea), headaches, defects of coordination, vertigo, halucinations; rash, pruritus, bradycardia, nightmares
- Contraindication: epilepsy, psychic disorders, retinopathy, pregnancy, lactation; severe malfunction of liver and ren
- Drug interactions: increased effect of peroral anticoagulans and cardioglycosides, primachine increasing its plasma levels; increased risk of sinus bradycardia when treating with quinine, quinidine, halophantrine, beta-blocators, Ca^{2+} blocators

QUININE

- Mechanism of effect: inhibition of Hb detoxification in a food vacuole
- Indication:
  - *Plasmodium sp.*: schizontocide, gametocide(*Pl. vivax, ovale, malariae*), prophylaxis of malaria
  - Complicated malignant malaria resistent to chlorquinine
  - Babesiosis
- Side effects: hypoglycaemia, vertigo, tinnitus, visual disturbances
- Contraindications: bradycardia, AV blockage, decompensated heart insuficiency, intoxication with digoxine, pregnancy (except for vital indication)
- Drug interactions: increase effect of peroral antikoagulans and peripheral myorelaxans, increase plasma levels and toxicity of digoxine a meflochine, ritonavir increase its plasma levels and toxicity
- Dosage: 20 mg/kg in a first dose, after 10 mg/kg á 8 h.

DERIVATES OF ARTEMISINES

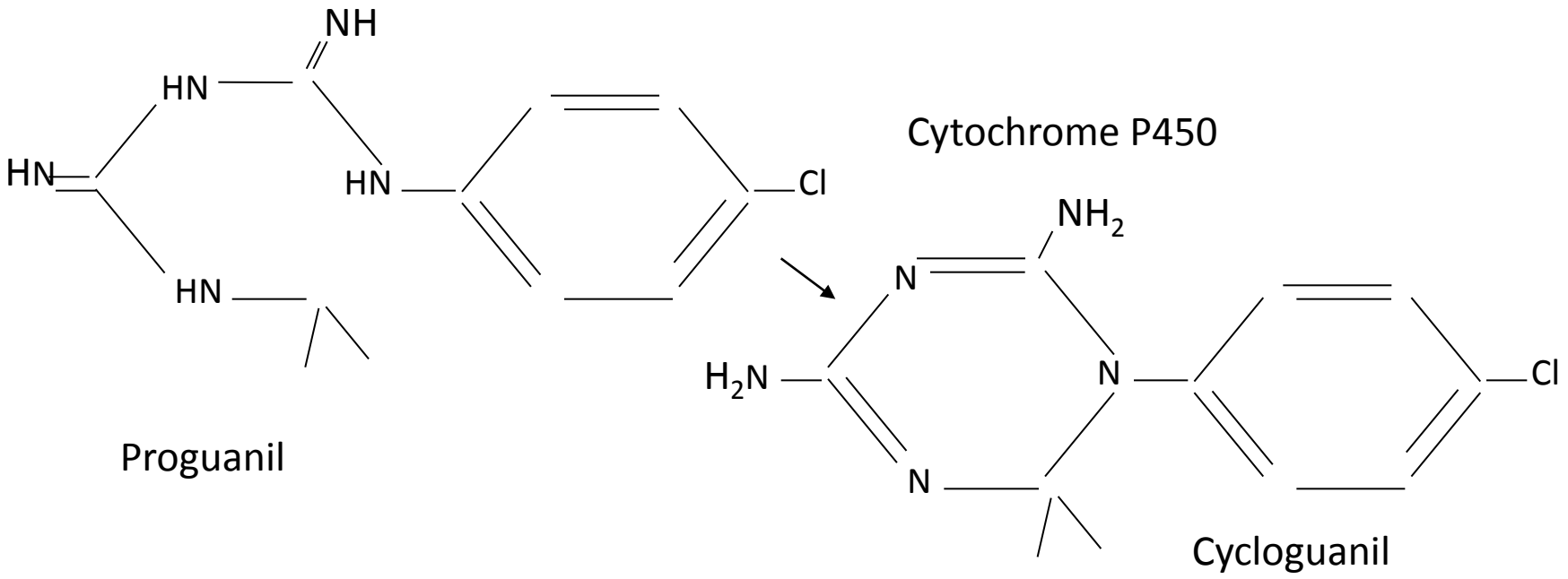
- Dihydroartemisinine
- Artemether
- Arteether
- Artesunate



Artemisinin

DERIVATES OF GUANIDINE

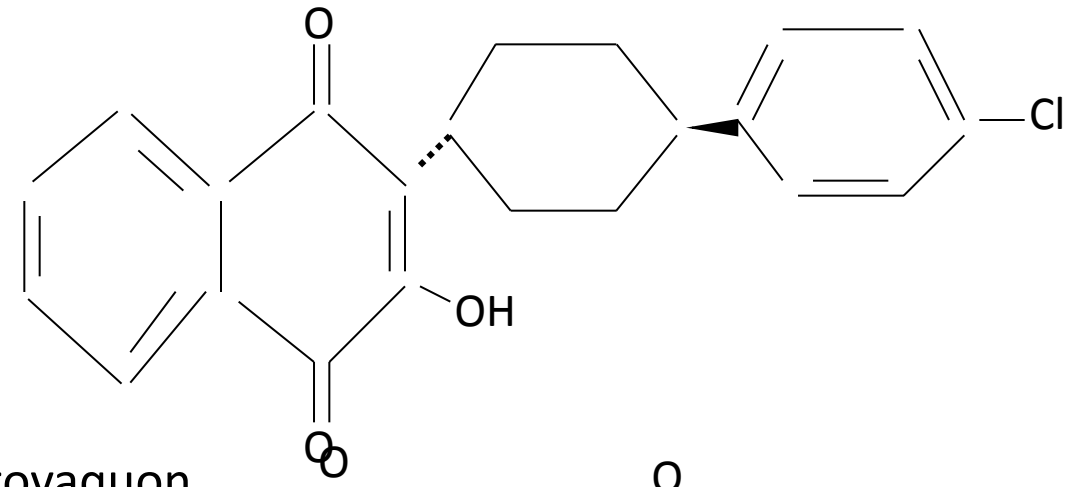
- Proguanil = 1-(4-chlorfenyl)-5-isopropylbiguanid (PALUDRINE, tbl. 100mg)
- Cykloguanil
- Chlorproguanil



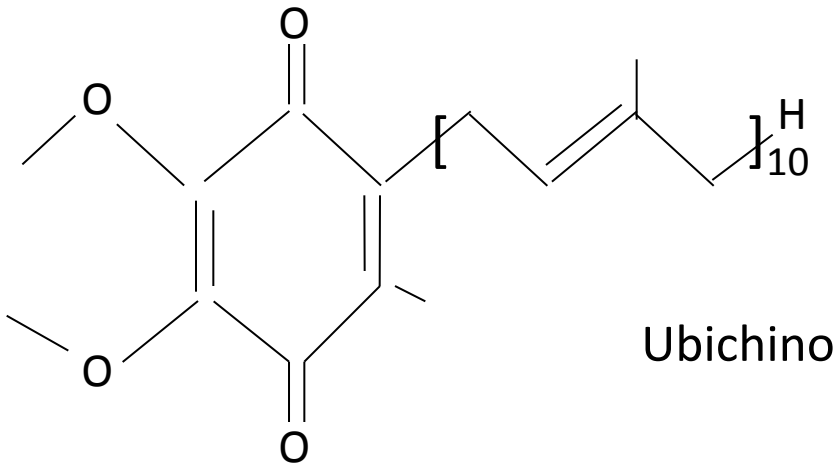
PROGUANIL

- Mechanism of effect: inhibition of dihydrophalate dehydrogenase
- Good absorbtion from GIT, $T_{1/2}$ = 12-16 hrs., metabolised in liver, eliminated by bile
- Indication: prophylaxis of malaria
- Side effects: GIT, stomatitis, granulocytopeania, hrombocytopenia
- Contraindication: severe nephropathy
- Drug interactions: increasing the effect of peroral anticoagulans

HYDROXYNAFTOCHINONY



Atovaquon



Ubichinon

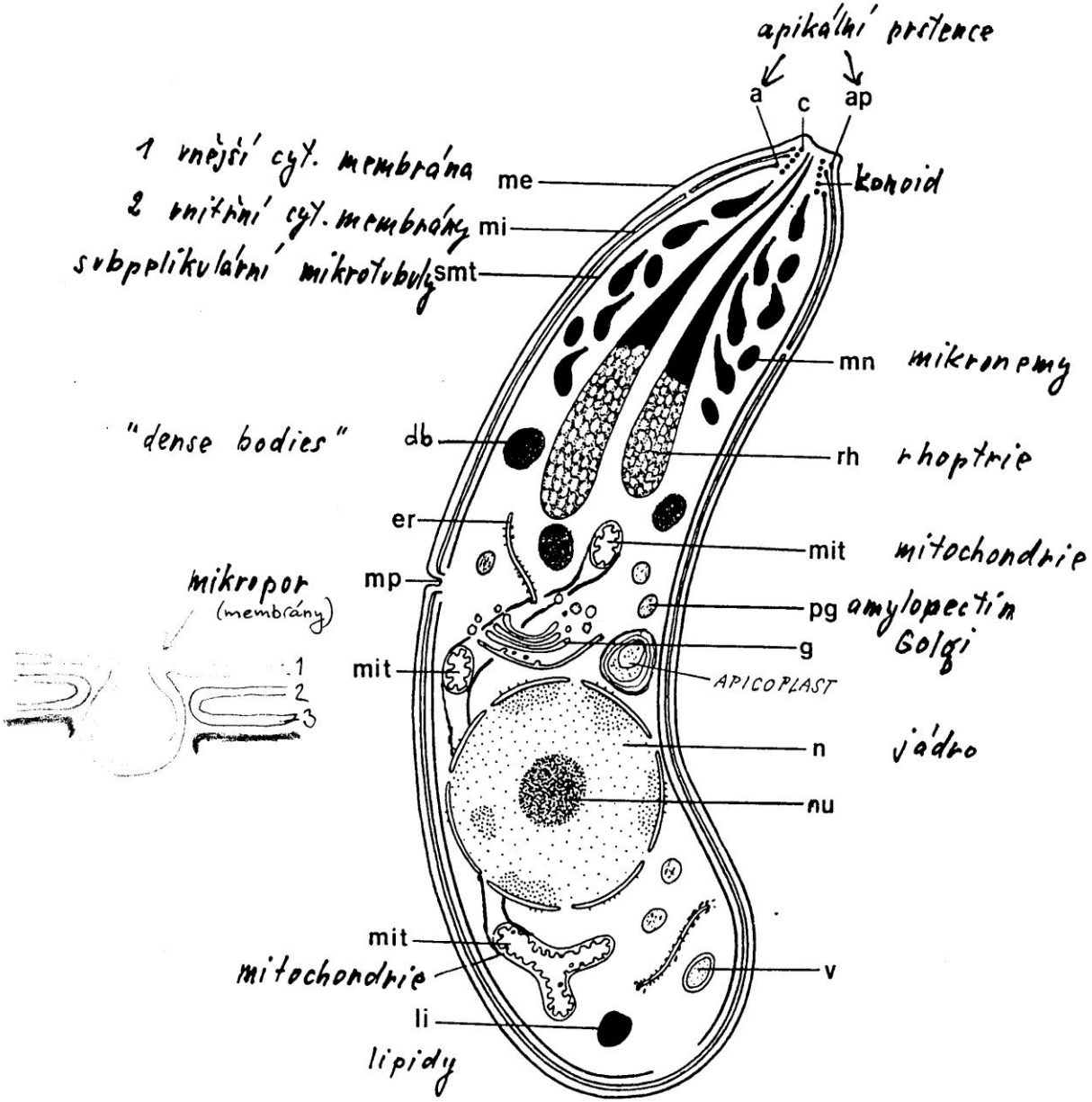
ATOVAQUON

- Mechanism of effect: blocking the transport of electrons in respiratory chain
- Good absorbtion from GIT
- Indication: therapy and prophylaxis of malaria resistent to chloroquine, toxoplasmosis (effective in tissue cysts?); pneumocystosis
- Side effects: GIT (nausea, vomiting, diarrhoea); rash (20%); headache; anemia, neutropenia, hypotension
- Contraindication: pregnancy, careful in people above 65 years
- Drug interactions: metoclopramide a rifampicin are decreasing its plasma levels

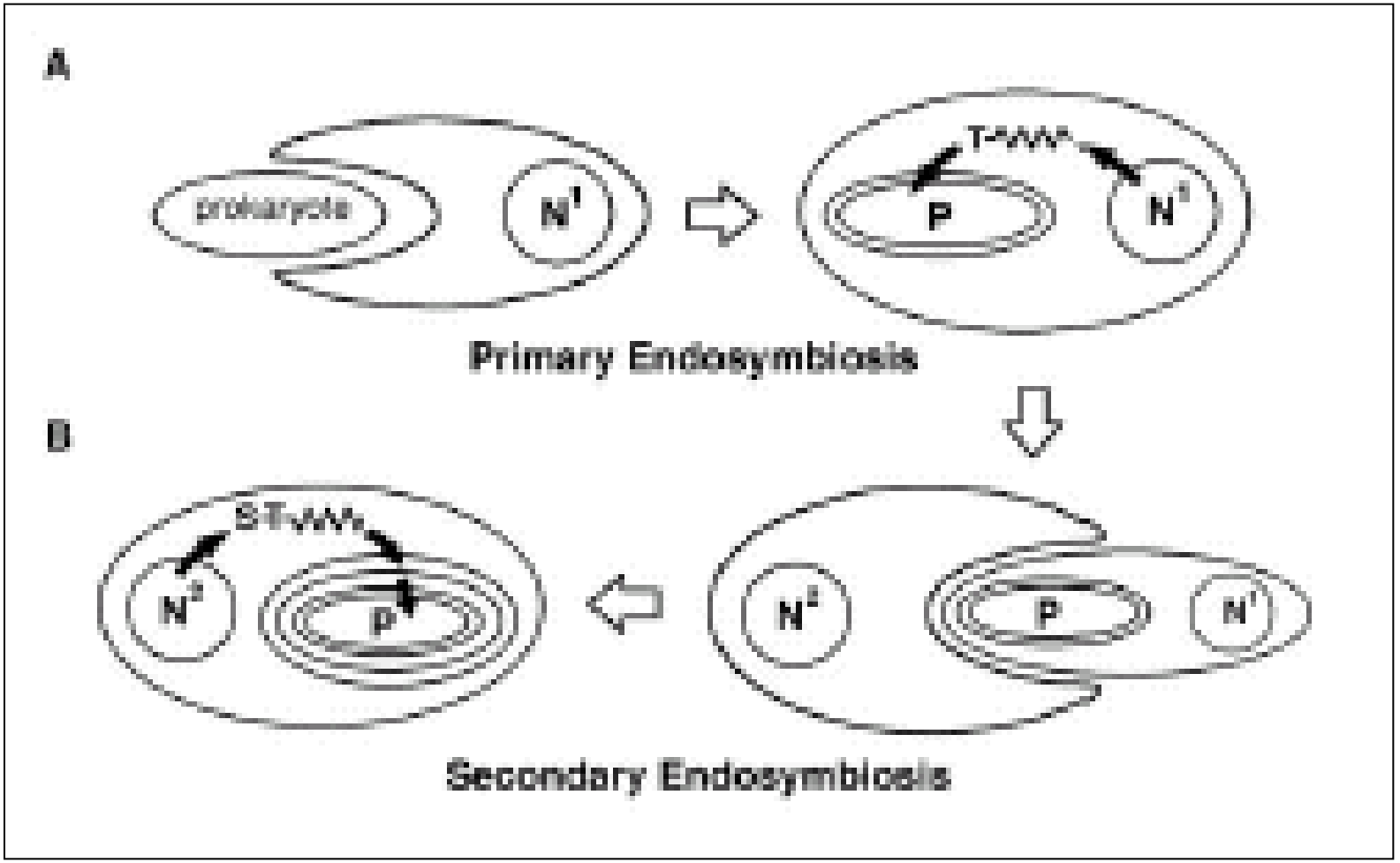
ANTIBIOTICS WITH ANTIMALARIAL EFFECT

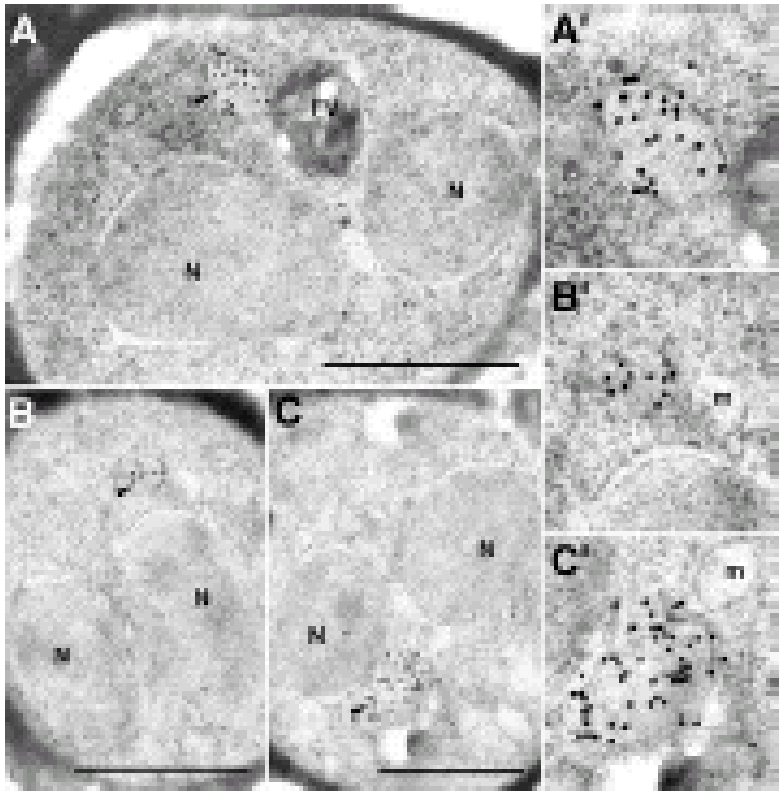
- Tetracyklines
  - Doxycykline (DEOXYMYKOIN, DOXYBENE)
- Makrolides
  - Spiramycin (ROVAMYCIN)
  - Azitromycin (SUMAMED)
- Clindamycine (DALACIN)
- Rifampicine

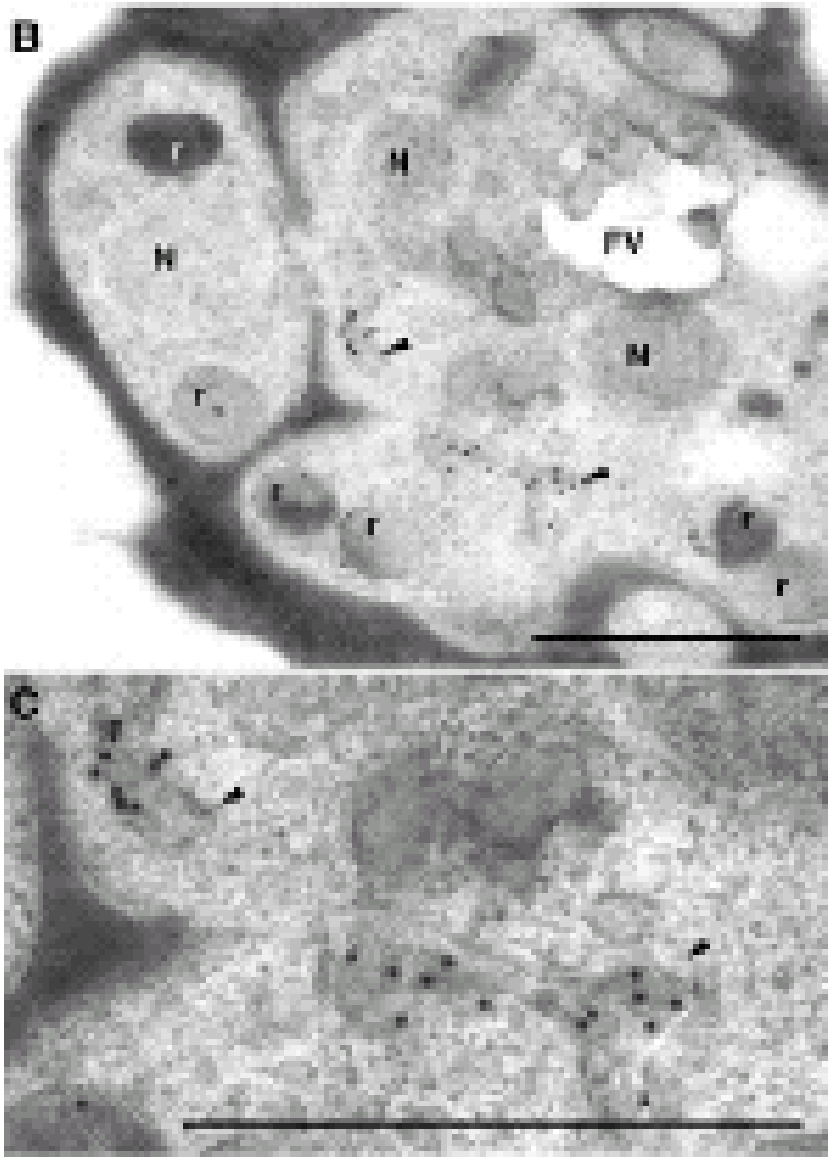
APICOMPLEXAN CELL - ULTRASTRUCTURE



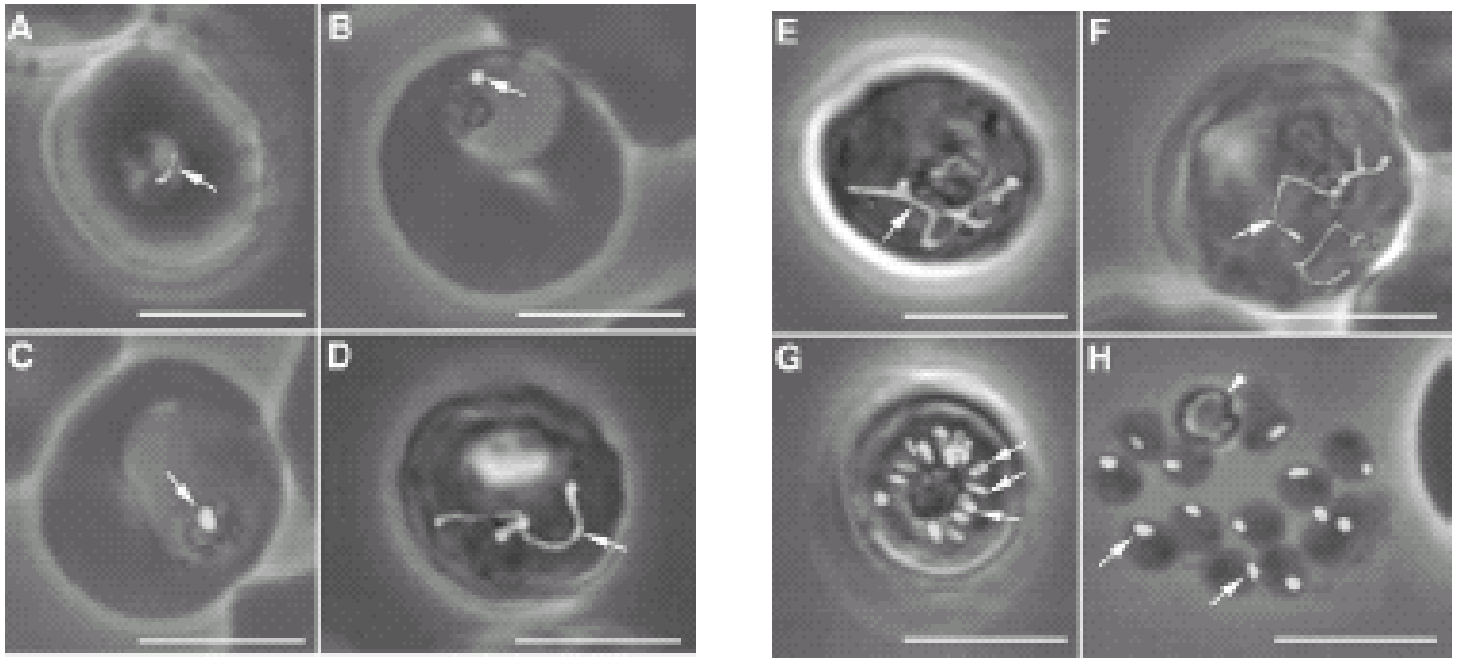
ENDOSYMBIOTIC THEORY





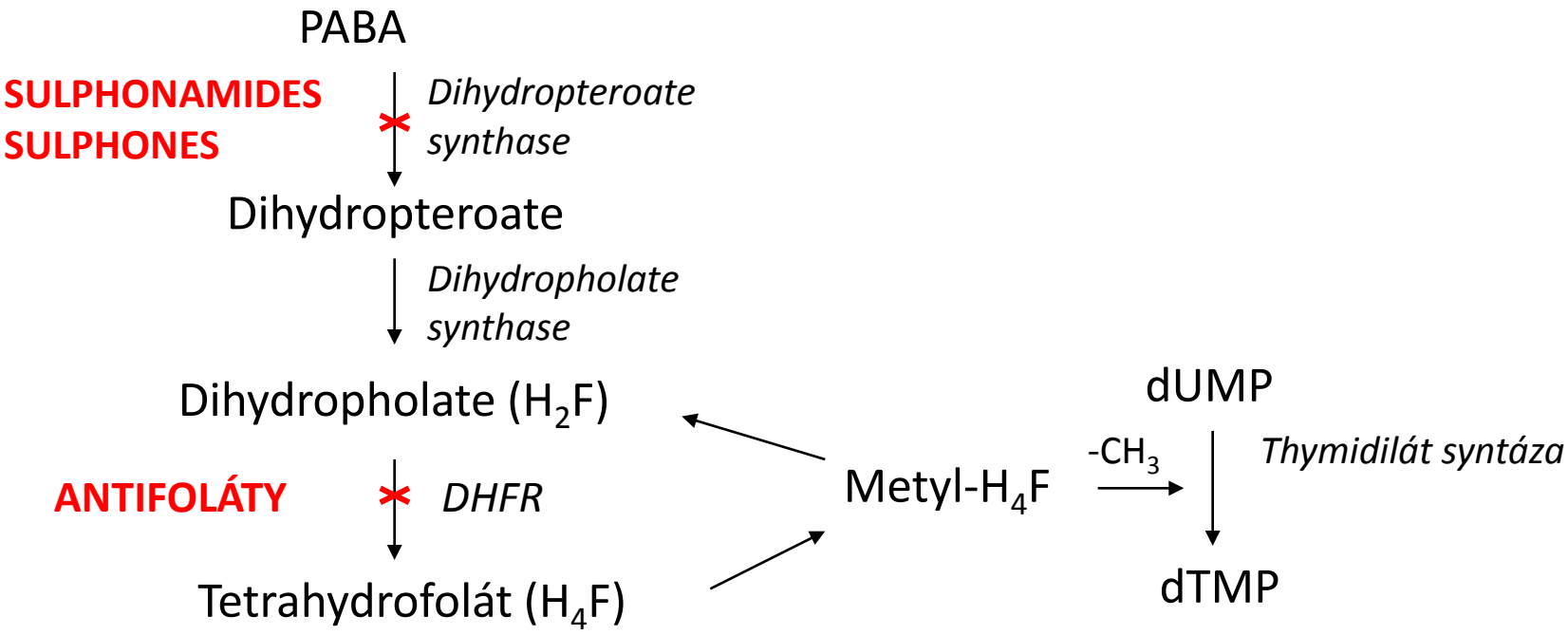


APICOPLAST – EM (gold labeling)



APICOPLAST morphology during life cycle of *P. falciparum* in RBC

ANTIPHOLATES



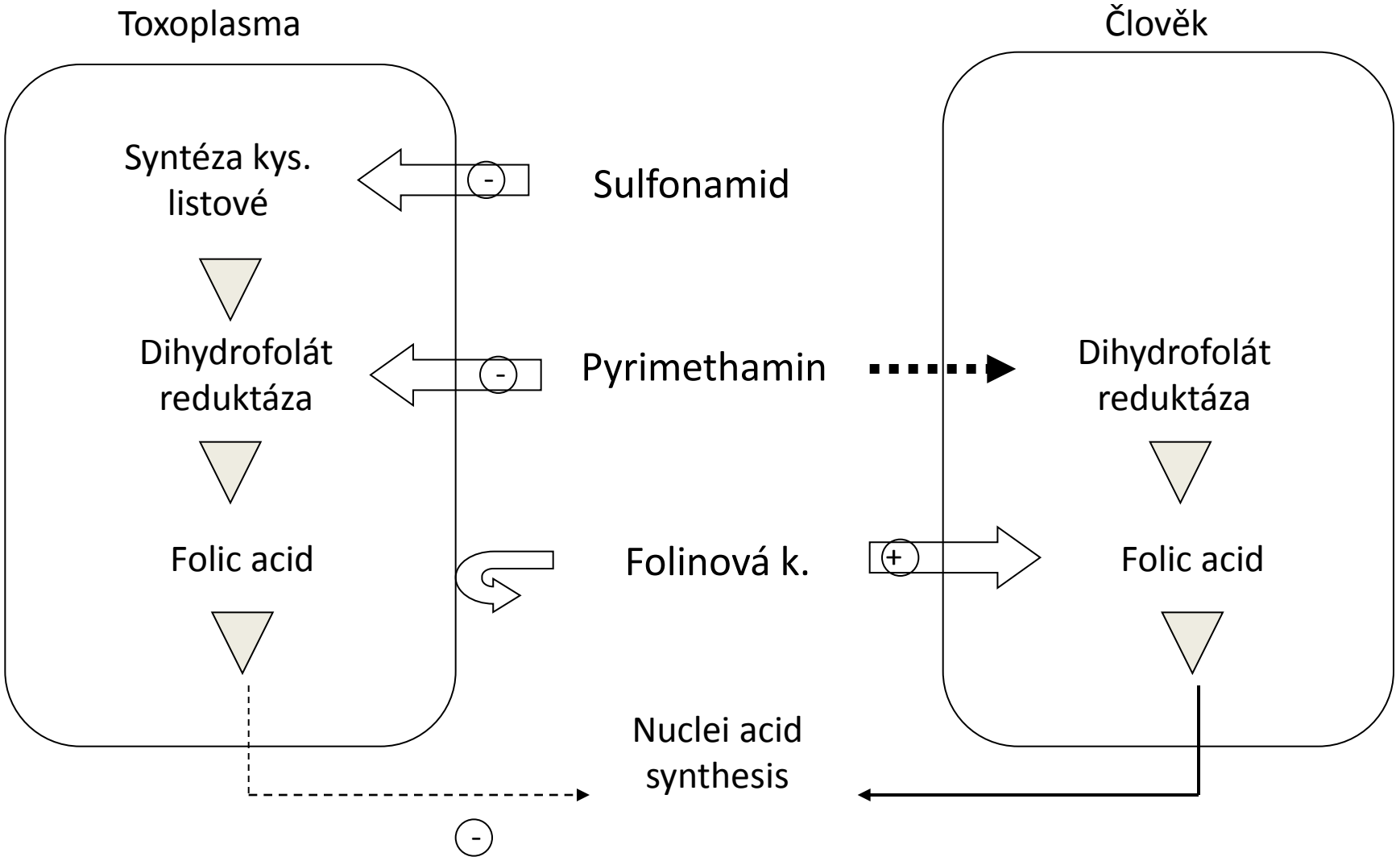
INHIBITORY DHFR:

Trimethoprim
Pyrimethamin
Trimetrexát Piritrexim

SULFONAMIDY, SULFONY:

Sulfametoxazol
Sulfadiazin
Sulfadoxin
Dapson

Effect of antipholates



Therapy of malaria

Species	Antiparoxysmal	Antirelaps
P. vivax *P. ovale*	Chloroquinum basis 10 mg/kg and 5 mg/kg after 12, 24 a 36 hrs.	Primaquin basis 0,25 mg/kg (0, 375 mg/kg) daily, 14 days
P. malariae	Same	No
P. falciparum chloroquinum sensitive	Same	No
P. falciparum Chloroquinum resistant	Quinine, mefloquin, Fansidar, Malarone, artemisinins, doxycyclins, clindamycin	No

Therapy of tropical malaria

Non-complicated		Complicated	
Mefloquin (LARIAM)	750 – 500 – 250 mg every 8 hrs	Quinine	20 mg/kg i.v. + 10 mg/kg after 8 hours
Atovaquone + proguanil (Malarone)	4 tbl./day for 3 dni	Artesunat	2,4 mg/kg i.v. n. i.m. + 1,2 mg/kg each 12, 24 h + another 3 dni
Qunine sulfate + doxycyclin or clindamycin	10 mg/kg po 8 hrs	Artemether	3,2 mg/kg i.m. + 1,6 mg/kg/day min. 3 days
Pyrimethamin + sulfadoxin (FANSIDAR)	2 - 3 tbl. once		

Development of resistancy against antimalarial treatement

Drug	Therapy since	Resistance
Quinine	1632	1970
Chloroquinine	1945	1957
Proguanil	1948	1949
Pyrimethamine/ sulfadoxine	1967	1967
Meflochine	1977	1982
Atovaquon	1996	1996
Artemisinins	China ancient era 1990	2009

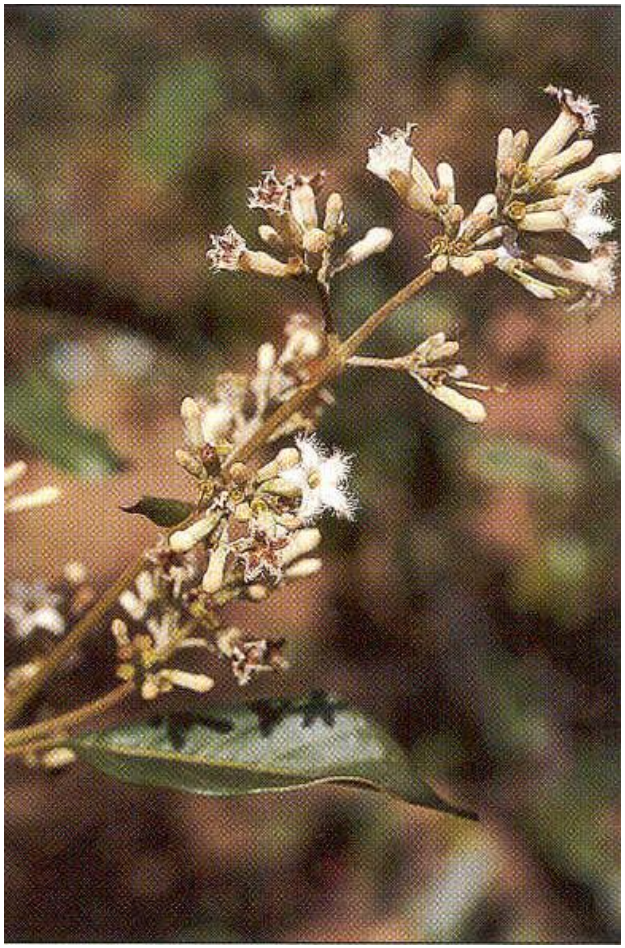
Resistency of plasmodia against antimalaric treatment

- *Pl. falciparum*
  - Chloroquine: sensitive only in the meso America
  - Fansidar: Asia, Africa (especially eastern), South America; sensitivity – Arabian penisula
  - Meflochin: SE Asia (Thailand,Cambodia, Barma, Vietnam), Amasonia only some parts
  - Quinine: decreased sensitivity in SE Asia, subsaharan Africa and Amasonia
  - Artemisinins: resistency described in january 2009 in SE asia
- *Pl.vivax*
  - Chloroquine: Oceania, PNG, some parts of Indonesia, SE Asia, Brasilia, Guayana, Peru, Columbia
  - Primachine: Indonesia, PNG, Western Pacific
- *Pl.malariae*
  - Chloroquine: occasionally Sumatra

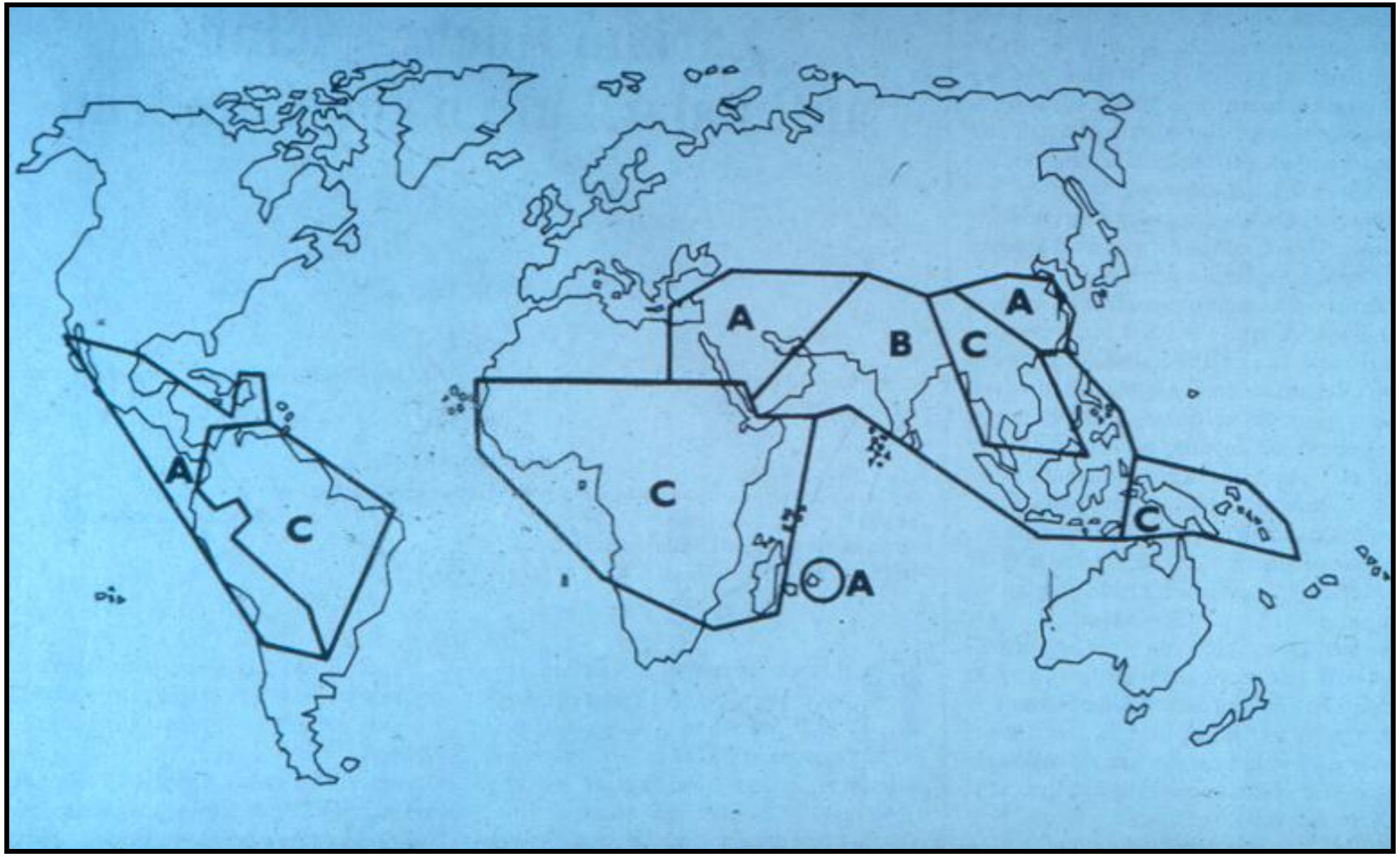
Antimalaric prophylaxis I.

- Depending on the presence and resistency of

  Pl. falciparum
- Always combine with expositional prophylaxis
- Efficiency never 100%, protects from fatal course of the disease
- In the highly endemic areas better inadequate prophylaxis than none prophylaxis



ANTIMALARIAL PROPHYLAXIS – WHO ZONES



Antimalaric prophylaxis II

- Zone A:
  - Meso America, North Africa, Middle East, N. China
  - Chloroquine (DELAGIL) – 2 tbl./week
    - Begin 1 week before travel, continue 4 weeks after return
- Zone B:
  - India, Indonesia
  - Chloroquine + proguanil (PALUDRINE) - 2 tbl./day
    - proguanil: begin 1-2 days before and continue 4 weeks after return
- Zone C:
  - Trop. Africa, S America, SE. Asia, Oceania
  - Meflochine (LARIAM) – 1 tbl./week
    - Begin week before travel, continue 4 weeks after return
  - Atovaquon + proguanil (MALARONE) - 1 tbl./day
    - Begin 1 day before travel, continue 7 days after return
  - Doxycykline (DEOXYMYCOIN) – 1 tbl./day
    - SE. Asia – begin 1-2 days before and continue 4 weeks after return

Non-specific prophylaxis

- Mosquito nets
- Repelents
- Insecticides

Recommended repelents

Name	Active compound	Conc	Form	Producer
REPELENT R 378	DEET	15%	water, spray	Astrid, CR
AUTAN	DEET	20%	water, spray, milk, nebulizer	Bayer, Germany
SKIN TASTIC	DEET	16%	spray, milk, nebulizer	SC Johnson, Italy
DIPTEROL	DEET	20%	spray, napkin, stick	Pliva, Croatia