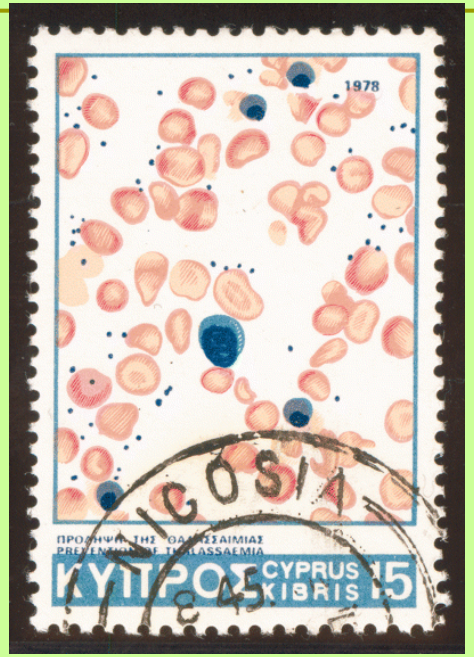
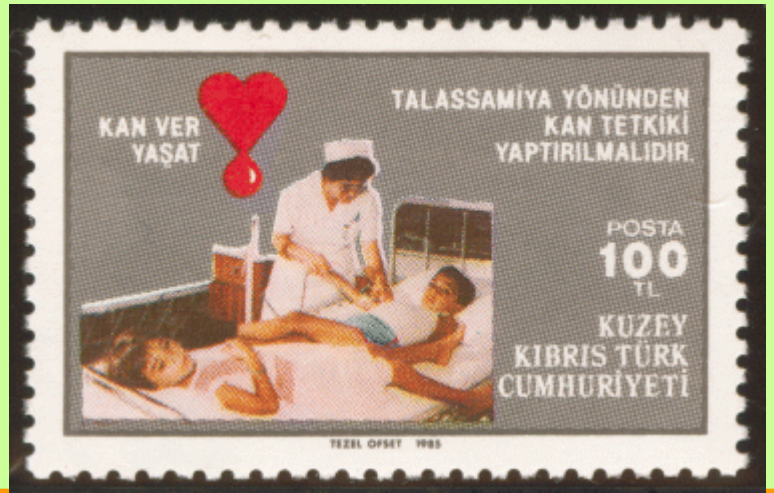
Theories as to why people with sickle cell trait have milder cases of malaria

- The parasite inside the red cell produces **acid**. In the presence of acid, HbS has a tendency to polymerize which causes the cells to sickle. Since sickled cells are destroyed as the blood circulates through the spleen, the parasites are destroyed as well.
- Malarial parasites do not live long under **low oxygen conditions**. Since the oxygen concentration is low in the spleen, and since infected red cells tend to get trapped in the spleen, they may be killed there.
- Another thing that happens under low oxygen conditions is that **potassium leaks** out of HbS-containing cells. The parasite needs high potassium levels to develop. This may be the reason the parasite fails to thrive in red blood containing Hb S.

Thalassaemia Trait and Malaria

Willcox M, Bjorkman A, Brohult J. Falciparum malaria and beta-thalassaemia trait in northern Liberia. *Ann Trop Med Parasitol.* 1983;77:335–347





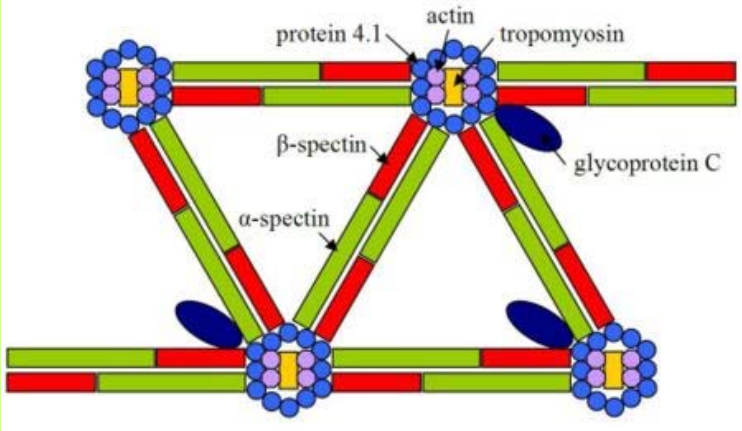
- Carrier of thalassaemia trait make the red blood cells *more* susceptible to the less lethal species *Plasmodium vivax*, simultaneously making the host RBC environment unsuitable for the merozoites of the lethal strain *Plasmodium falciparum*. This is believed to be a selective survival advantage for patients with the various thalassemia traits.
- ß-thalassaemia heterozygotes one-to-four years old appear to have a relative risk of 0.45 for contacting malaria (Willcox 1983)

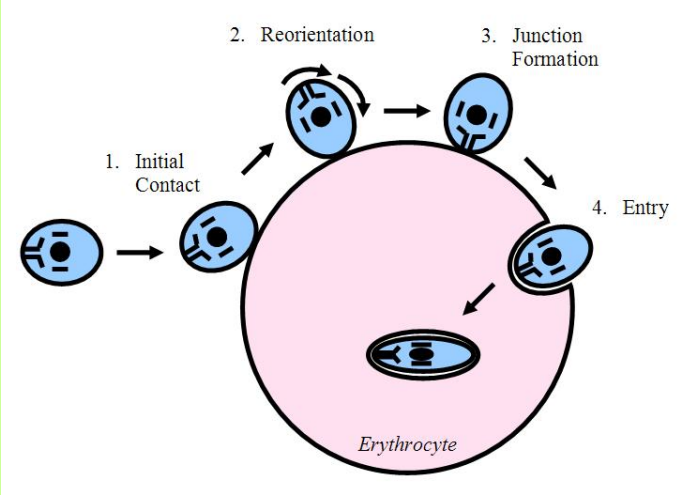
A-Thalassaemia and Malaria

Wambua S, Mwangi TW, Kortok M, Uyoga SM, Macharia AW, et al. The effect of a +-thalassaemia on the incidence of malaria and other diseases in children living on the coast of Kenya . *PloS Med.* 2006;3:e158. doi: 10.1371/journal.pmed.0030158.

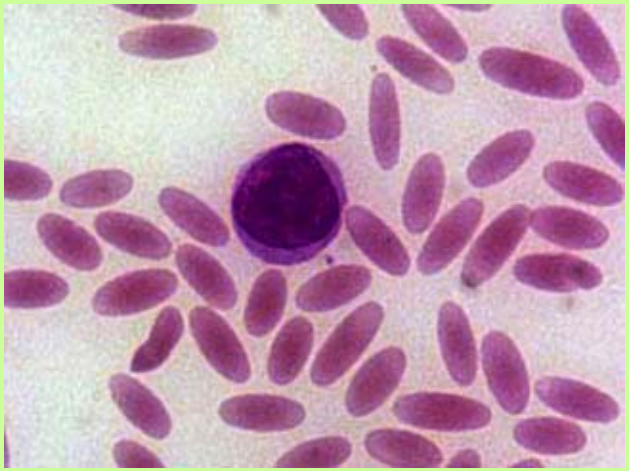
- α +-thalassaemia did not protect against parasitisation in asymptomatic individuals.
- α +-thalassaemia did not protect against symptomatic malaria, nor did it lead to a reduction in the density of parasites in peripheral blood.
- In the birth cohort, there was reduced admission to hospital of α +-thalassaemic children with malaria or severe malaria.
- Thalassaemia provided no protection against cerebral malaria unless accompanied by anaemia—**the protection by α +-thalassaemia appeared to be mainly confined to severe anaemia.**

Hereditary Elliptocytosis and Southeast Asian ovalocytosis and Malaria



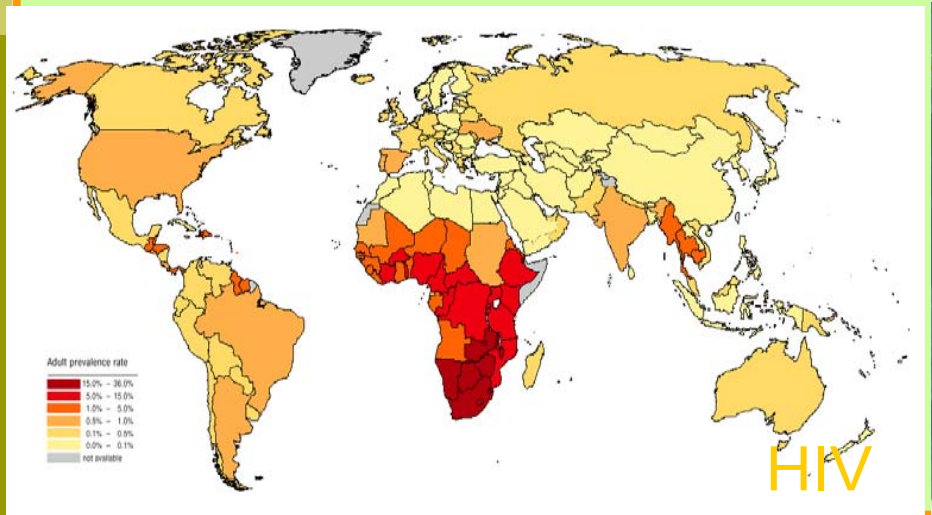


- Some mutation of elliptocytosis are due to glycophorin C deficiencies Plasmodium falciparum has a surface protein called erythrocyte-binding antigen 140, which is now known to bind to glycophorin C.
- Southeast Asian ovalocytosis reduce the capacity of the band 3 proteins to cluster together, thereby making it more difficult for the malaria parasite to properly attaching to and enter the cell.

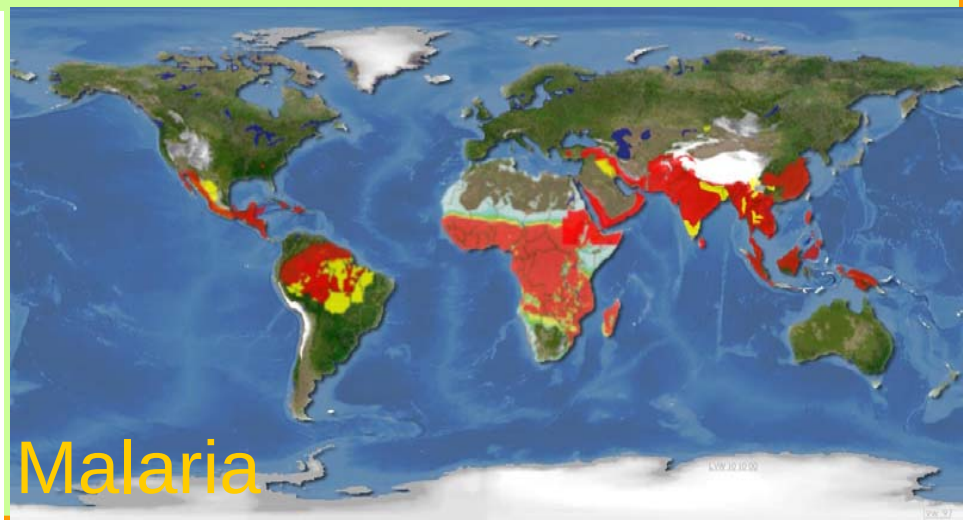


Malaria and HIV disease in sub Saharan Africa

- Malaria and HIV are leading causes of morbidity and mortality, particularly in sub Saharan Africa
- Both diseases are highly endemic and have a wide geographic overlap
  - A small effect of malaria on HIV or vice-versa could have substantial population-level implications



HIV

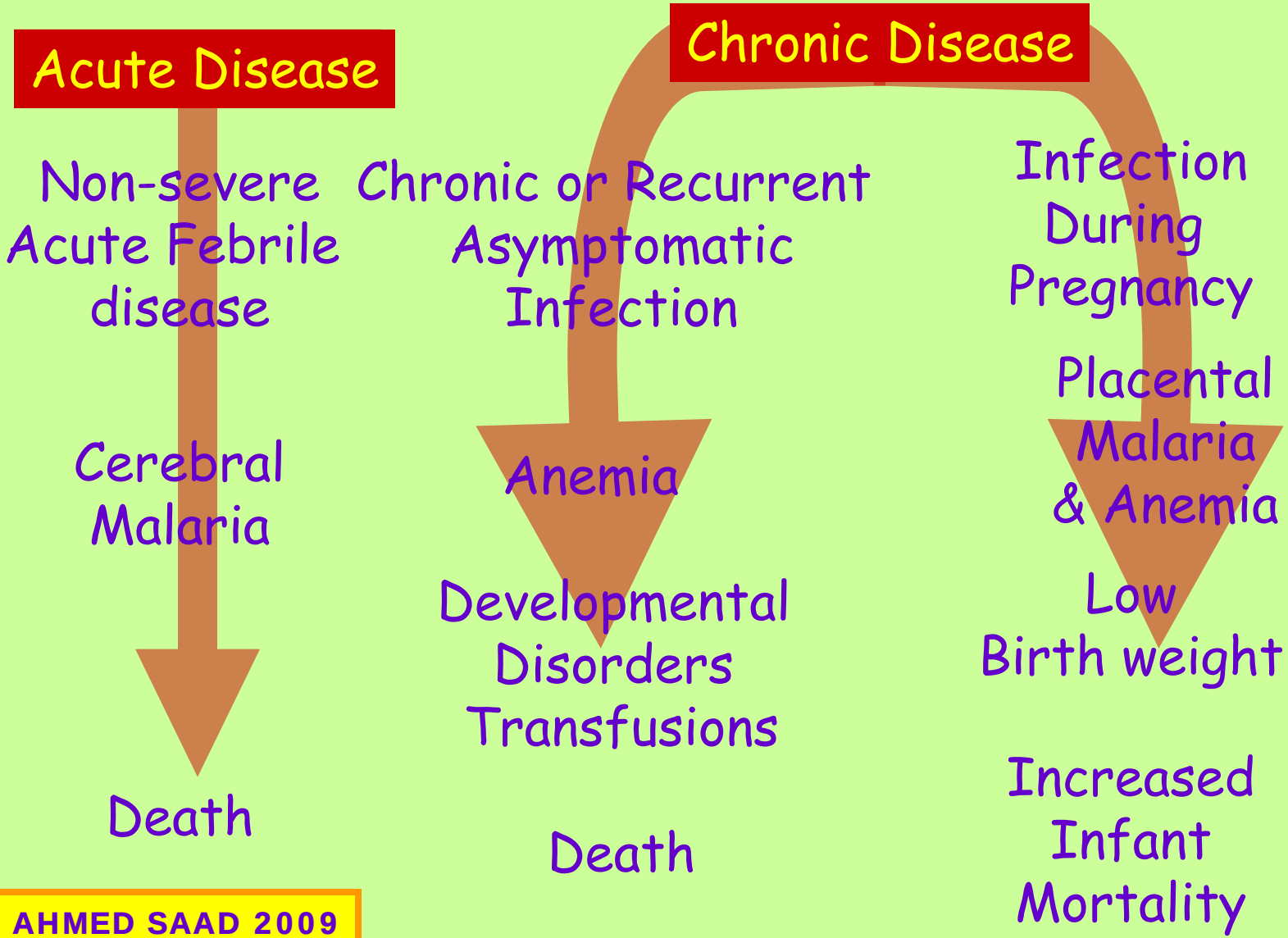


Malaria

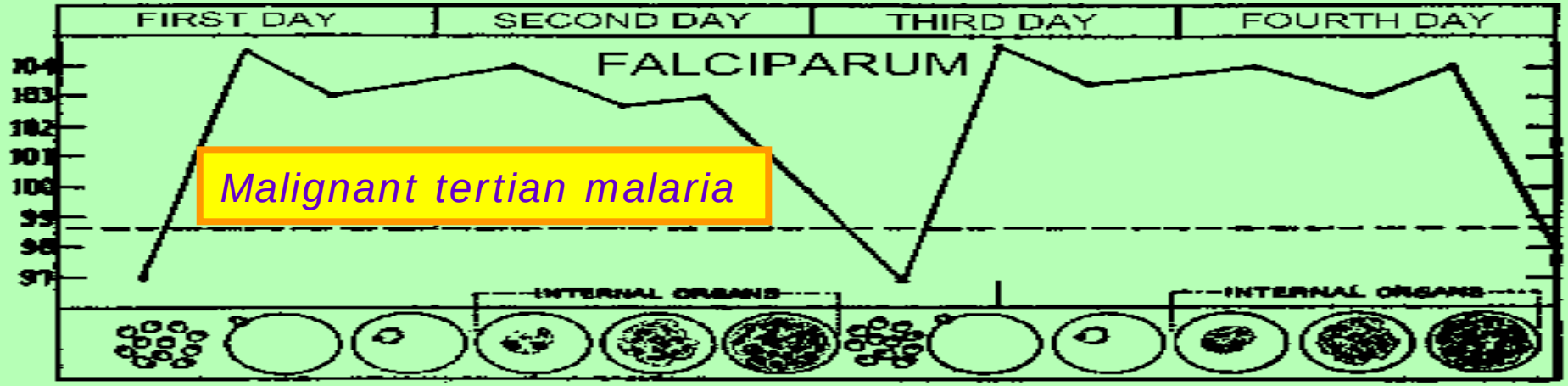
Malaria and HIV biologic interactions

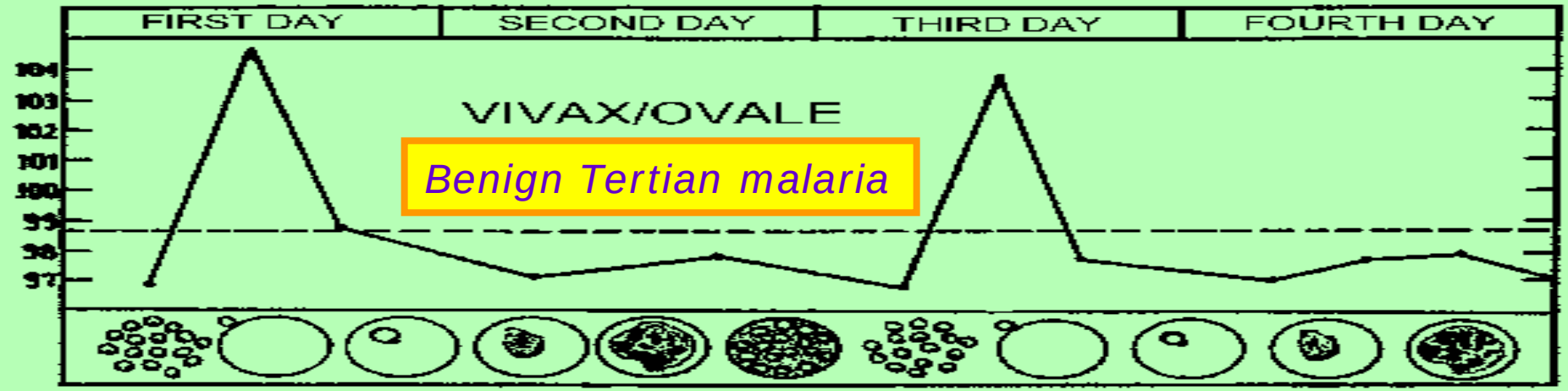
- HIV-associated immunosuppression contributes to more and worse malaria and it's consequences in adults, pregnant women, and children.
- Malaria contributes to stimulus of HIV replication and possibly(?) to its consequences: disease progression, transmission in adults, and MTCT.
- Co-infection with Malaria and HIV in pregnant women contributes to anemia, low birth weight,and their risk for poor infant survival.
- Malarial anemia in children too frequently requires blood transfusion and may still lead to HIV transmission

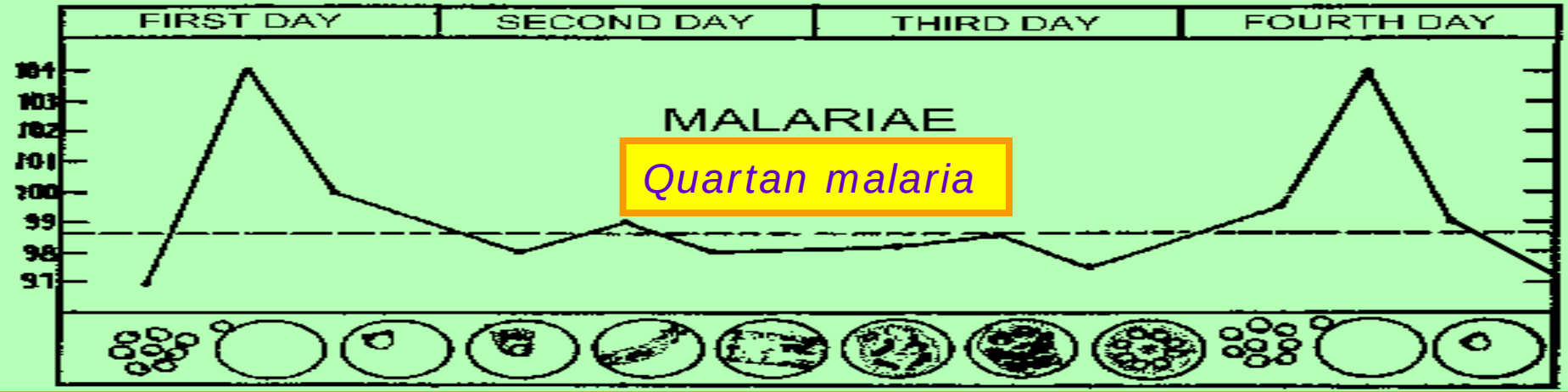
MALARIA – clinical syndromes

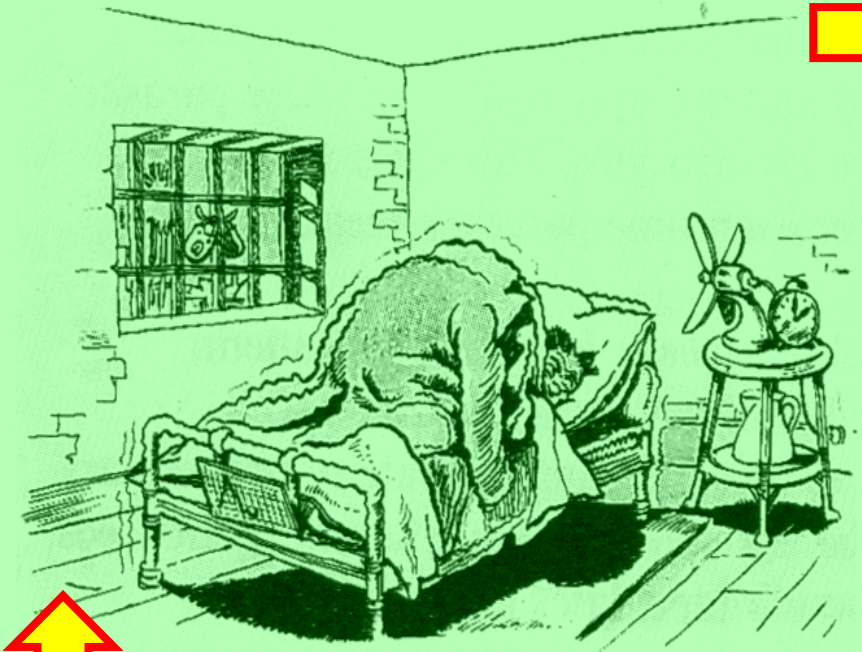


DR AHMED SAAD 2009


FIRST DAY
SECOND DAY
THIRD DAY
FOURTH DAY
FALCIPARUM
Malignant tertian malaria
INTERNAL ORGANS
INTERNAL ORGANS


FIRST DAY
SECOND DAY
THIRD DAY
FOURTH DAY
VIVAX/OVALE
Benign Tertian malaria

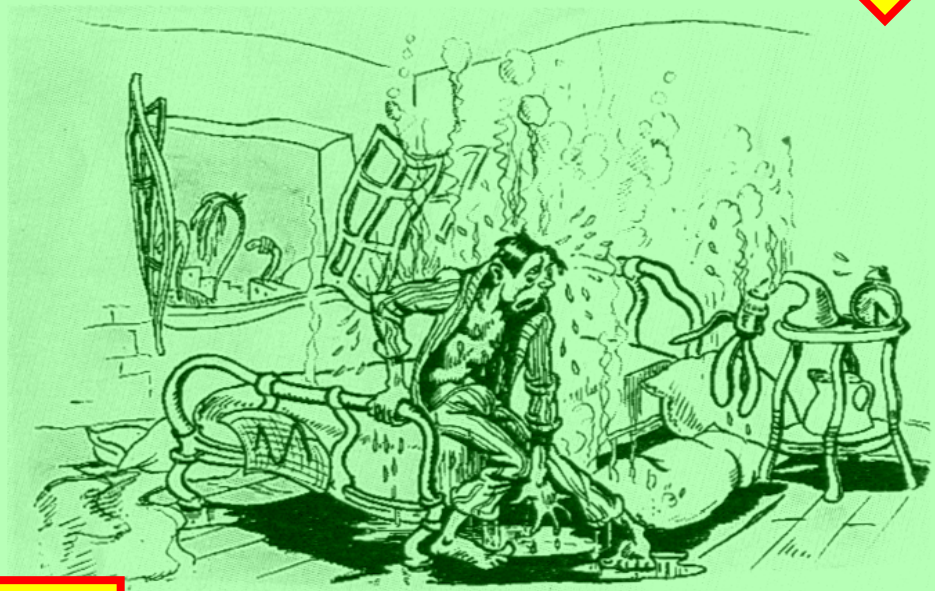

FIRST DAY
SECOND DAY
THIRD DAY
FOURTH DAY
MALARIAE
Quartan malaria



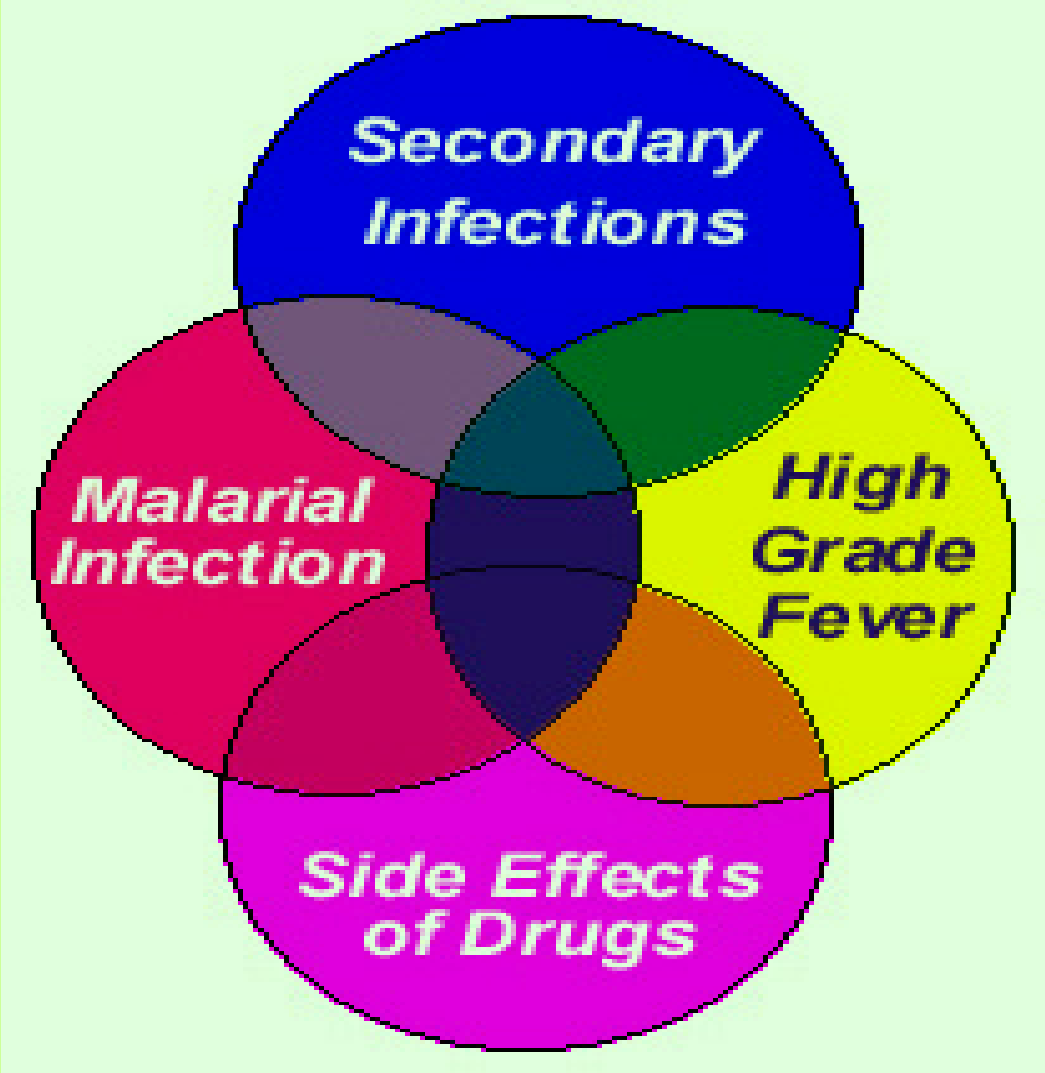
The cold stage

The hot stage

The patient may not appear to be very ill



The sweating stage



Etiologies of Fever In Malaria

Symptoms of Malaria

Central
- Headache

Systemic
- Fever

Muscular
- Fatigue
- Pain

Back
- Pain

Skin
- Chills
- Sweating

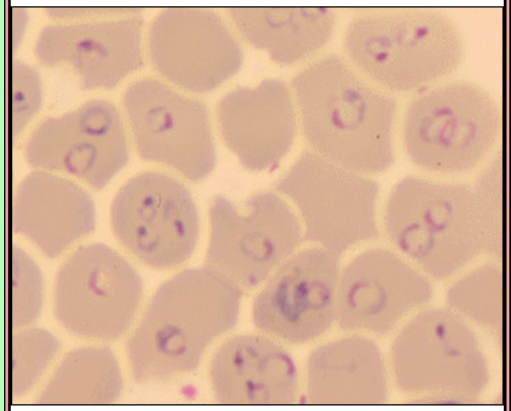
Respiratory
- Dry cough

Spleen
- Enlarge-ment

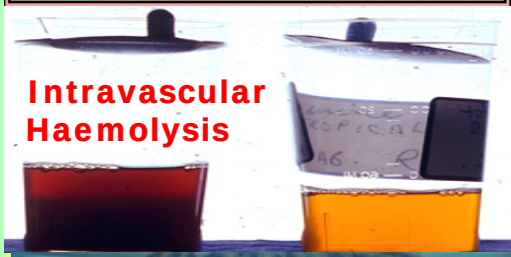
Stomach
- Nausea
- Vomiting

Signs:
- Fever
- Jaundice
- Pallor
- Tachycardia
- Hypotension
- Splenomegaly

Plasmodium falciparum



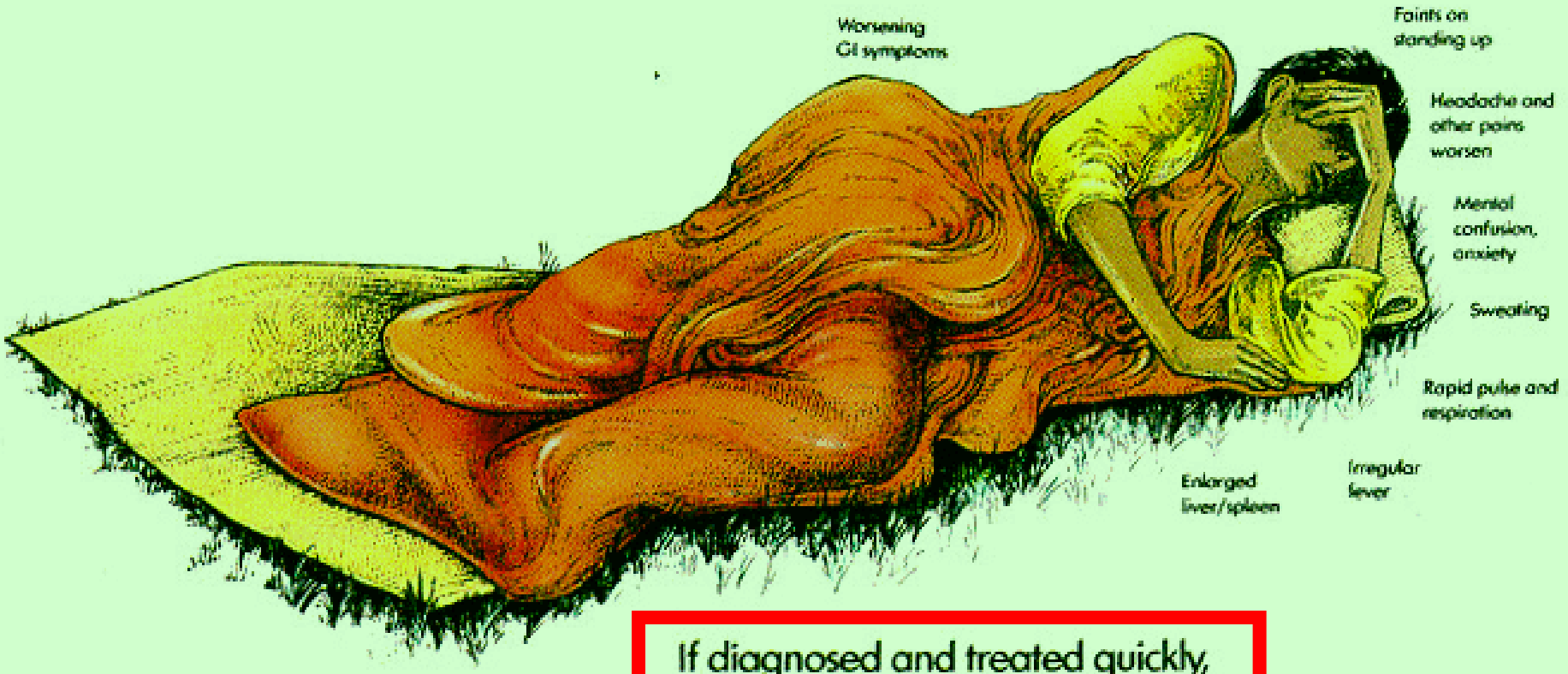
Blackwater Fever



Cerebral Malaria
- Hypoglycaemia should always be excluded

DEVELOPMENT

Symptoms intensify.
New symptoms may appear



If diagnosed and treated quickly, the patient will probably recover

Early Diagnosis and prompt Treatment is necessary

SEVERE MANIFESTATIONS

Cerebral malaria

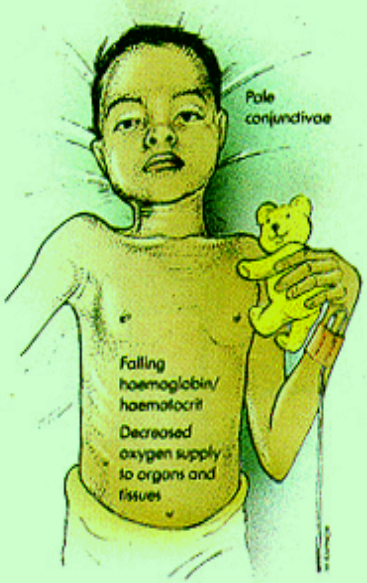
May begin slowly or suddenly

Outcome

- High fatality rate: 20%
- With successful treatment, complete recovery
- Permanent disablement rarely occurs

Severe anaemia

Inevitable consequence of severe infection

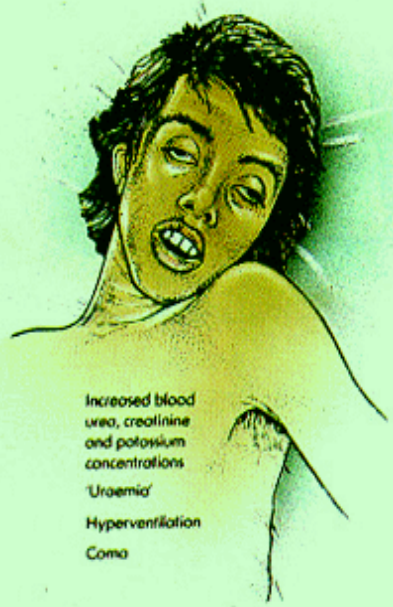


Outcome

- May be fatal unless a blood transfusion is given

Renal failure

Dwindling urine output



Outcome

- Cautious rehydration is effective in most cases
- Peritoneal dialysis may be needed sometimes
- Bad prognosis

Others

- Hepatic dysfunction
- Hypoglycaemia
- Shock ('algid' malaria)
- Pulmonary oedema
- Fluid/electrolyte imbalance
- Vomiting and diarrhoea
- Secondary bacterial infection
- Bleeding and clotting disturbances
- Haemoglobinuria and blackwater fever

High Mortality Rate if Treatment is Delayed

Clinical features suggesting *P. falciparum* infection:

- Presence of any of the complications of *P. falciparum* malaria viz. altered sensorium; convulsions; coma; jaundice; severe anemia; hypotension; prostration; hyperpyrexia; renal failure etc.
- Atypical presentation.
- Not responding to chloroquine therapy within 48 hours.
- Recurrence within 2 weeks.

P falciparum accounts for about 50% of cases but **95% of malarial deaths** worldwide

Plasmodium Falciparum

Increased Parasitemia (> 5% Vs < 2%)

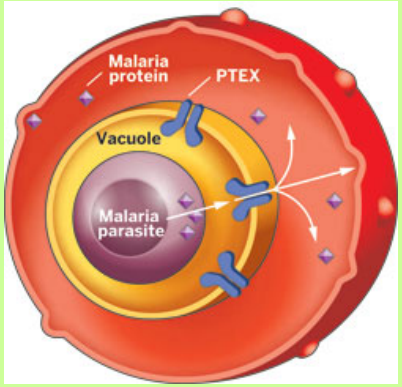
Anaemia & Haemolysis

Renal failure

Proteinaceous Knobs cytoadhere To endothelial cell

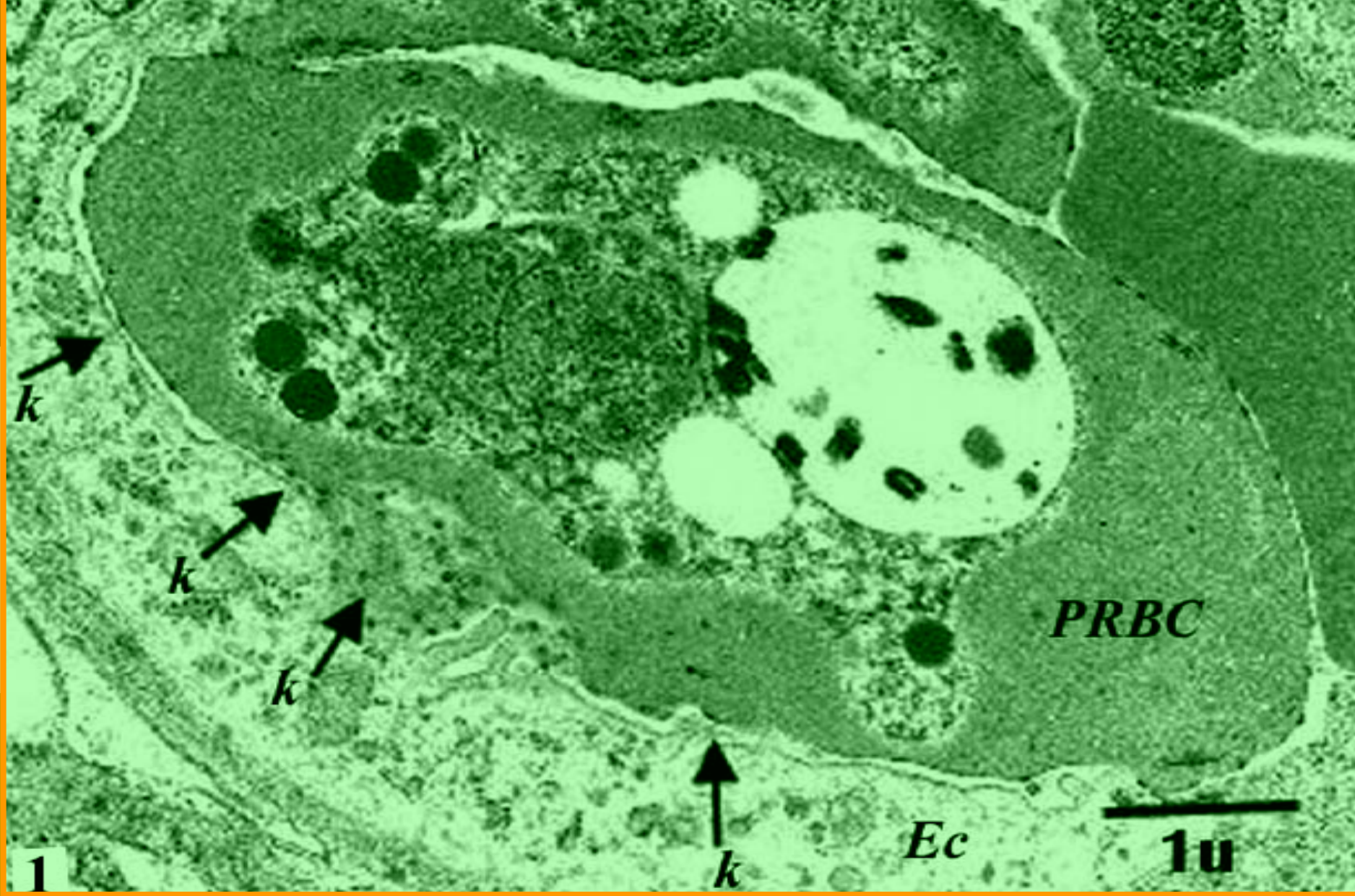
Thrombosis & Ischaemia

Cerebral malaria Pulmonary edema

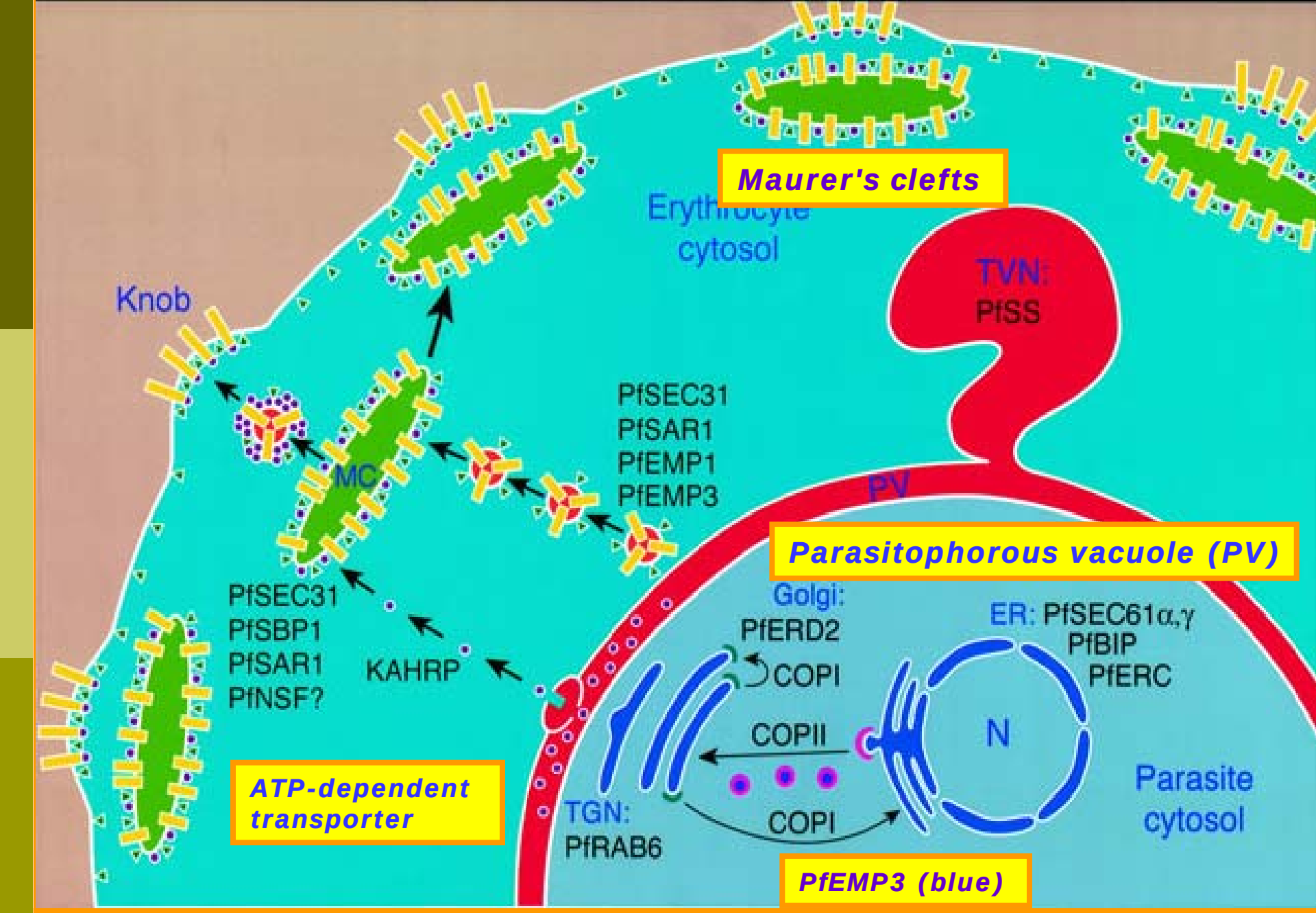


The adhesion prevents the spleen from clearing diseased cells

P vivax and *P ovale* infects only immature RBCs, leading to limited parasitemia



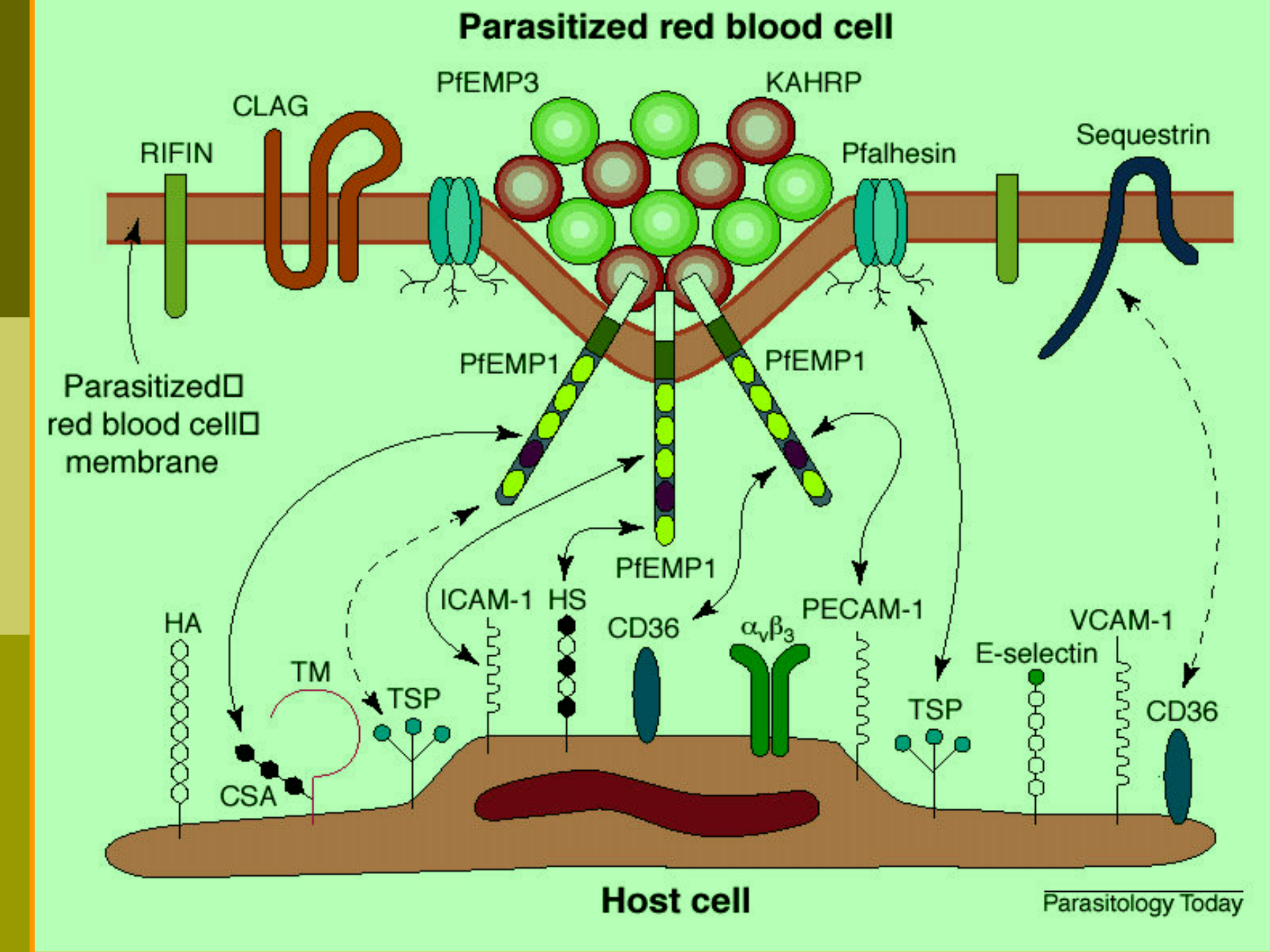
→ Knobs of histidine rich proteins is the points of attachment to endothelial cells



Trafficking of KAHRP to the knobs of P.falciparum-infected erythrocytes

•THE EMBO JOURNAL (2001) 20, 5636 - 5649

Model of PfEMP1 trafficking to the surface of *P falciparum*–parasitized erythrocytes. PfEMP1 and KAHRP carry protein export element (PEXEL) motifs that enable them to traverse the PVM, perhaps in association with specific translocases or helper proteins. In knobs, KAHRP binds the ATS of PfEMP1 and ties it to actin-spectrin-band 4.1 in the cytoskeleton.[5]

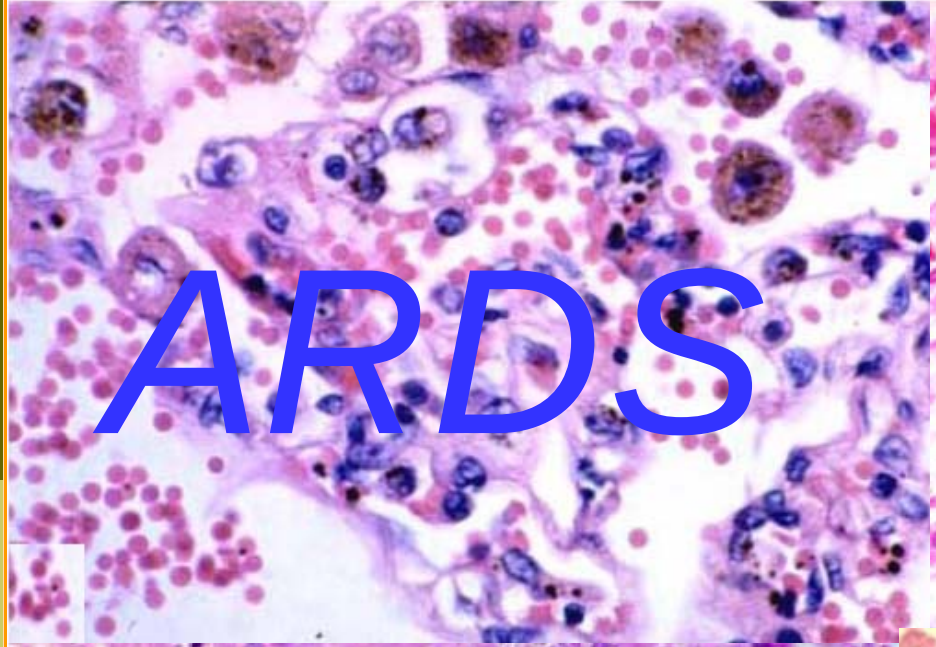

Parasitized red blood cell
PfEMP3
KAHRP
CLAG
RIFIN
Pfalhesin
Sequestrin
Parasitized red blood cell membrane
PfEMP1
PfEMP1
PfEMP1
ICAM-1
HS
CD36
$\alpha_v\beta_3$
PECAM-1
VCAM-1
E-selectin
HA
TM
TSP
TSP
CD36
CSA
Host cell
Parasitology Today

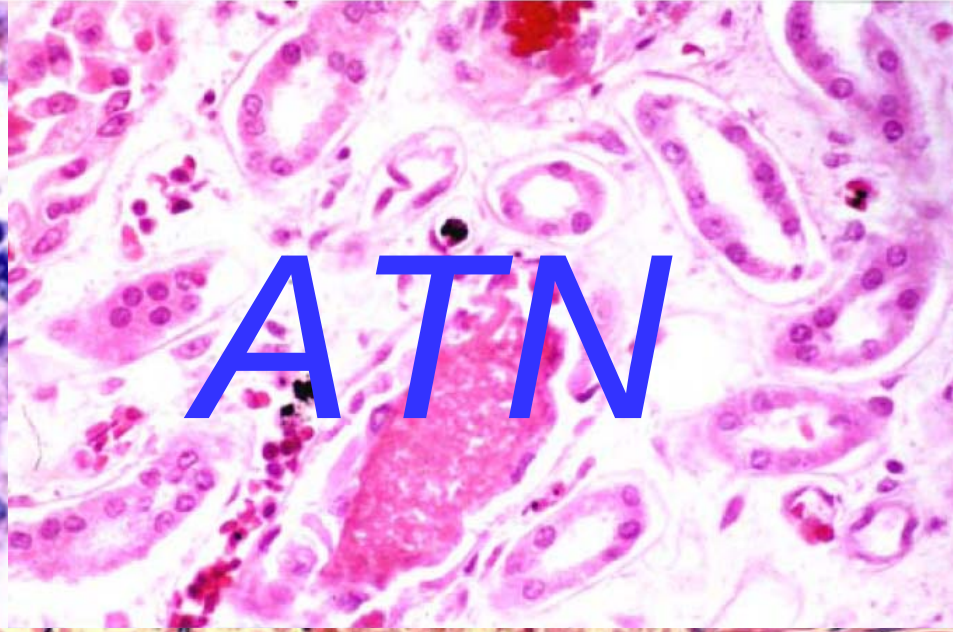
Why is falciparum malignant ?

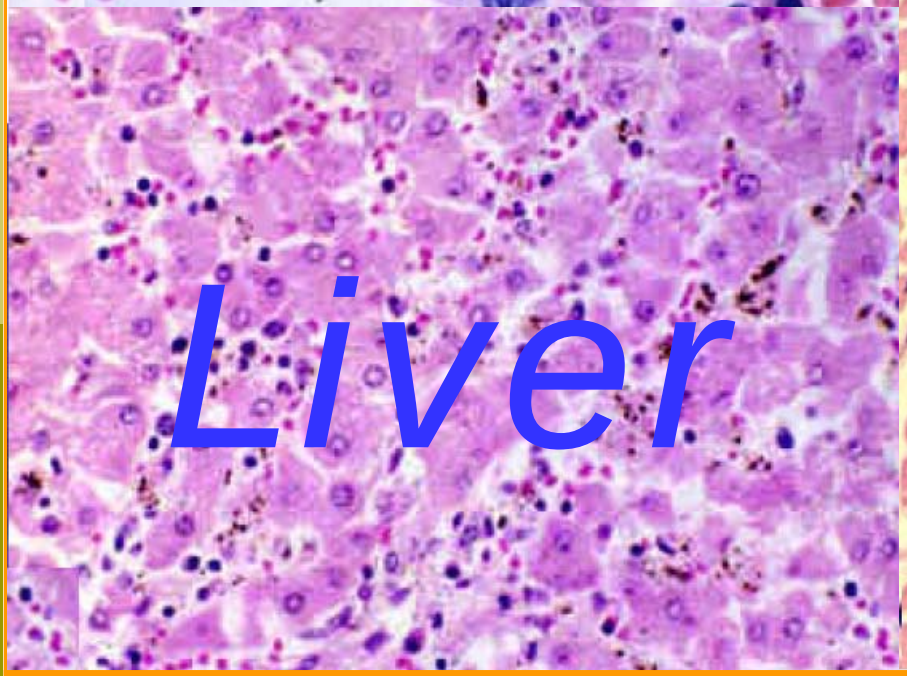
- Each cycle releases 20 times more merozoites than vivax
- Multiple infestation of both mature and immature RBC.
  - **P vivax and *P ovale* infects only immature RBCs, leading to limited parasitemia**
- Early hemolysis and endotoxin release, cerebral toxicity
- Bilirubin load affects kidneys, liver
- Hypovolemia and shock occur
- Usually resistant to Chloroquine

- The parasites derive their energy solely from glucose, and they metabolize it **70 times** faster than the RBCs they inhabit, thereby causing hypoglycemia and lactic acidosis.

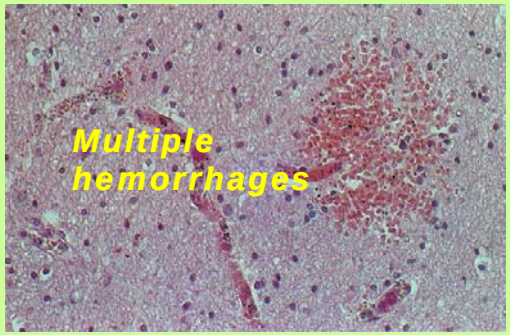
Plasmodium Falciparum:Hyperparasitaemia







Multiple Organ Failure



Cerebral Malaria

(1) *Unrousable coma--no localizing response to pain persisting for more than six hours if the patient has experienced a generalized convulsion;*

(2) *asexual forms of **P. falciparum** found in blood;* and

(3) *exclusion of other causes of encephalopathy, i.e. viral or bacterial.* (Newton and Warrell)

The Blantyre Coma Scale, a related diagnostic tool, has been devised for young children.

Even with appropriate antimalarial therapy and intensive care, 15%–25% of patients die, and mortality may reach 50% if more than 10% of erythrocytes are parasitized

Cerebral Malaria

Mortality 20-50 %
Majority in children <10 yr

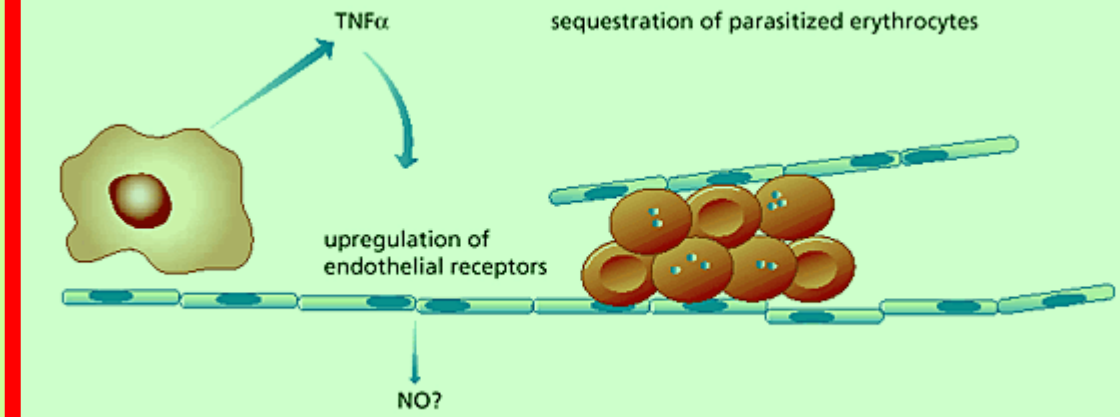
Fatal in 24-72h
If untreated

Plasmodium GPI induces "strong TH1 "over-reaction" (IFN γ and TNF α etc)

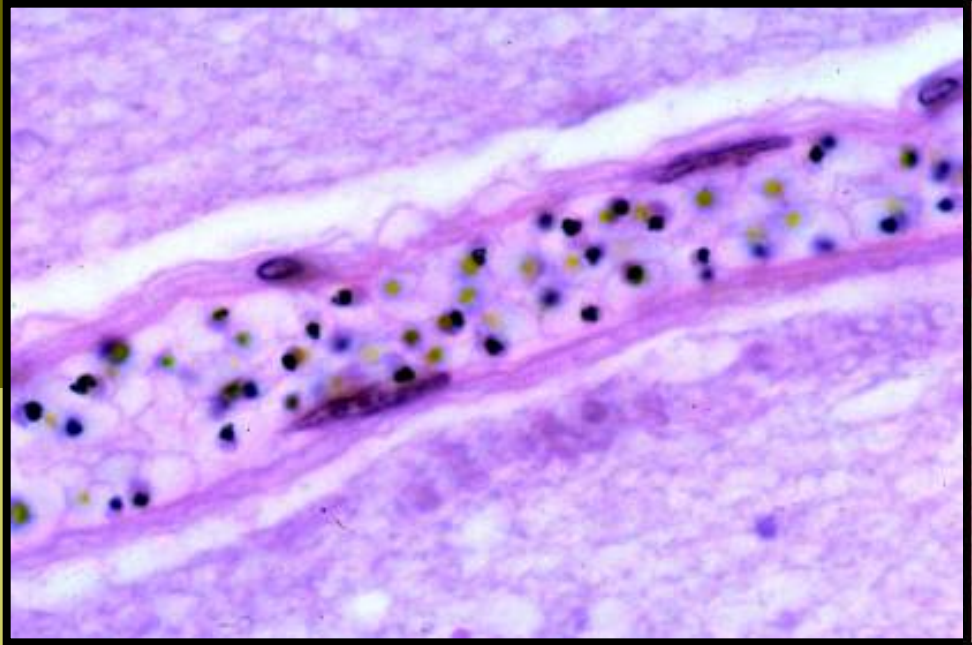
Cytokines
Inducible NO synthase
(potentially reversible)

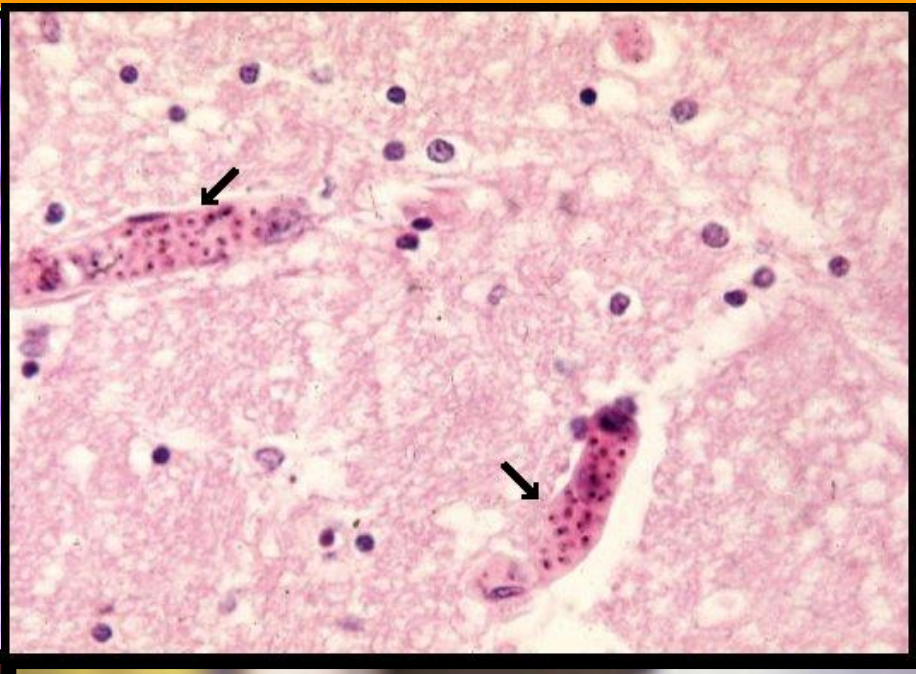
Sequestration of cerebral capillaries and venules with PRBCs & non-PRBCs

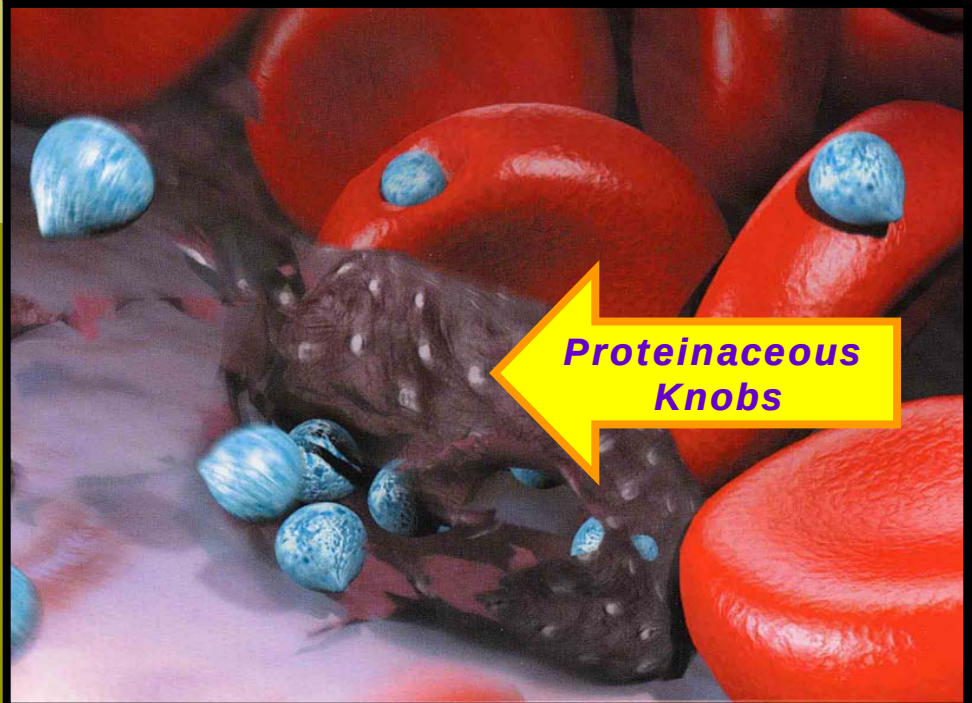
Cytoadhesion
Rosette formation
Platelet clumps
RBC less deformable

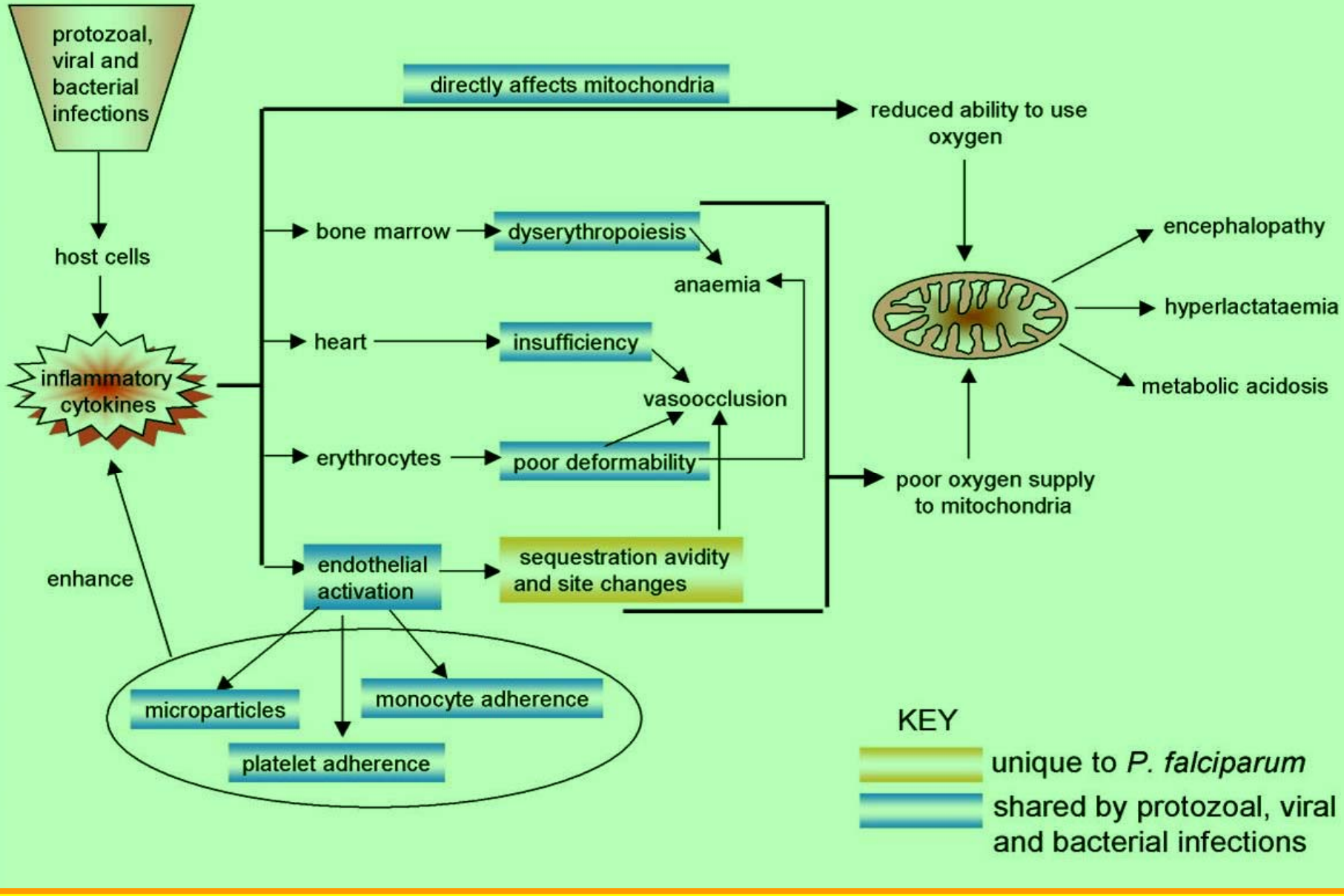


Malaria - Cytoadherence





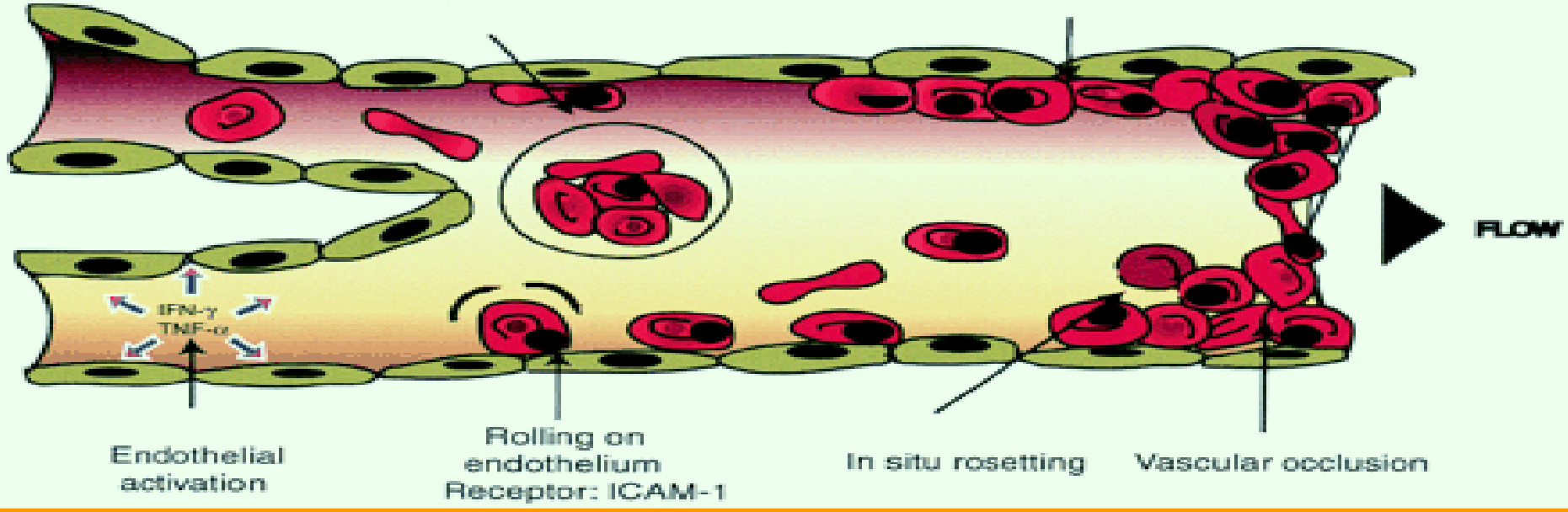




Sequestration of RBC *is unique to the pathogenesis of Plasmodium falciparum infection*

Rosetting
Receptor: Blood group antigens
CD36, CR1 and HS

Endothelial
cytoadherence
Receptor: CD31, CD36, CSA,
E-selectin, ICAM-1,TSP, and VCAM-1

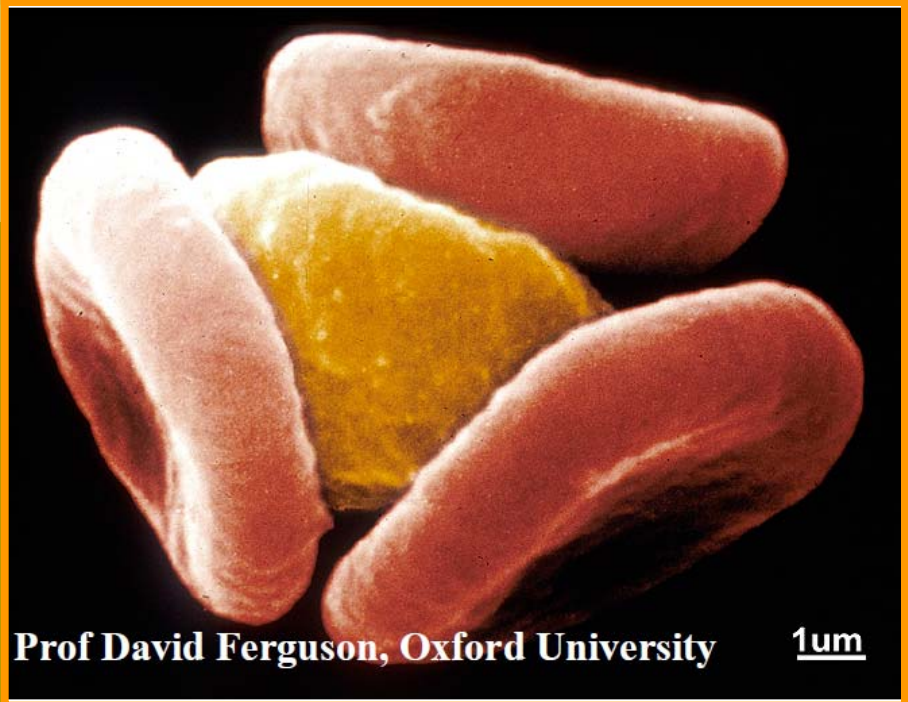


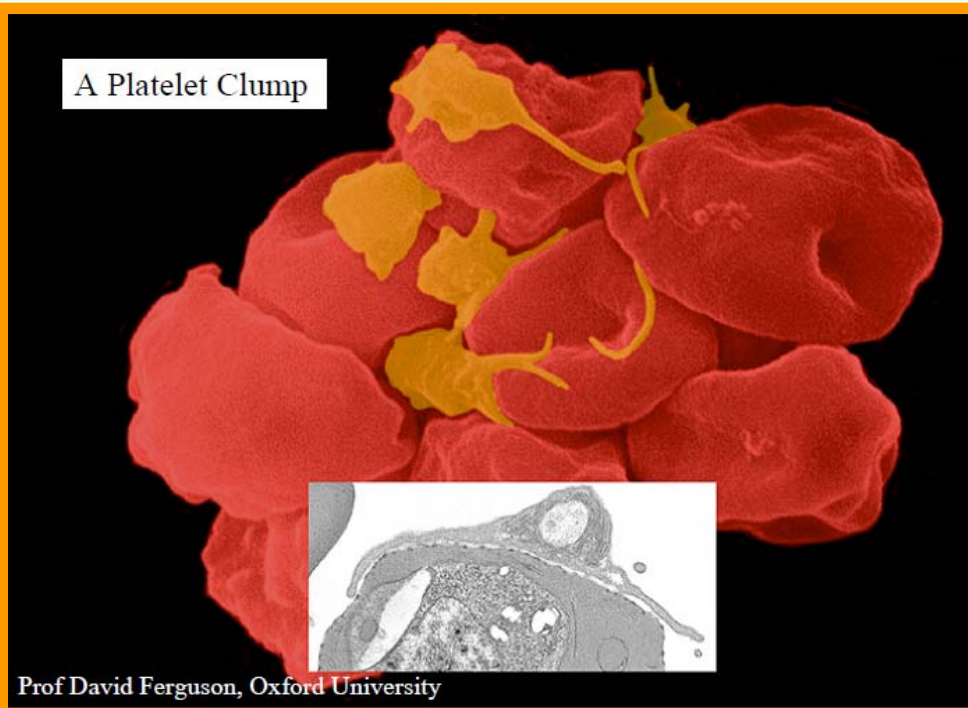
Endothelial activation

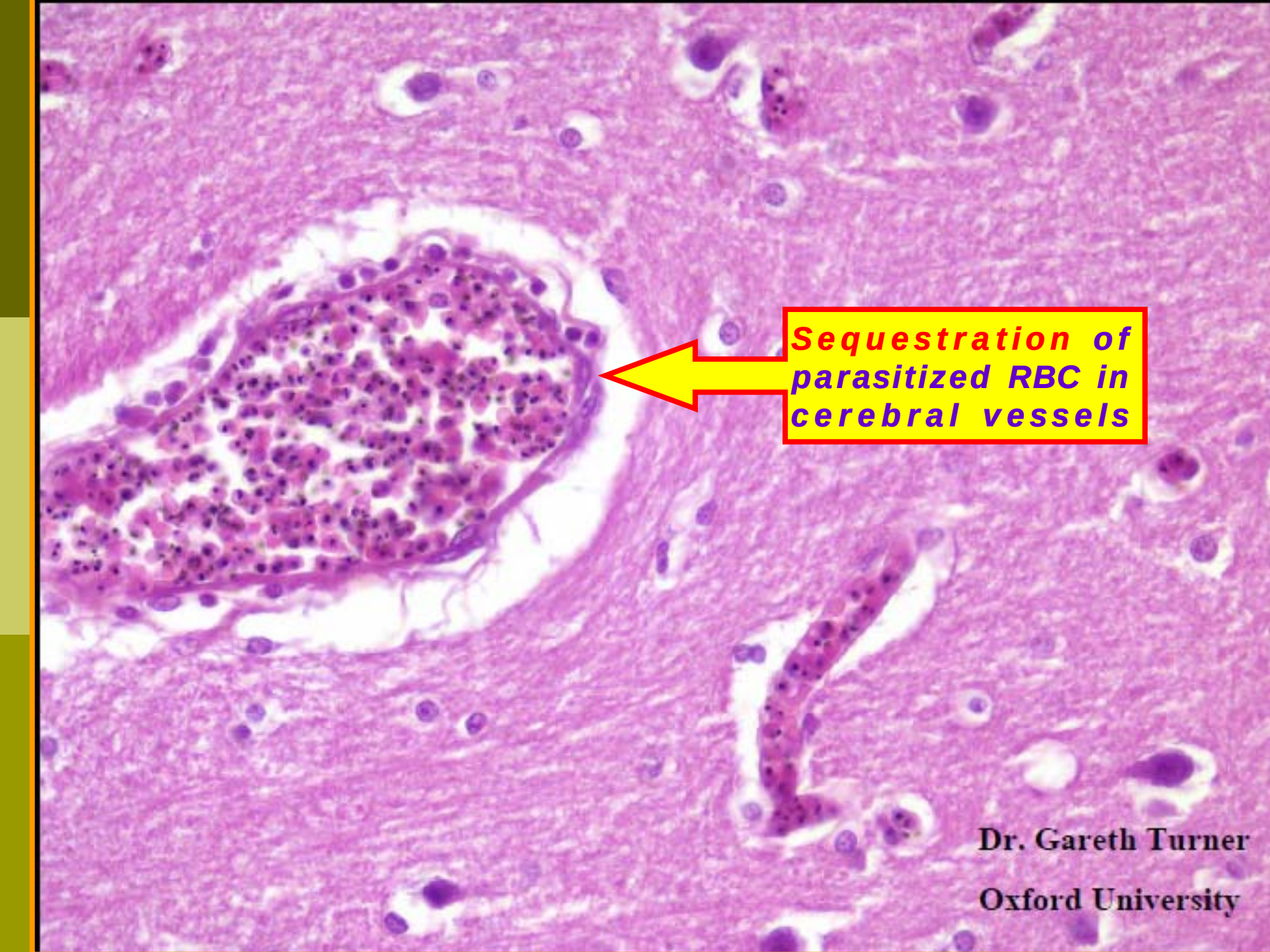
Rolling on endothelium
Receptor: ICAM-1

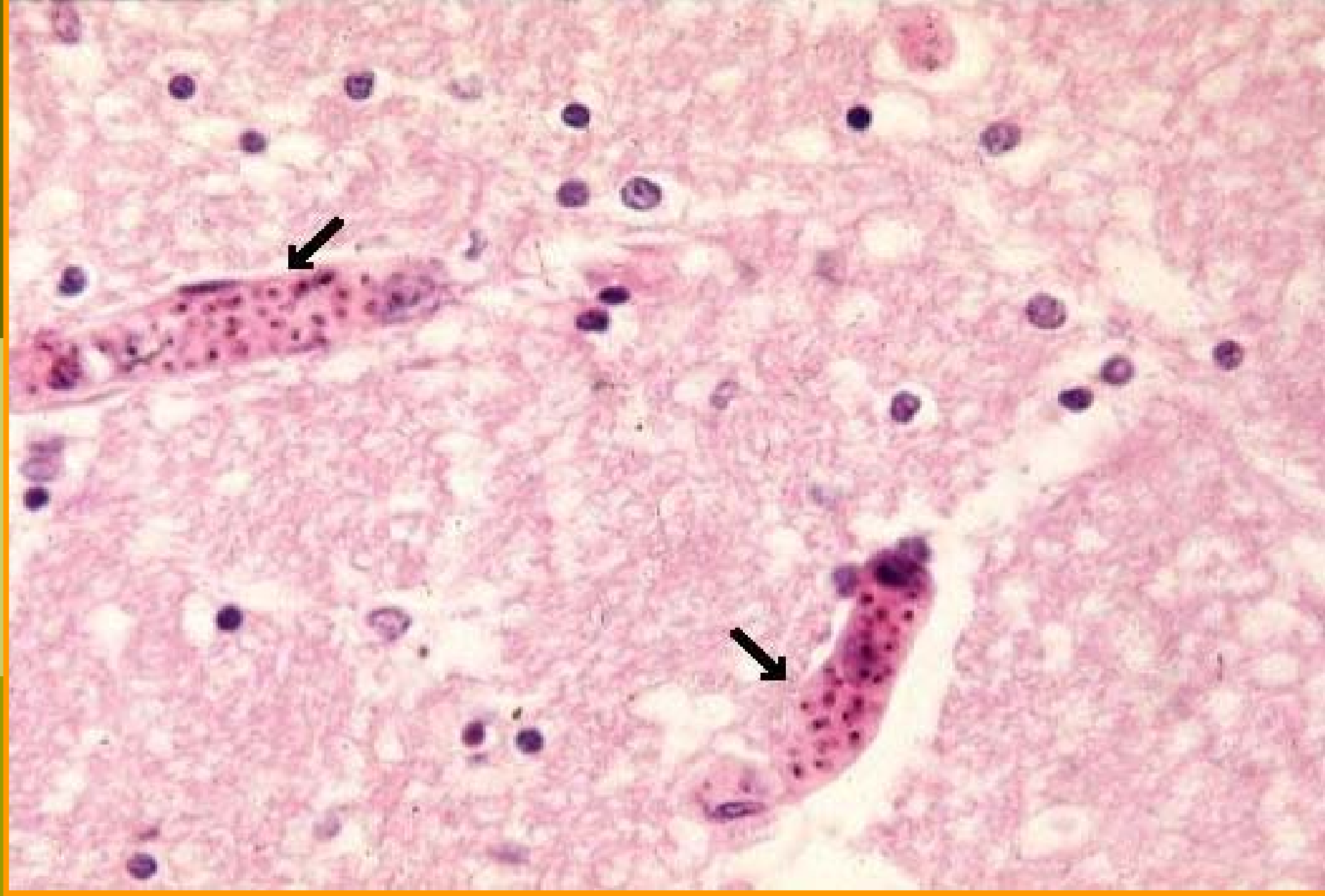
In situ rosetting

Vascular occlusion



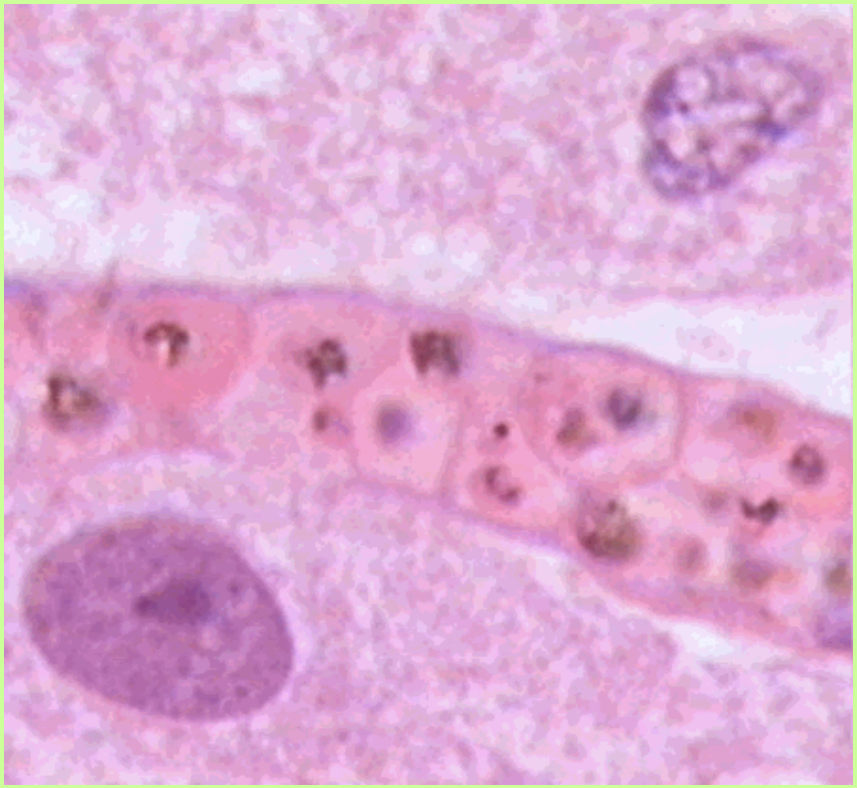



Sequestration of parasitized RBC in cerebral vessels
Dr. Gareth Turner
Oxford University



Sequestration of cerebral capillaries and venules with parasitized red blood cells (PRBCs)

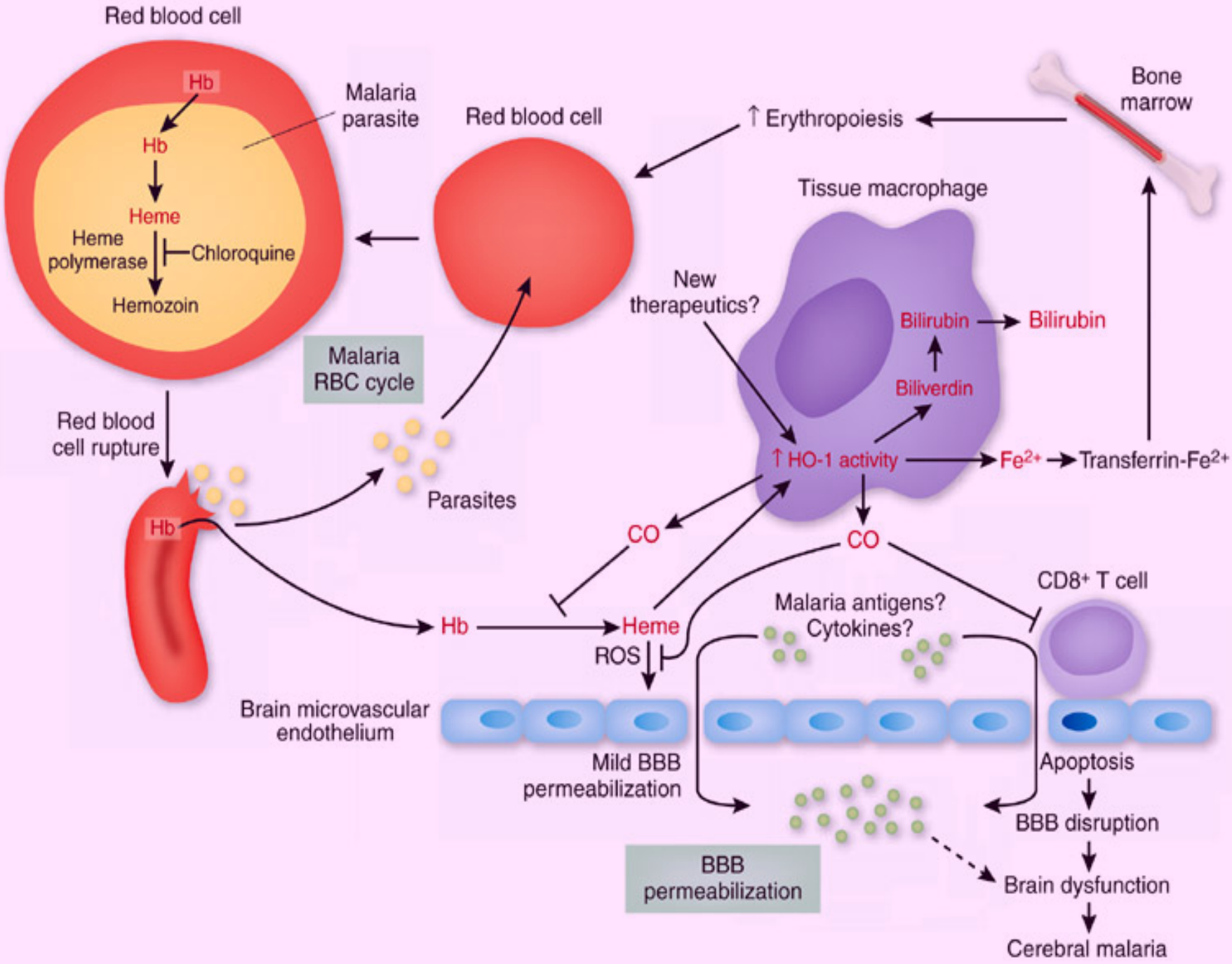
Sequestration of parasites and obstruction of brain vessels

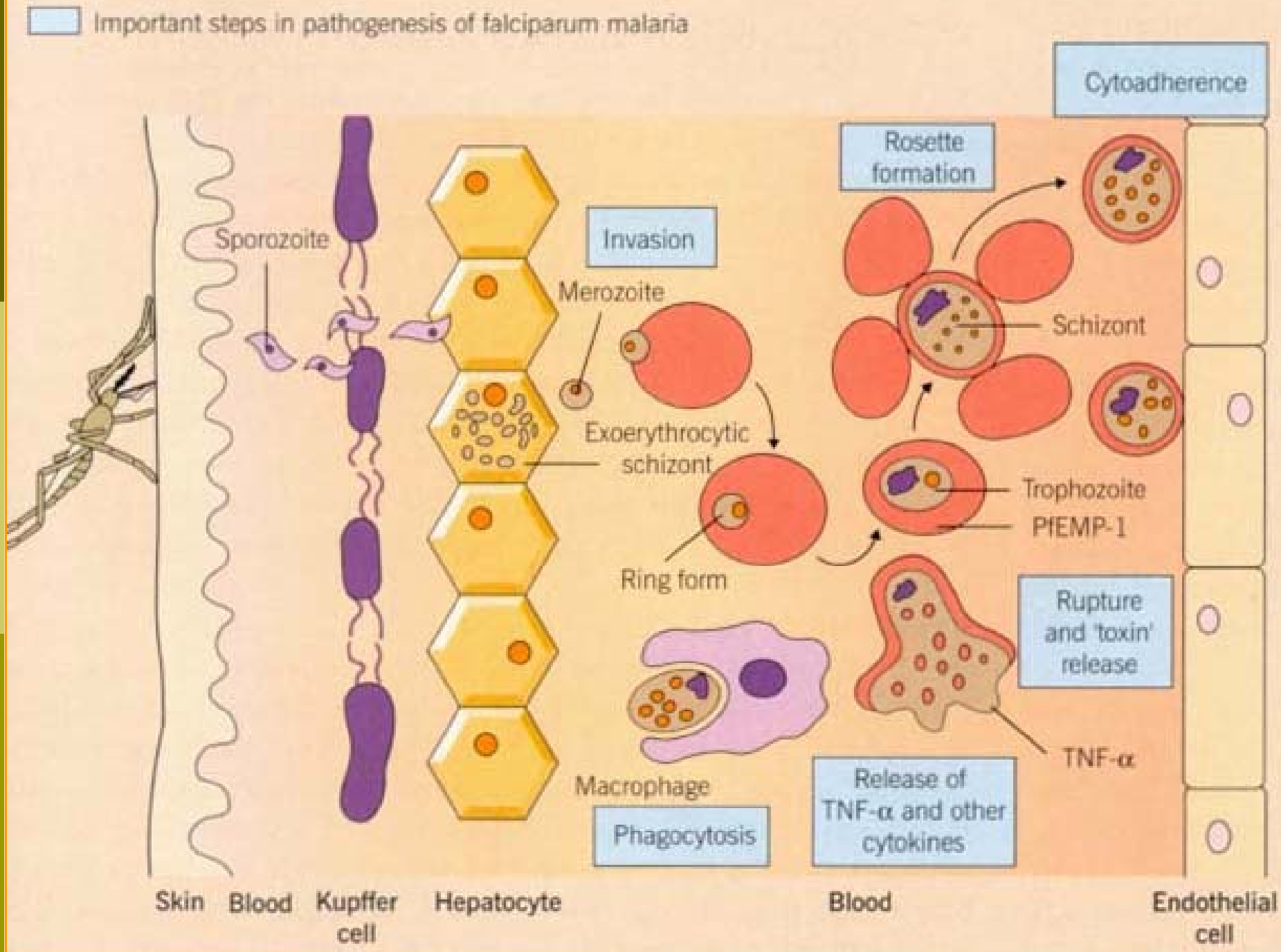


- The mechanical hypothesis asserts that a specific interaction between a *P. falciparum* erythrocyte membrane protein (PfEMP-1) and ligands on endothelial cells, such as ICAM-1 or E-selectin, reduces microvascular blood flow and induces hypoxia. This selective cytoadherence of PRBCs *and* non-PRBCs, also known as rosetting, can apparently better account for CM's histopathological hallmark and its characteristic coma condition. However, this hypothesis is inadequate in explaining the relative absence of neurological deficit even after days of unconsciousness.

Humoral hypothesis for the explanation of the relative absence of neurological deficit even after days of unconsciousness.

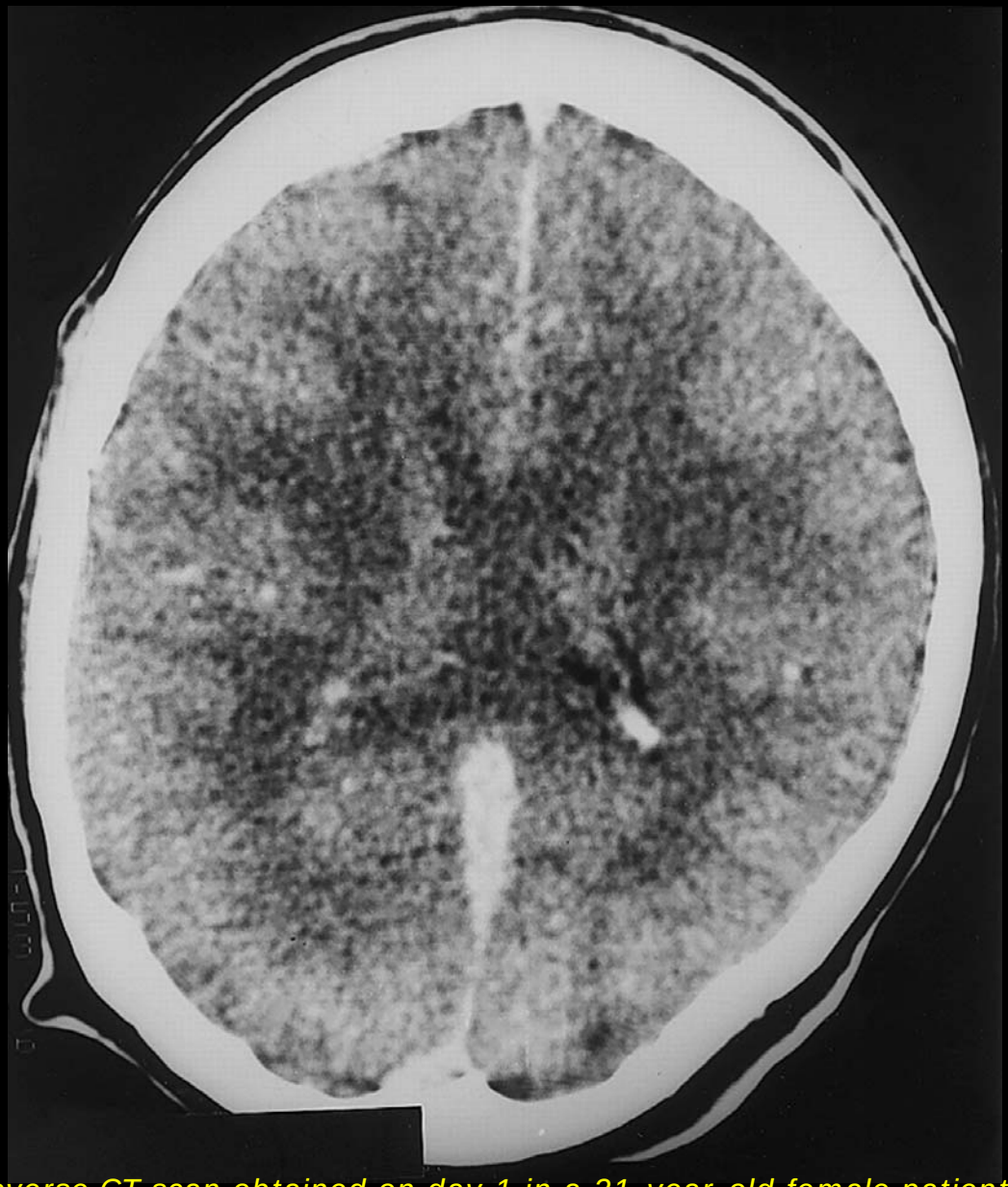
The humoral hypothesis suggests that a malarial toxin may be released that stimulates macrophages to release TNF-a and other cytokines such as IL-1. The cytokines themselves are not harmful, but they may induce additional and uncontrolled production of nitric oxide. Nitric oxide would diffuse through the blood-brain barrier and impose similar changes on synaptic function as do general anesthetics and high concentrations of ethanol, leading to a state of reduced consciousness. The biochemical nature of this interaction would explain the reversibility of coma.


Red blood cell
Hb
Hb
Heme
Heme polymerase
Chloroquine
Hemozoin
Malaria parasite
Red blood cell
↑ Erythropoiesis
Bone marrow
Tissue macrophage
New therapeutics?
Bilirubin
Bilirubin
Biliverdin
Malaria RBC cycle
Red blood cell rupture
↑ HO-1 activity
Fe2+
Transferrin-Fe2+
Parasites
Hb
CO
CO
CD8+ T cell
Malaria antigens?
Cytokines?
Hb
Heme
ROS
Brain microvascular endothelium
Mild BBB permeabilization
Apoptosis
BBB disruption
BBB permeabilization
Brain dysfunction
Cerebral malaria
Kim Caesar

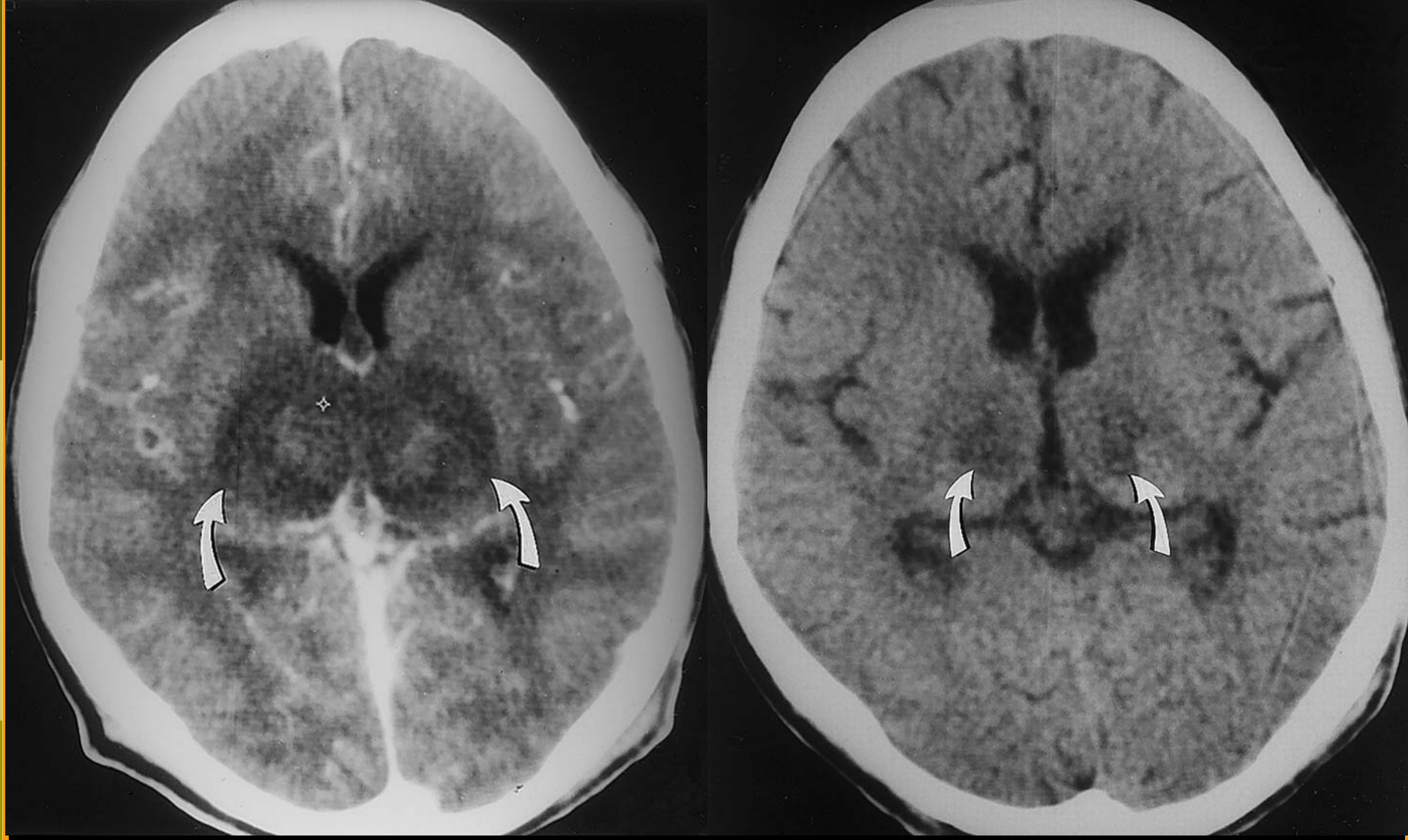

Important steps in pathogenesis of falciparum malaria
Cytoadherence
Rosette formation
Sporozoite
Invasion
Merozoite
Schizont
Exoerythrocytic schizont
Trophozoite
PfEMP-1
Ring form
Rupture and 'toxin' release
TNF-α
Macrophage
Release of TNF-α and other cytokines
Phagocytosis
Skin
Blood
Kupffer cell
Hepatocyte
Blood
Endothelial cell

CT Findings for Cerebral Malaria

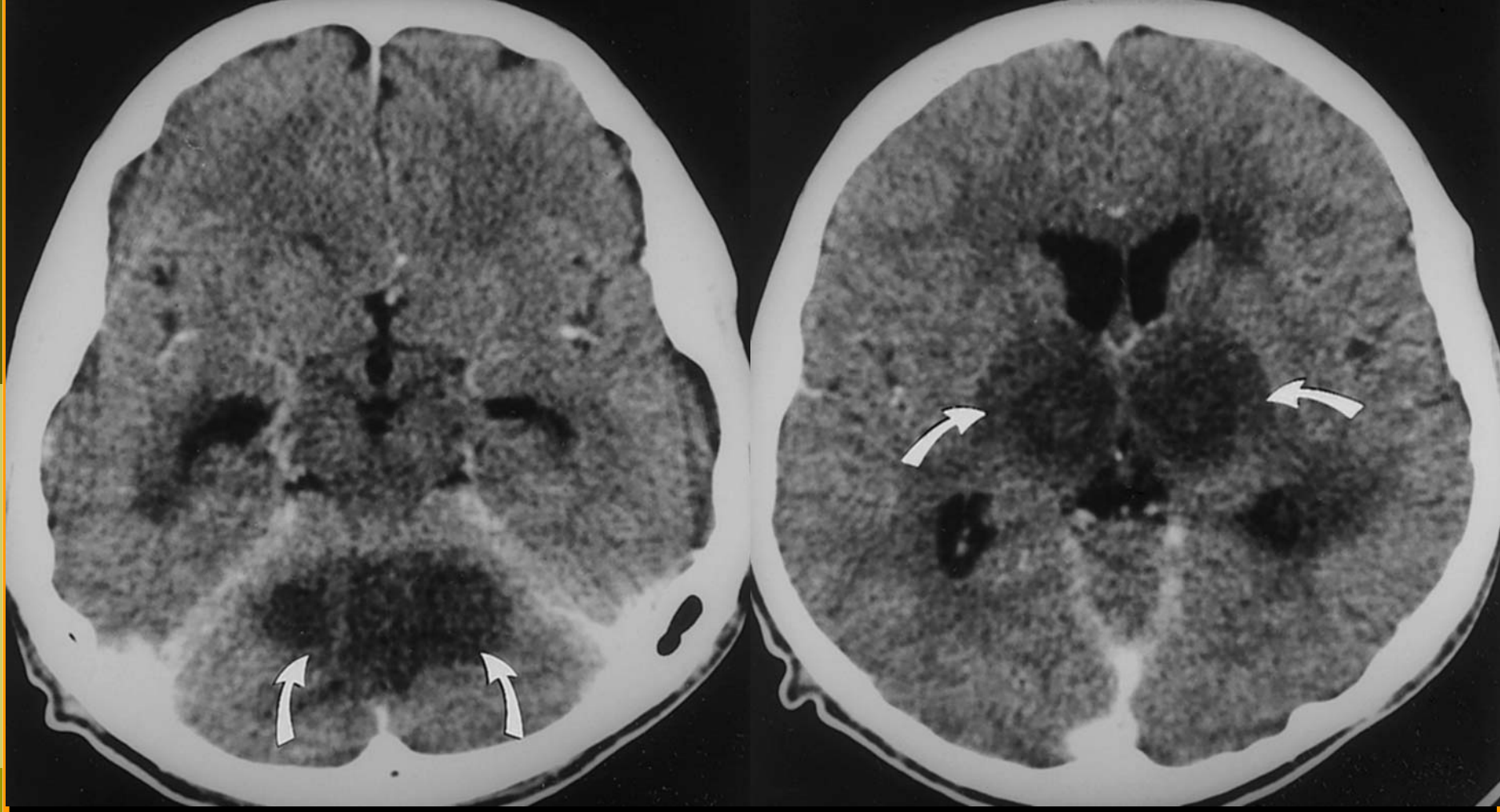
- *4 major patterns of CT brain findings that closely correlated with the clinical severity of malaria, as well as outcome.*
  - *Normal CT findings*
    - *Excellent prognosis; usually regain consciousness after anti-malarial therapy and without neurological deficit*
  - *Diffuse cerebral edema*
    - *Moderately severe malaria;*
  - *Diffuse cerebral edema with bilateral thalamic hypoattenuation*
    - *Severe malaria; survivors may have residual neurological deficit*
  - *Diffuse cerebral edema with bilateral thalamic and cerebellar hypoattenuation*
    - Usually died



Contrast-enhanced transverse CT scan obtained on day 1 in a 31-year-old female patient shows effacement of cerebral cortical sulci and compression of the body of the ventricles, suggestive of generalized cerebral edema.
Tufail F. Patankar et al, September 2002 Radiology, 224, 811-816.



- *Contrast-enhanced transverse CT scan of the brain in a 17-year-old male patient demonstrates bilateral thalamic hypoattenuation (arrows) with central areas of higher attenuation.* ***(b)*** *Follow-up transverse CT scan obtained on day 10 in same patient reveals residual thalamic hypoattenuation (arrows).*
- *Tufail F. Patankar et al, September 2002 Radiology, 224, 811-816.*



*In P. falciparum there is **selective clogging of the cerebellar capillaries with parasitized red blood cells**, which leads to microscopic infarcts, perivascular hemorrhages, shrinkage of the Purkinje cells, and perivascular clusters of microglia*

- ***Contrast-enhanced transverse CT scan obtained in a 20-year-old male patient shows bilateral symmetric cerebellar hypoattenuation (arrows). (b) Contrast-enhanced transverse CT scan at the level of thalamus in the same patient at the same time demonstrates***
- ***Tufail F. Patankar et al, September 2002 Radiology, 224, 811-816.***