

# History of malaria and sleeping sickness

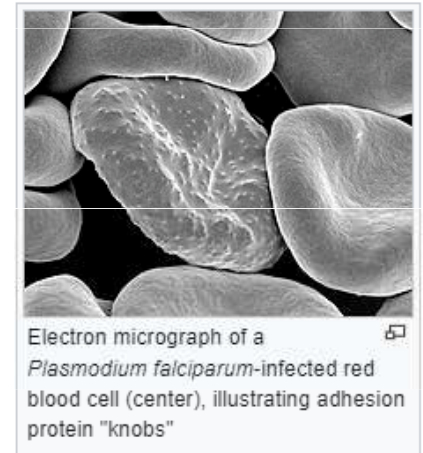
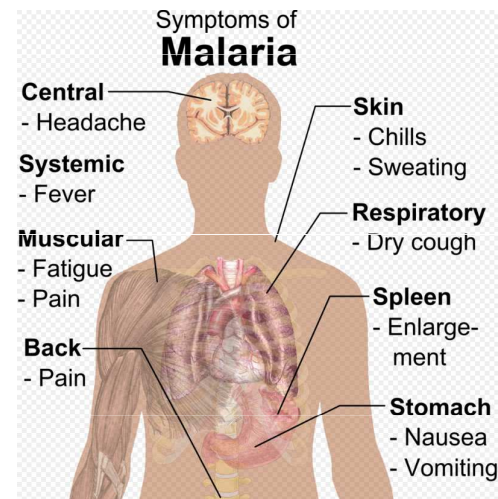
## Treatment development

# Plasmodium

- › **Hematozoa**
- › many species were discovered in various hosts and classified
- › mammals ~ 50 species; birds ~ 40 species; reptiles ~ 60 species
- › **five species that regularly infect human**
  - › *P. vivax*, *P. falciparum*, *P. malariae*, *P. ovale*, and *P. knowlesi*



- › **Malaria**
- › 249 millions cases worldwide (2022)
- › 608 000 deaths (80% of being five and under)
- › Mainly in sub-Saharan Africa
- › Every minute a child dies
- › Associated with poverty
- › Negative effect on economic development
- › 12 billions USD loss



# Plasmodium

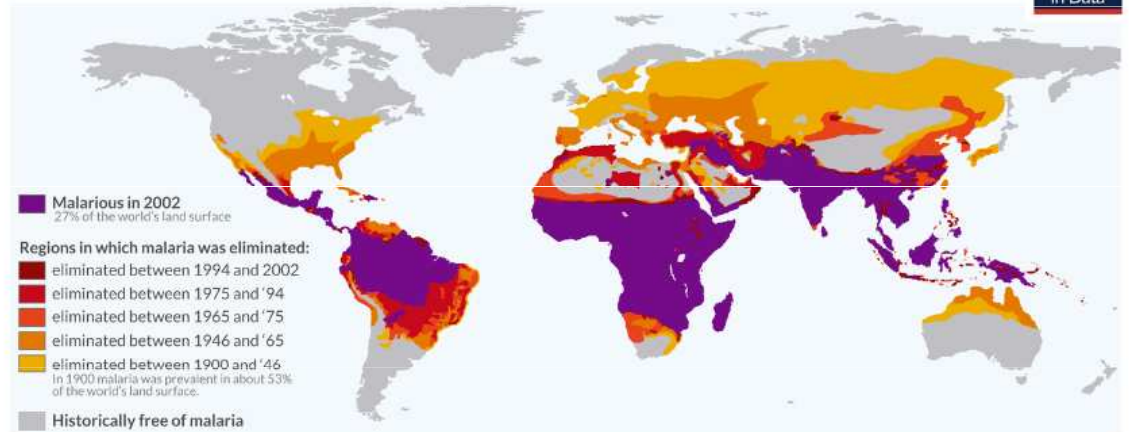
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Malaria was prevalent in many parts of the world that are free of malaria today

Our World  
in Data



Source: Hay et al. (2004) - The global distribution and population at risk of malaria: past, present, and future. In The Lancet Infectious Diseases. Redrawn by Our World in Data.  
OurWorldinData.org - Research and data to make progress against the world's largest problems. Licensed under CC-BY by the author Max Roser

# History of malaria

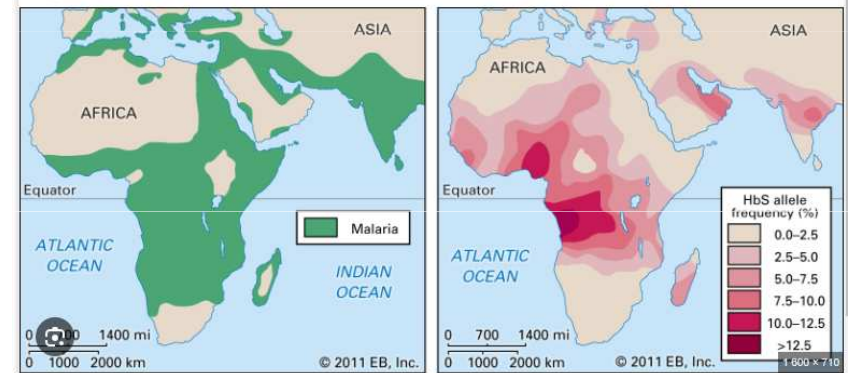
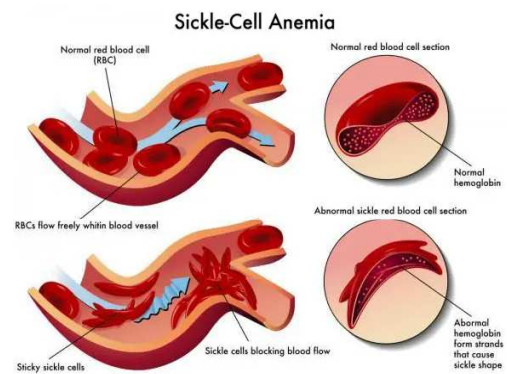
› *P. falciparum* – very ancient human parasites, co-evolved with humans (host cospeciation)

› The others parasites species transferred to humans from primates

› Sickle cell anemia (srpkovitá)

› Point mutation in beta-globing chain

› Hetezygotes children – 10 times less likely to dies from malaria



› Thalassemias

› Anemia, loss of alpha- or beta globin chains

› Binds less oxygen

› 50 less chance to get infected



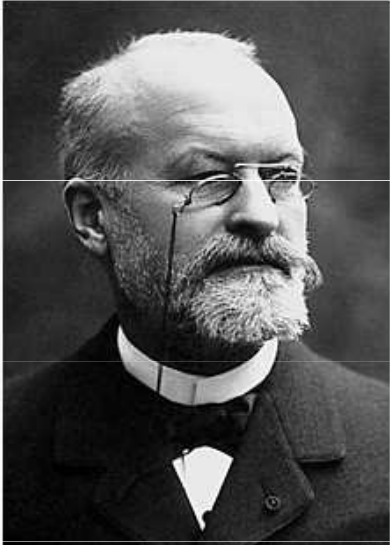
# History of malaria

- › **Huge effect on human population**
  - › **Barrier to social and economic development (detrimental and mental effects of repeated malarial infections)**
- › **First effective treatment for malaria, South America**
  - › 17<sup>th</sup> century
  - › Jesuit's bark
  - › Powdered bark of cinchona tree (tropical Andes) contains alkaloids
  - › trade, variable content, religious reasons (Oliver Cromwell)
  - › Only for wealthy (alternatives failed – willow bark)
  - › 19<sup>th</sup> century – isolation of quinine (Caventou and Pelletier)
    - › Procedure not patented
    - › Rapid establishment of factories (modern pharmaceutical industry)
    - › 1826 – Pelletier produced 3600 kg annually
  - › Huge pressure on import of cinchona tree
    - › European plant hunters
    - › Finally smuggled – plantations in British and Dutch colonies in Asia
    - › *Cinchona ledgeriana* – plantations in Java (Dutch) 13% of quinine content, 97% world's supply (monopoly until 1942)
  - › Resistance to quinine reported in 1910

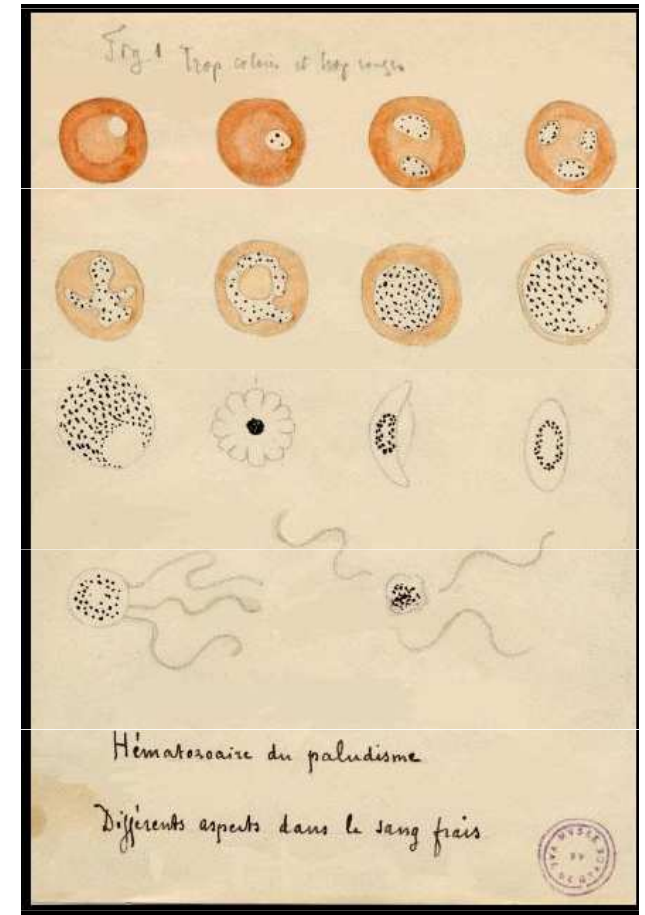


Peru offers a branch of cinchona to Science (from 17<sup>th</sup>-century [engraving](#))

# Discovery of the parasite



- › **Charles Louis Alphonse Laveran (1848-1922)**
  - › 1878 – Algiers, military hospitals
  - › Detected pigment, “crescents” in patients
  - › *Oscillaria malariae* (1880)
  - › First protozoan parasite detected in man
- › 1884 finally accepted (Pasteur and Koch)
- › 1889 – report on a possibility that mosquitos play role in malaria transmission
- › 1907 – Nobel Prize in Physiology  
“in recognition of his work on the role played by protozoa in causing diseases”



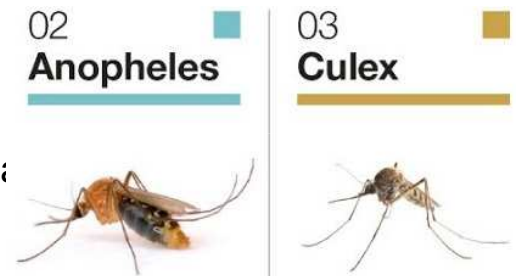
# Mosquito-malaria hypothesis



- › **Patrick Manson (1844 – 1922)**
  - › Scottish physician
  - › Filariasis is transmitted by mosquitoes
  - › Suggested that malaria can be also transmitted with mosquitoes
  - › Maintain fruitful collaboration with Ross
  - › Introduced preventive measures to reduce exposure to mosquitoes



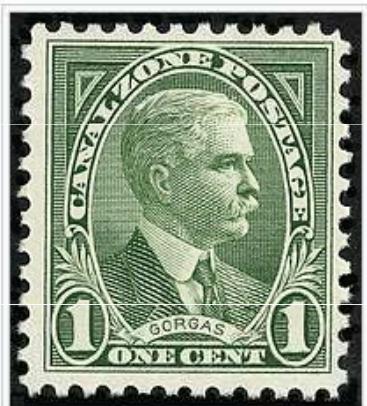
- › **Sir Ronald Ross (1857 – 1932)**
  - › British medical doctor
  - › 1894 - search for malaria transmission in Secunderabad, he examined wrong mosquitoes!
  - › Finally in 1897 he looked at different mosquito (dapple-winged) that fed on the malaria patient and described a stage in the mosquito gut
  - › Transferred to Calcutta (no malaria), upon Manson advice he studied bird malaria
    - › Life cycle of *P. relictum*
  - › 1899 –sent to Sierra Leone and implied first measures to control transmission (draining puddles, rivers straightened)
  - › 1902 – Nobel prize for his work on the transmission of malaria:
    - › Battista Grassi (infections of healthy volunteers)





# Malaria control - The Case of Panama Canal

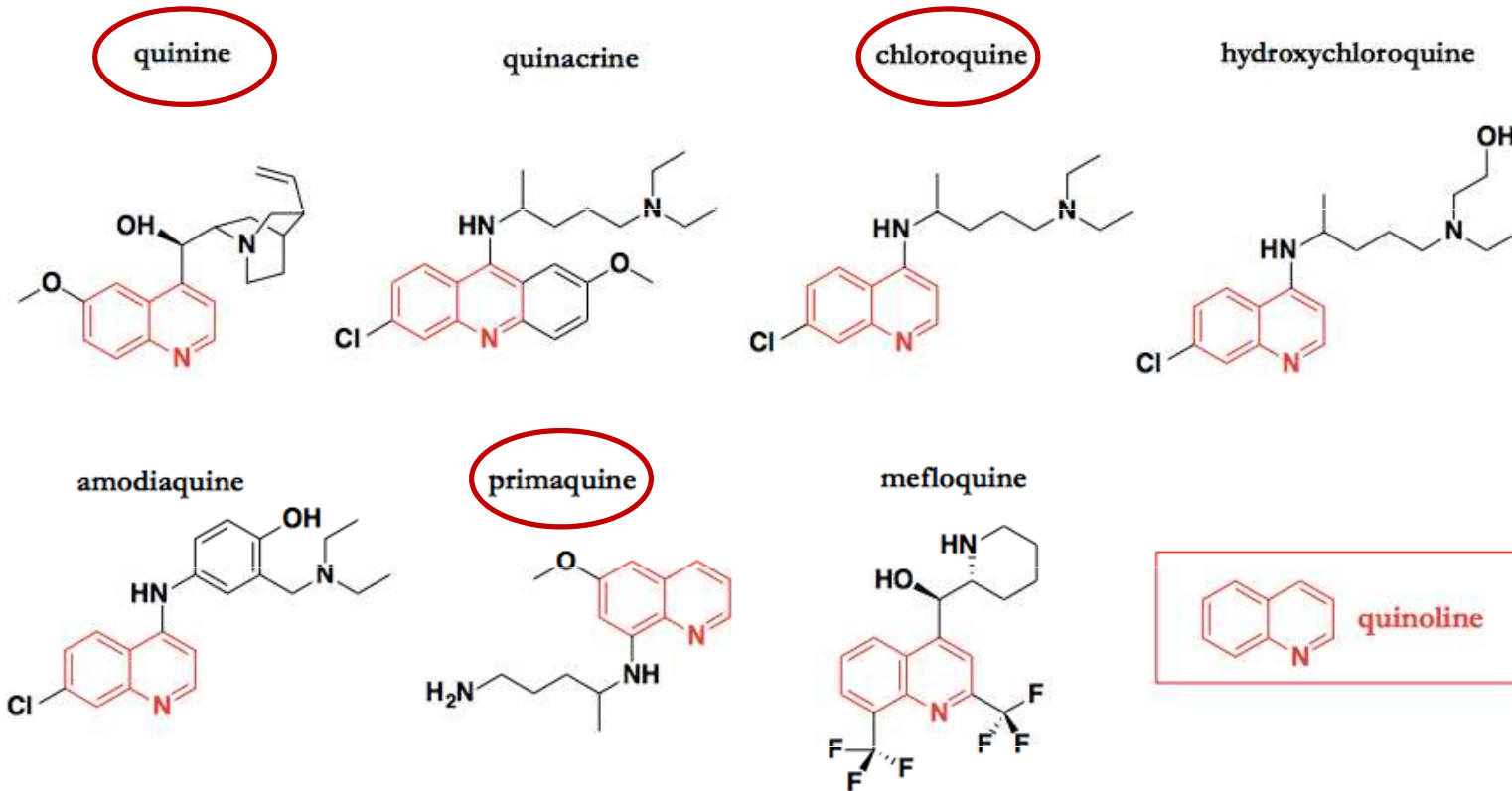
- › 1882 – 1889 – bankruptcy of the French company (F. de Lesseps)
  - › Mosquitoes did not recognize as a problem
  - › 30 000 deaths
- › 1904 – major William Gorgas appointed as a advisor (experienced from Cuba)
- › 1914 – funds to control malaria in US
- › 1939 – DDT (Nobel prize in 1948)
- › 1951 – USA malaria free



Maj. Gen. William C. Gorgas,  
honored on [Canal Zone Postage](#)



# QUININE and its derivatives



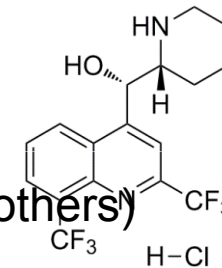
- › derivatives are some of the oldest drugs around
- › all stem ultimately from quinine
  - › a natural product isolated from the bark of the Andean cinchona tree
  - › the first antimalarial drug by the early 1800s

# MALARIA TREATMENT

- › types of drugs and the length of treatment will vary, depending on:
  - › species of malaria parasite
  - › the severity of symptoms
  - › age of patient
  - › pregnancy
- › **chloroquine phosphate** = the preferred treatment for any malaria parasite
  - › in many parts of the world the parasites are resistant to chloroquine



- › combination of **atovaquone** and proguanil (Malarone)
- › **quinine sulfate** (Qualaquin) with **doxycycline** (Vibramycin, Monodox, others)
- › **mefloquine** (prophylaxis)
  - › results of a huge effort Walter Reed Inst (Vietnam war), screen of 250 thousands compounds
  - › trials in prison populations
- › **artemisinin-based combination therapies (ACTs)** = the first line treatment

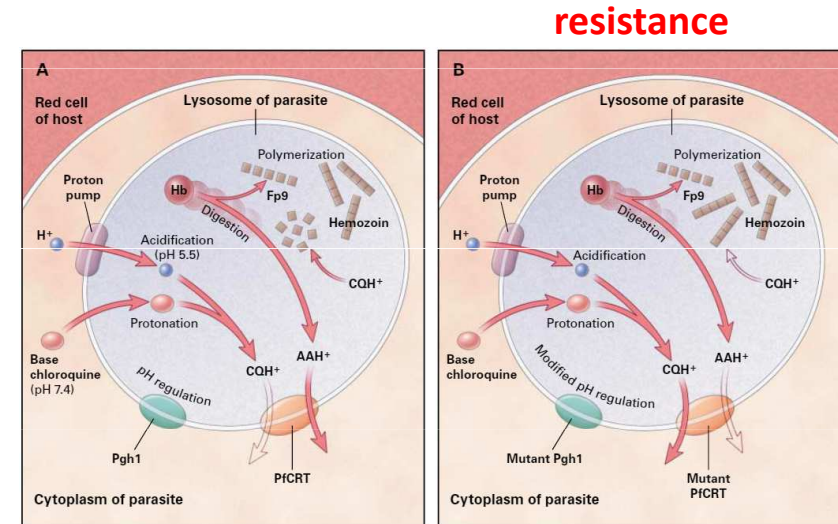


***demonstrated resistance to nearly all of the available antimalarial***



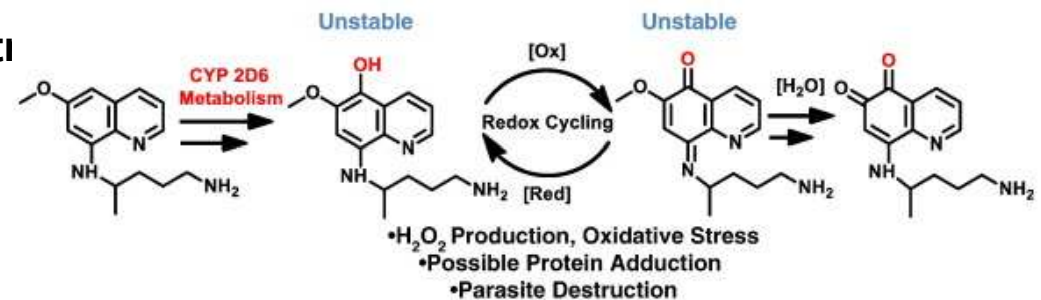
# CHLOROQUINE

- › 1950s
- › primarily used to prevent and treat malaria (Korean war)
- › inhibit parasite's ability to digest haemoglobin
  - › the drug concentrates in the **acidic food vacuole** of the parasite and interferes with essential processes
  - › caps hemozoin molecules to prevent biocrystallization of heme (hemozoin)
  - › binds to heme (or **ferriprotoporphyrin-IX, FP**) to form the FP-chloroquine complex
  - › this complex is **highly toxic to the cell** and disrupts membrane function



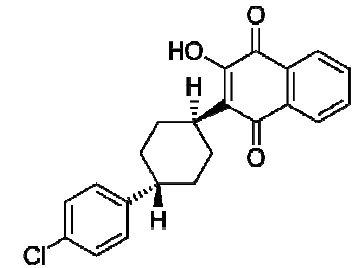
# PRIMAQUINE

- › 1952
- › to treat and prevent malaria and to treat *Pneumocystis pneumonia*
- › to prevent relapse of malaria → eliminates hypnozoites, the dormant liver form
- › the exact mechanism of action is not fully understood
- › oxidative damage to the cell **interfering with the electron transport**
- › effective against the gametocytes
- prevents spread to the mosquito



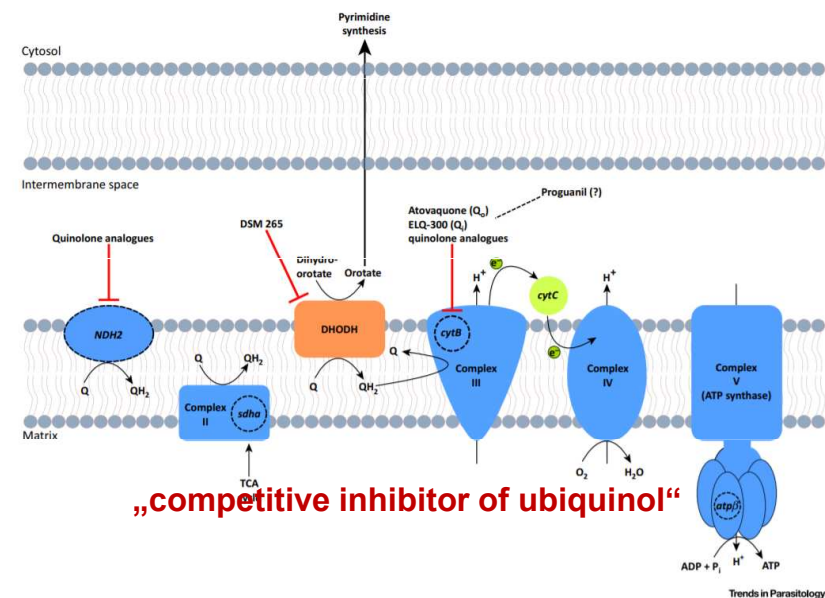
# Atovaquone

- › broad-spectrum activity against *Plasmodium*, *Babesia*, *Toxoplasma* and *Pneumocystis*
- › **collapse of the mitochondrial membrane potential**
- › **structurally similar** to the inner mitochondrial protein **ubiquinone (ubiquinol) = coenzyme Q**
  - › an integral component of electron flow in aerobic respiration
  - › ubiquinone accepts electrons from dehydrogenase enzymes and passes them to electron transport cytochromes → electrons from ubiquinone to cytochrome bc1 (complex III) requires binding of coenzyme Q-complex III at the Qo cytochrome domain
  - › **this step which is inhibited by atovaquone**



- › the structure of the Qo cytochrome binding site has been determined → **atovaquone to parasitic mitochondria**

- › collapse of the mitochondrial membrane potential
- › inhibition of dihydroorotate dehydrogenase that is required in the **biosynthesis of pyrimidines**
- › inhibition of ATP production



# Artemisinin

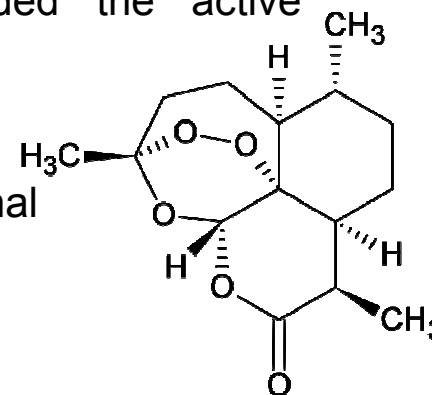
- › Vietnam war – *P. falciparum* chloroquine resistant parasites
- › People's Liberation Army Research Institute
  - › 1967 – huge research program called Project 523 (500 scientists, 60 institutions)
  - › Search for antimalarial by screening as well using traditional Chinese herbal medicines
  - › Military secret
  - › 1969 – **prof. Youyou Tu**



- › ancient literature
- › 640 recipes, tested against *P. berghei*
- › Sweet warmwood *Artemisia annua*
- › Extraction under low-temperature yielded the active compound
- › 1971 – 100% active against parasitemia
- › 1977 – X-ray structure
- › 1979 – artemisinin published in ENG journal



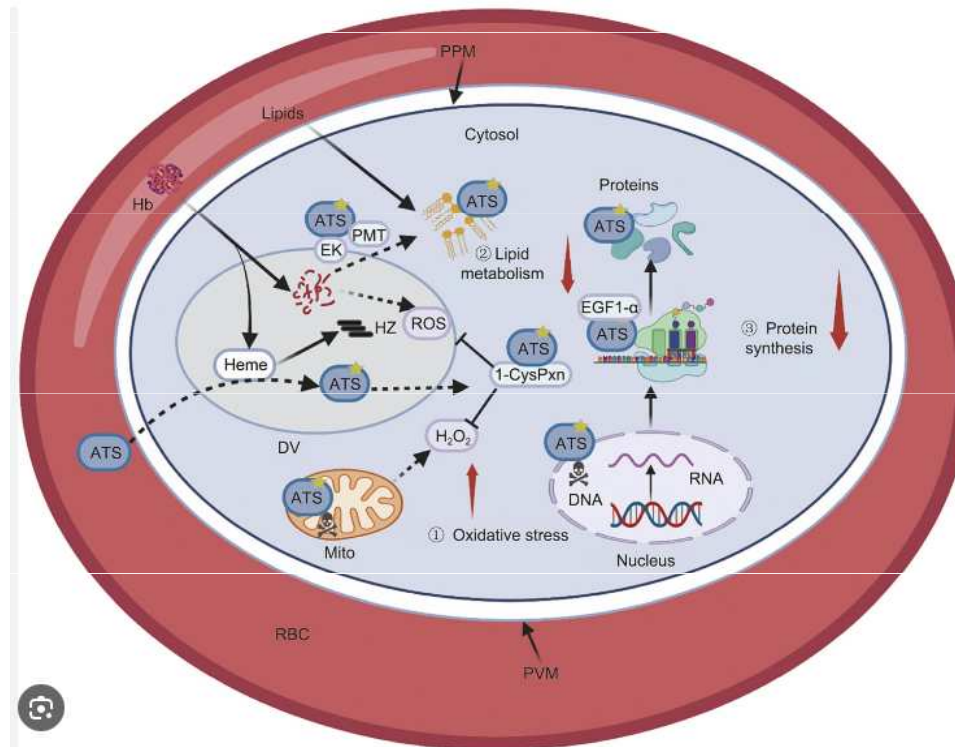
*Artemisia annua*



- › 2015 – Nobel prize in physiology and medicine

# Artemisinin

**ART reacts with accessible heme** and as a result, generate **ROS**, which is a potentially damaging agent. A portion of ART gets into mitochondria, where mitochondrial dysfunctions occur.

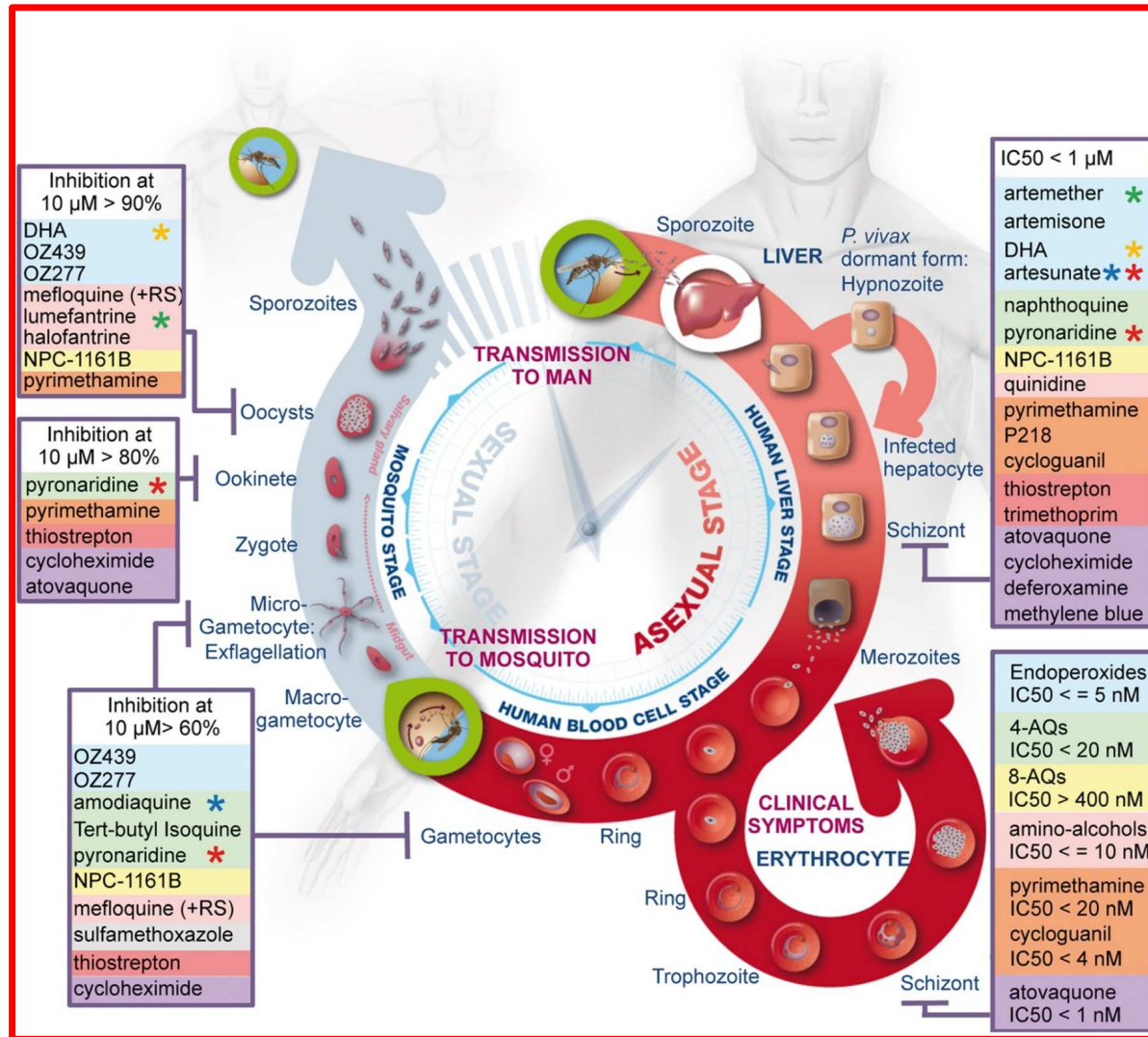


ATS simultaneously interferes with ① redox homeostasis, ② lipid metabolism, and ③ protein synthesis in *P. falciparum* to exert antimalarial effects by targeting several essential proteins. DV: digestive vacuole; HZ: hemozoin; Mito: mitochondrion

**Artesunate** ← the most widely used derivate of artemisinin, hydrophylic

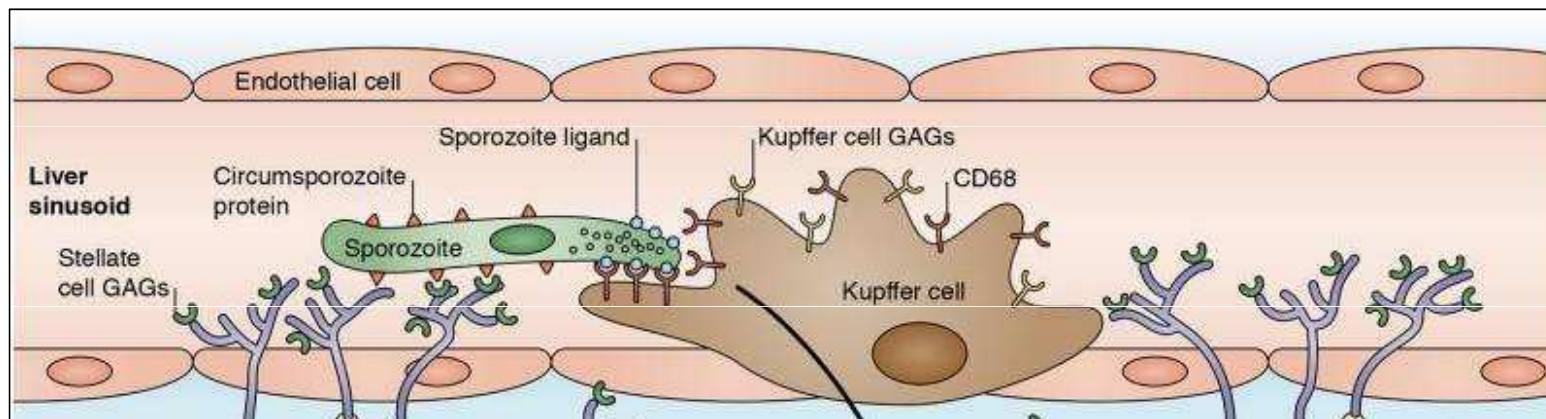
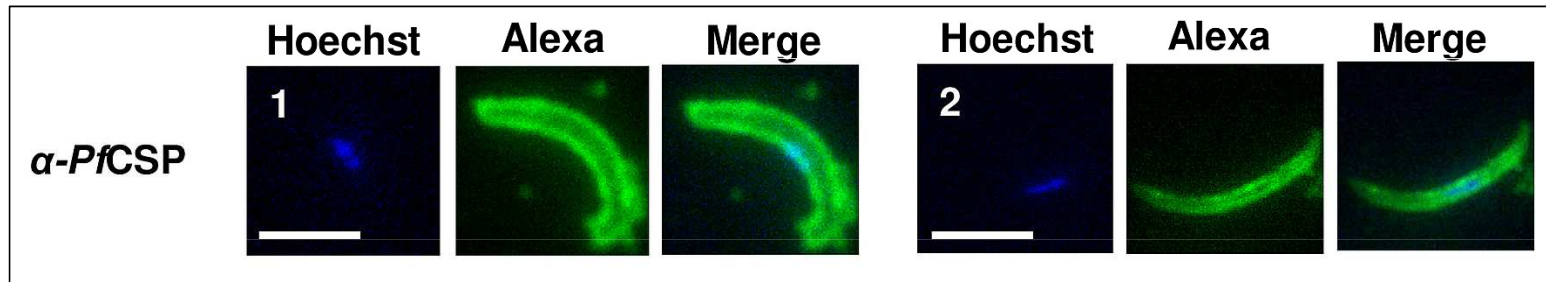


# Malaria treatment



## VACCINE AGAINST MALARIA

- › the only approved vaccine as of 2015 is **RTS,S** (trade name Mosquirix)
- › requires four injections, and has a relatively low efficacy
- › consists of the *P. falciparum* **circumsporozoite protein (CSP)**

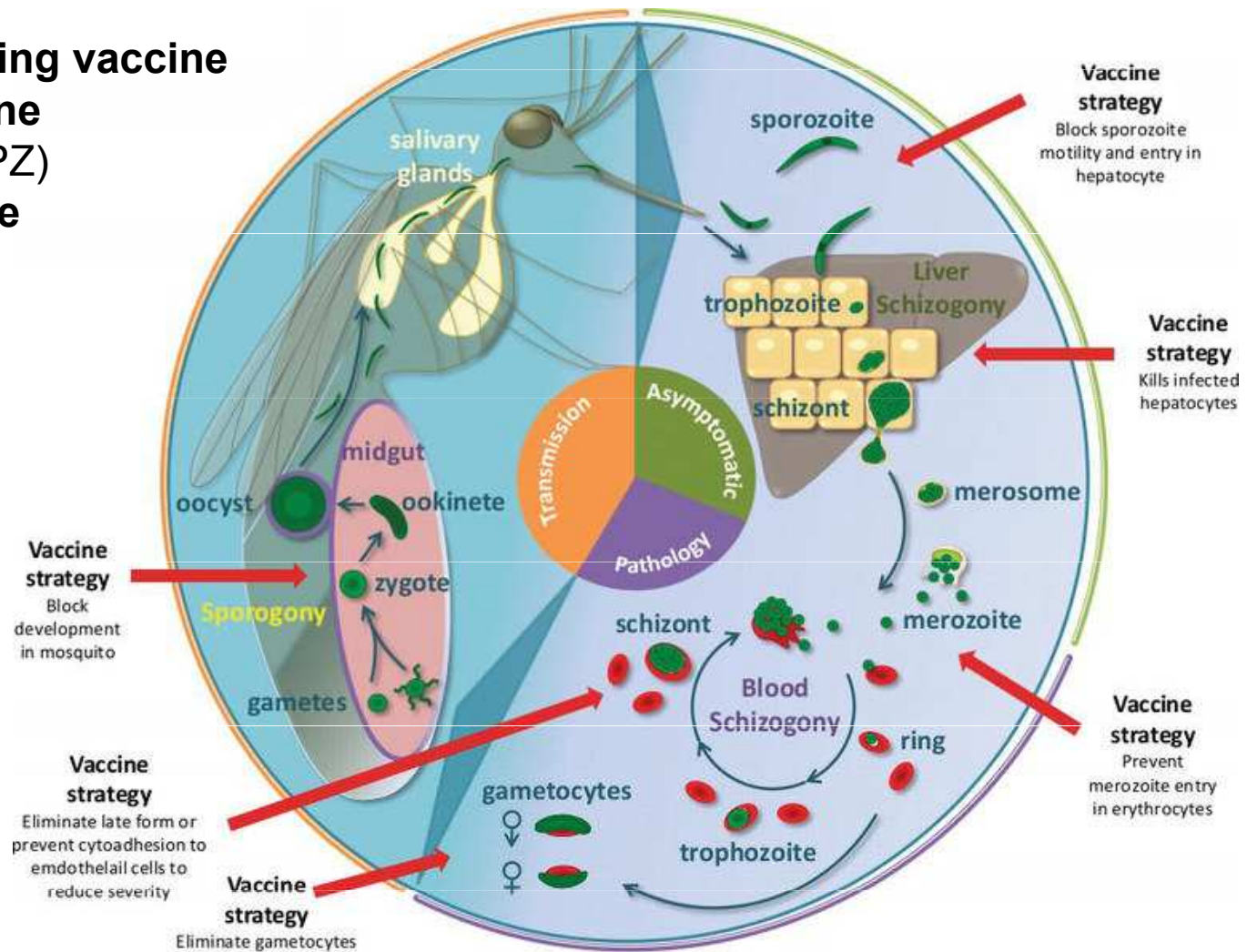


- › **PfSPZ** Vaccine is a candidate malaria vaccine
- › non-replicating irradiated whole sporozoites
- › PfSPZ is the acronym: *Plasmodium falciparum* (Pf) and sporozoites (SPZ)



# VACCINE AGAINST MALARIA

- › transmission-blocking vaccine
- › anti-infection vaccine
  - › (RTS,S and pfSPZ)
- › anti-disease vaccine



**Treating bed nets with antimalarial compound blocks parasite from developing in mosquitoes (atovaquone)**



**+ treatment with insecticides**

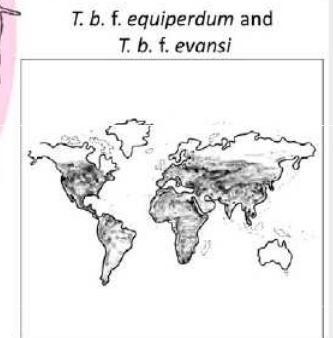
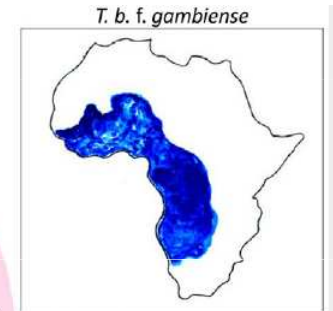
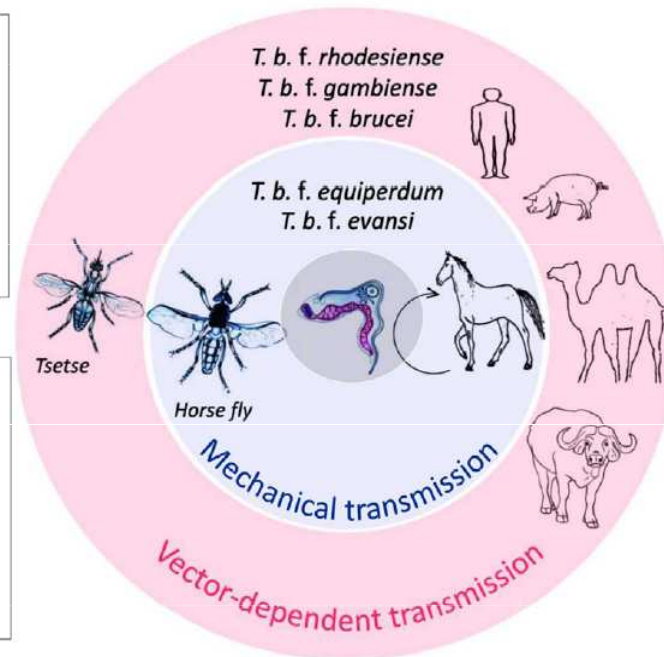
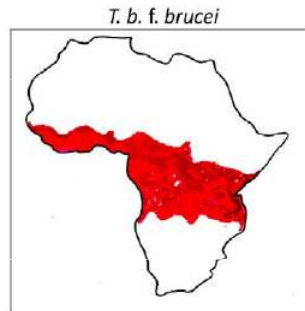
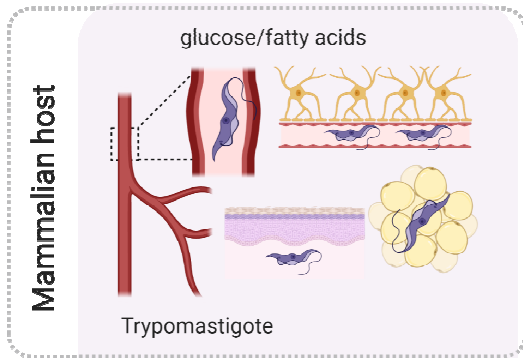


***Anopheles gambiae***

# African Trypanosomes

***Trypanosoma brucei*** (*T. b. brucei*, *T. b. gambiense*, *T. b. rhodesiense*, *T. b. evansi*, *T. b. equiperdum*)  
*T. congolense*, *T. vivax*

- Human African Trypanosomiasis (HAT)
  - 36 African states
  - 50 millions in affected areas
  - Always lethal if untreated
- Animal African Trypanosomiasis (AAT)
  - Direct loss of livestock products
  - Loss of crop productivity due to loss of the animals draught power





# First accounts of sleeping sickness

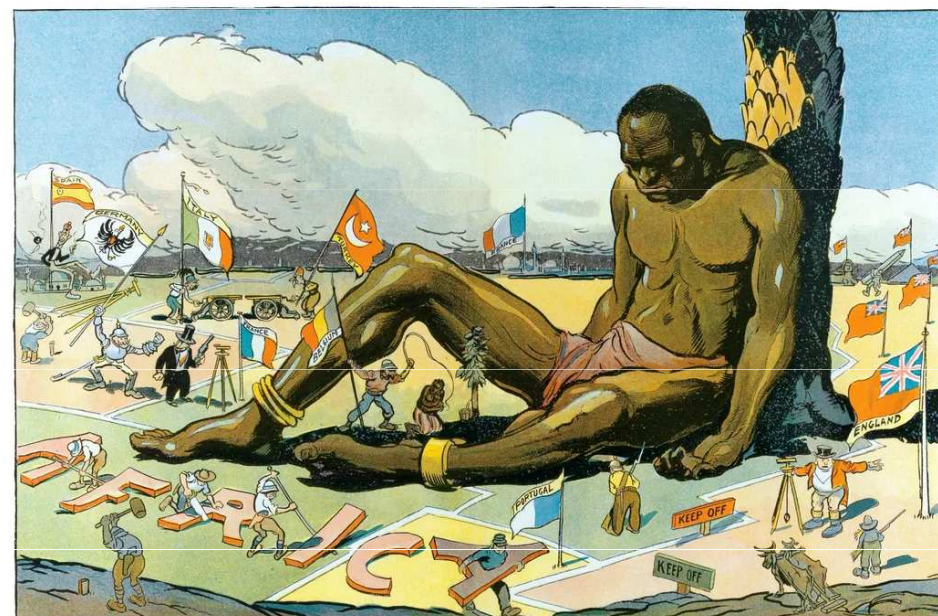
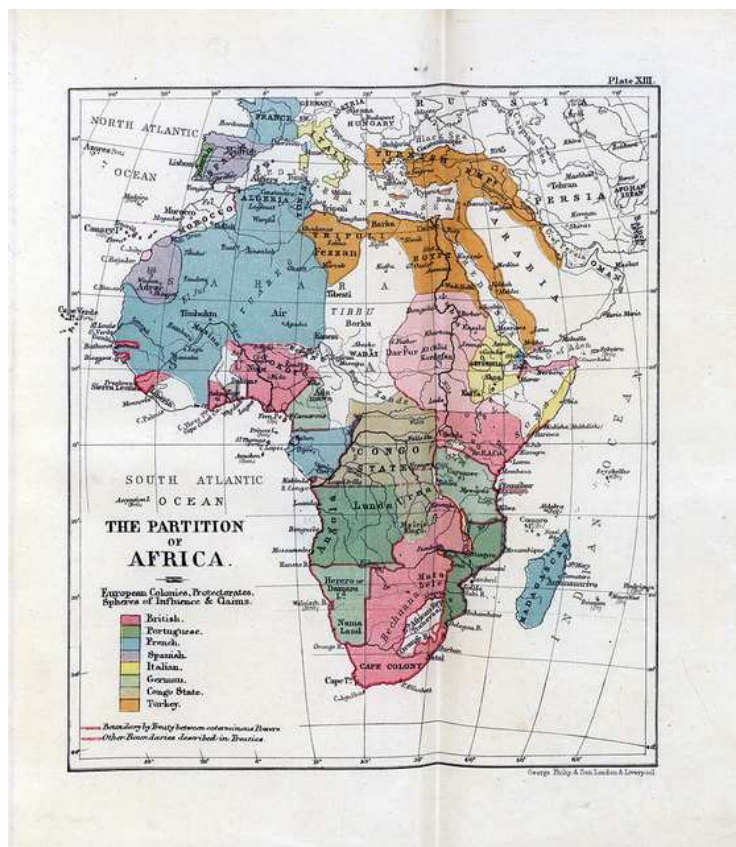


## Slave trade



Winterbottom syndrom

## Colonization of Africa



**THE SLEEPING SICKNESS:** Cutting a continent out from under him.

- political cartoon made by Gordon Ross ("Puck" magazine), United States, October 1911

# First accounts of sleeping sickness

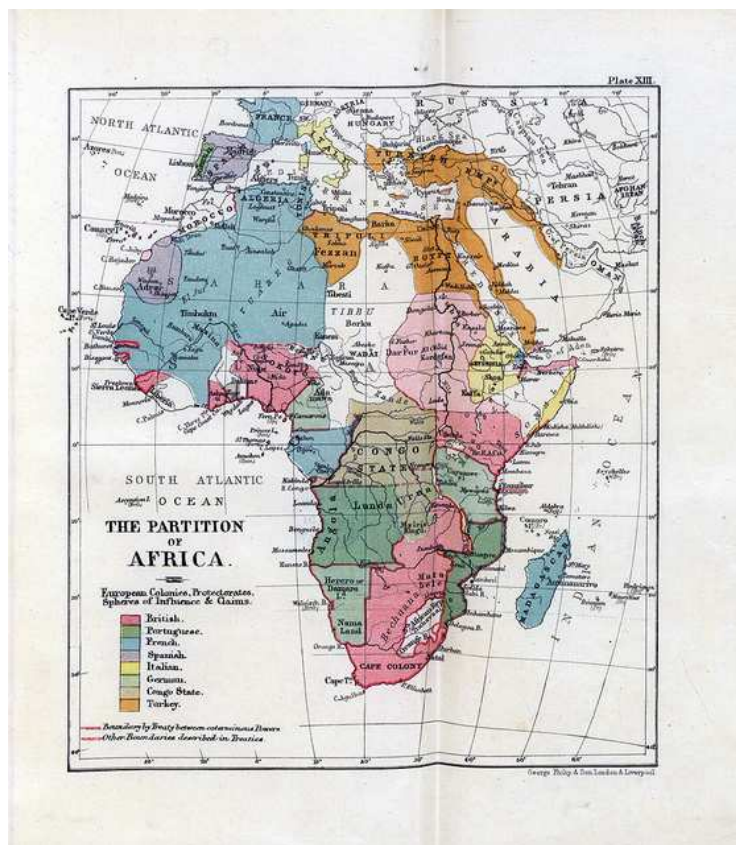


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Winterbottom syndrome

## Colonization of Africa



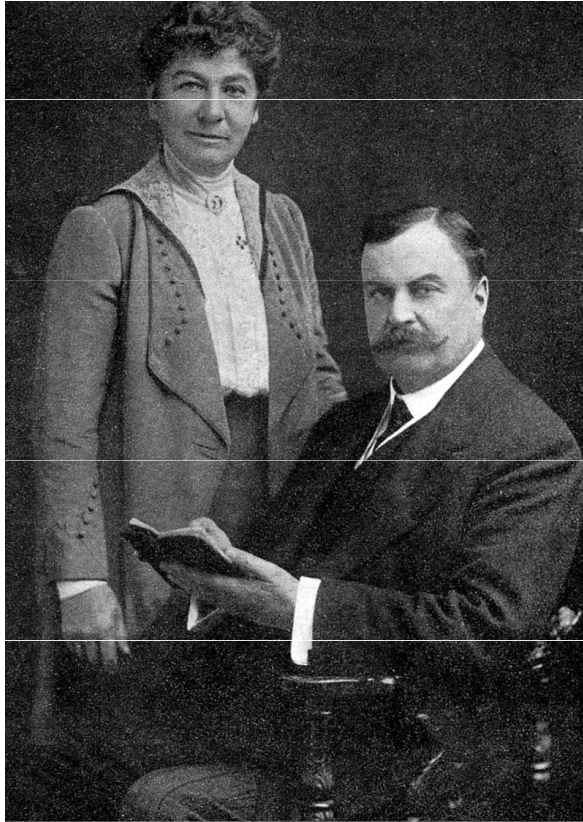
## 1<sup>st</sup> epidemic killed 250,000 Ugandans



ILLUSTRATIONS BY IVAN SENYONJO

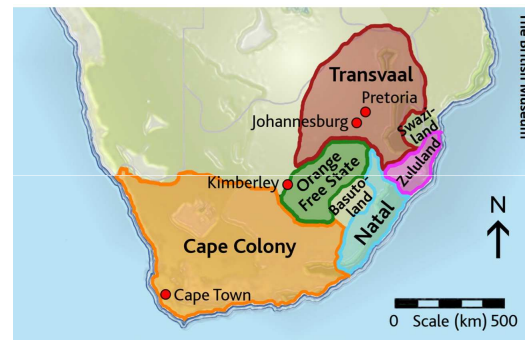


# The discovery of *Trypanosoma brucei*

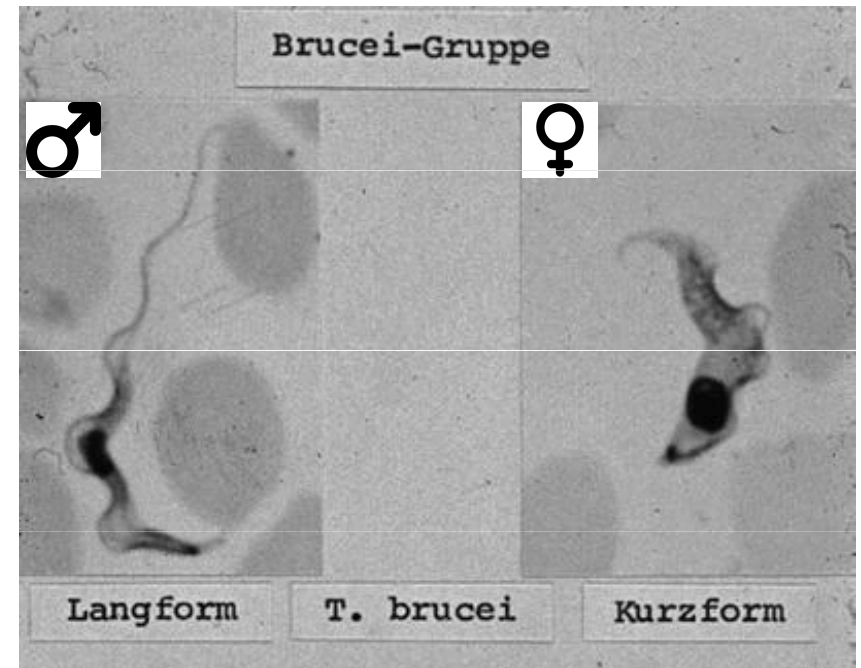


## David and Mary Bruce (1855 – 1931]

- Scottish pathologist and microbiologist
- 1894 – sent to Zululand to investigate an outbreak of nagana (the fly disease)



*T. b. brucei*





# The discovery of *Trypanosoma brucei*



David Livingston  
(1813 - 1875)  
reported death of  
cattle after tsetse  
fly bite (Zambezi  
river)

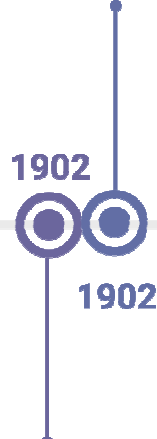


David Bruce  
(1855 - 1931)  
Discovery of *T. brucei brucei*  
AAT

Robert Michael  
Ford (1861 - 1948)  
unequivocal  
observation of  
trypanosomes in  
human blood



Aldo Castellani  
(1878-1971)  
trypanosomes in  
cerebrospinal fluid  
*T. b. gambiense*



Joseph Everett Dutton  
(1874 - 1905)  
*T. b. gambiense*



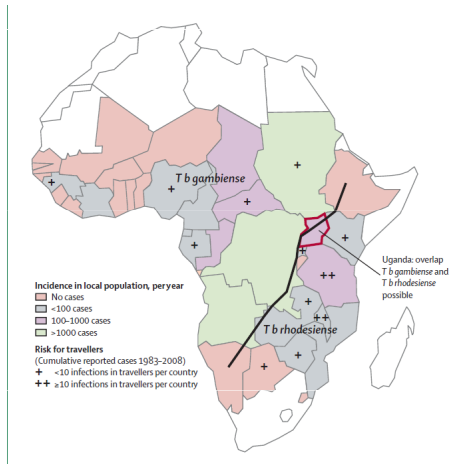
David Bruce  
(1855 - 1931)  
trypanosomes  
are transmitted  
by tsetse fly

Friedrich Karl Kleine  
(1869-1951)  
cyclical transmission of  
trypanosomes

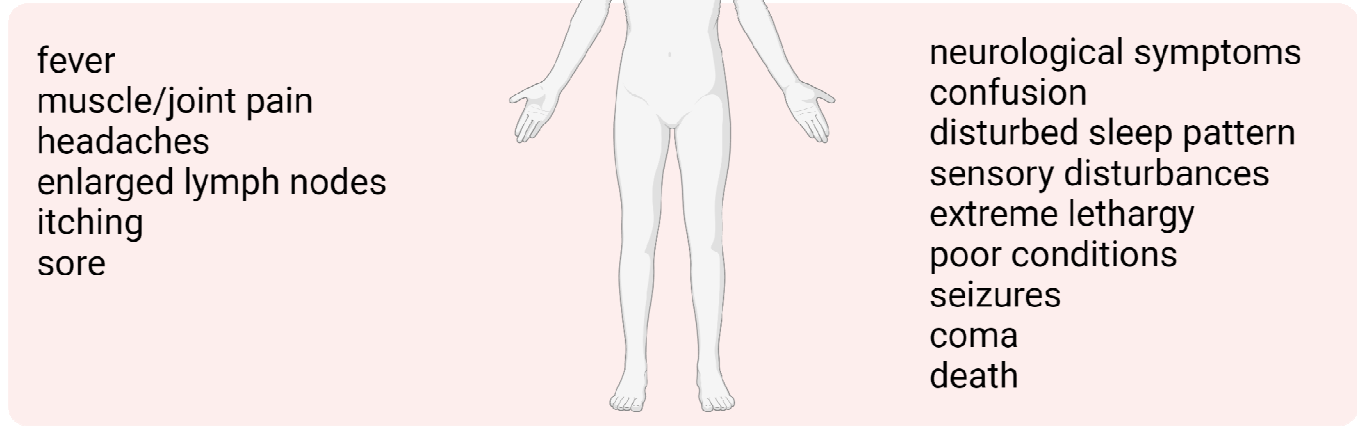
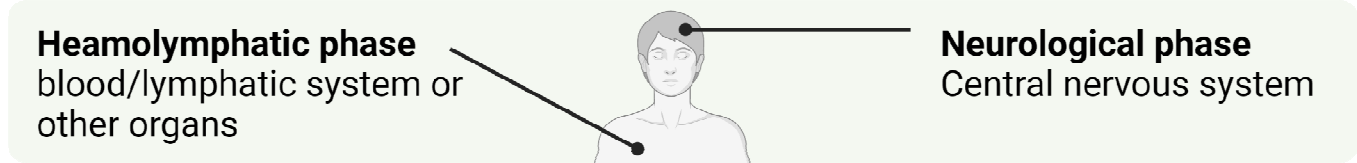
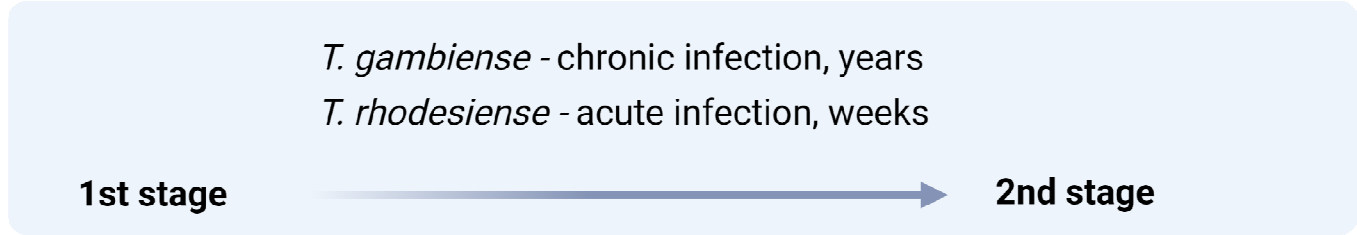


John Stephens  
(1865-1946)  
*T.b. rhodesiense*

# Two species, two diseases



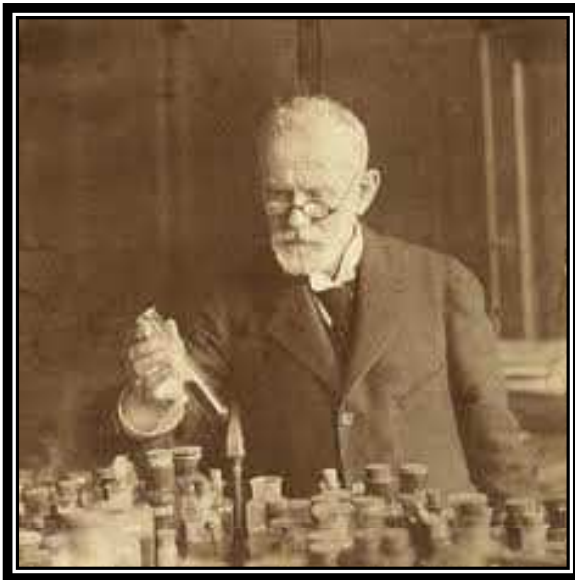
Brun et al., Lancet 2010, 375:148-159



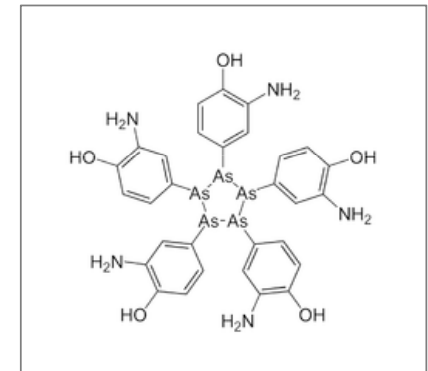
# Drug discovery for treating sleeping sickness



## Paul Ehrlich (1854 – 1915)



- the so-called father of the modern chemotherapy
- original proponent of the “magic bullet”
- 1900s - first synthetic drug
- 1905 – Atoxyl (toxic side effects – blindness)
- 1922 – Suramin (1<sup>st</sup> stage, T.b. rhodesiense, IV)
- 1937 – Pentamidine (1<sup>st</sup> stage, T. b. gambiense, IM)
- 1949 – Melarsoprol (2<sup>nd</sup> stage of the disease, highly toxic, IV)



# Epidemics and control of the disease



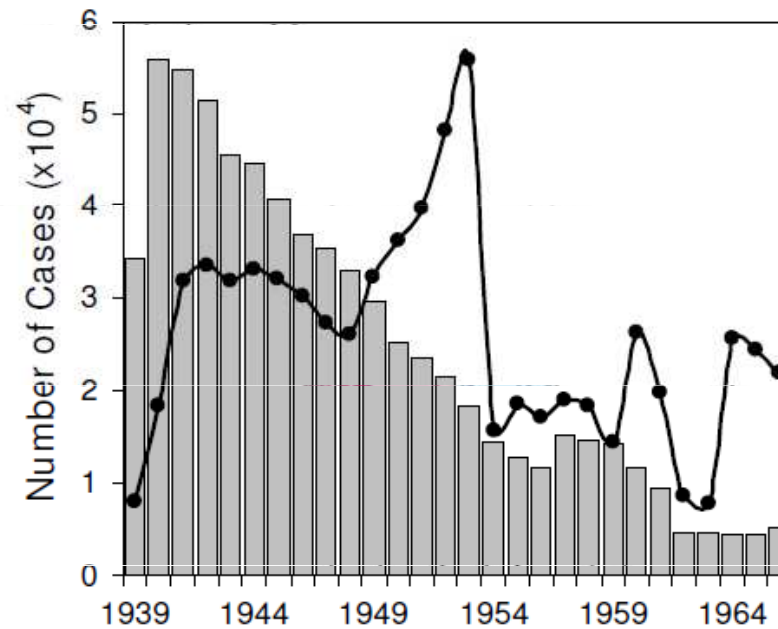
## Francophone colonies

### *T. gambiense*

Humans are only reservoir

#### Approach:

- focused on medical problems
- mobile team (E. Jamot)
- 1926 – atoxylisation
- 1950s – pentaminidiasation (2 mill. people)



## Anglophone colonies

### *T. rhodesiense*

Wild and domestic animals are reservoir

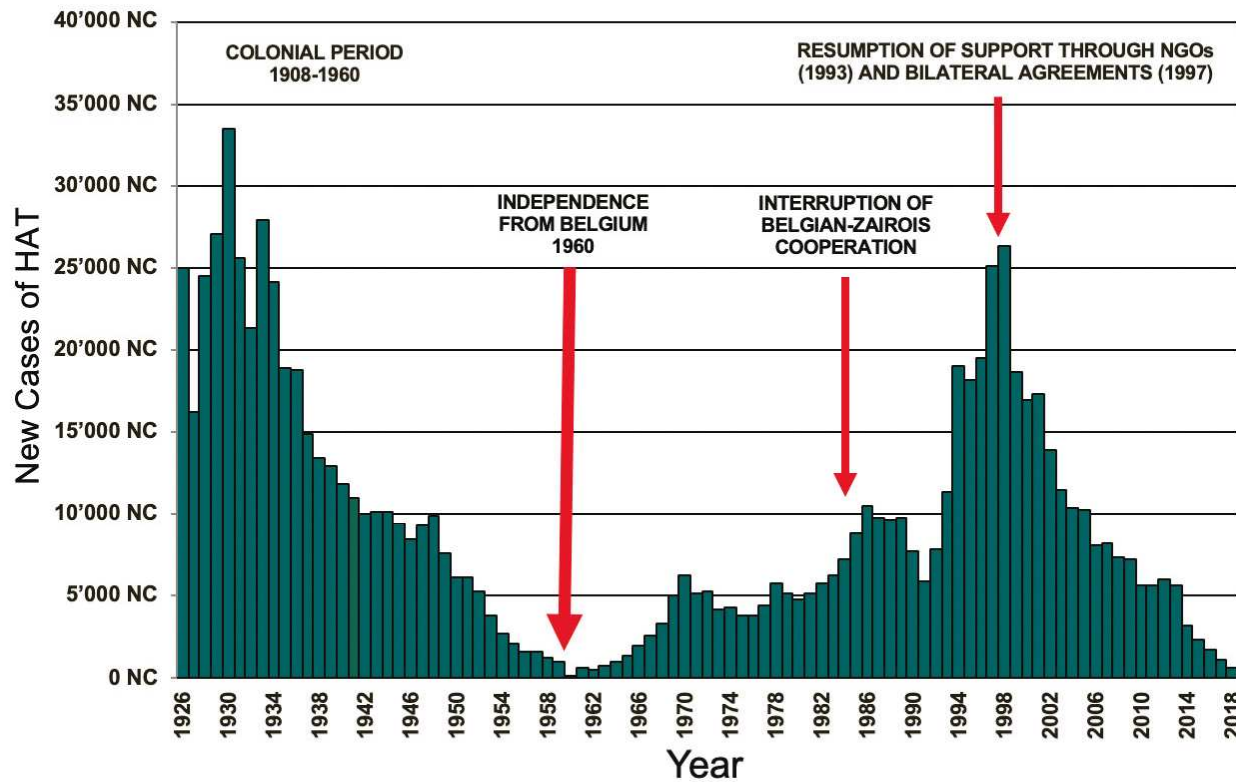
#### Approach:

- vector control (spraying, traps)
- bush clearing
- game destruction
- chemopreventive use of veterinary drugs

# First turning point and a colossal failure



## DRC: Overview of new HAT cases from 1926-2018



# DNDi - Drugs for Neglected Diseases Initiative



## MISSION:

- Developing drugs on a not-to-profit bases
- Needs-driven portfolio
- Raises awareness about lack of R&D for NTDs
- Strengthen R&D activities in endemic countries



## Nifurtimox-eflornithine combination therapy (NECT)

The first improved treatment for sleeping sickness. Before DNDi delivered nifurtimox and eflornithine combination therapy in 2009, doctors often had no choice but to treat sleeping sickness with melarsoprol, a highly toxic, arsenic-based drug that killed 1 in 20 patients.



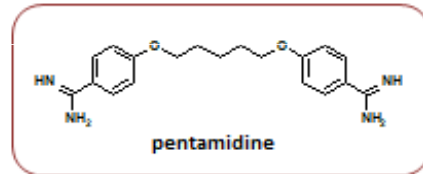
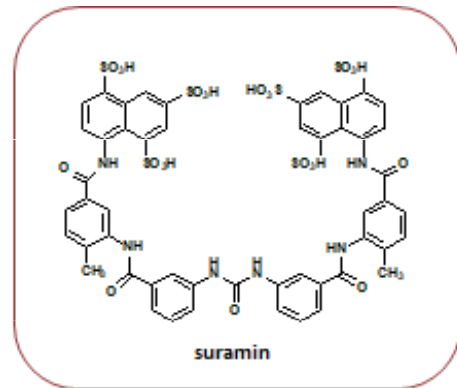
## Fexinidazole for *T.b. gambiense*

An all-new, all-oral patient-friendly treatment. Approved by the European Medicines Agency in 2018, DNDi's first 'new chemical entity' cures the most common form of sleeping sickness in just 10 days of simple, 1-pill-per-day treatment.



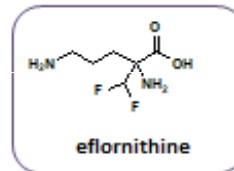
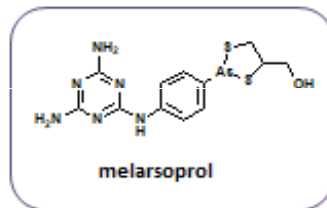
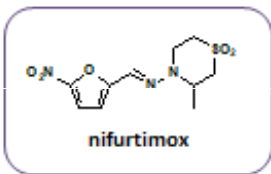
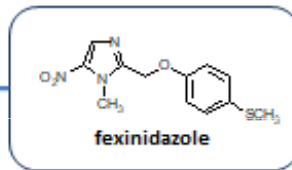
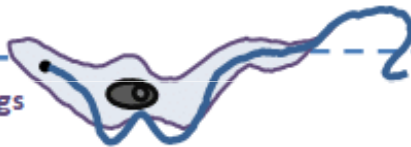


# Treatment



First-Stage Drugs

Second-Stage Drugs



the first line treatment:

**Pentamidine (1941)** resistance, ineffective against late stage

**Suramin (1921)** – severe side effects



the second line treatment:

**eflornithine**

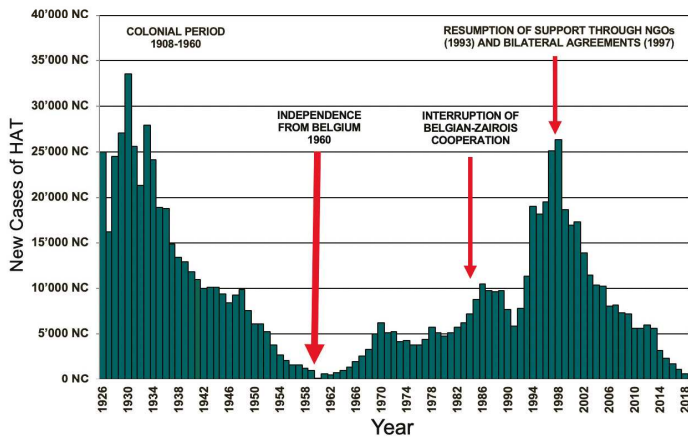
**nifurtimox-eflornithine** combination treatment (NECT)

**Melarsoprol** (1949) arsenic anti-freeze, sometimes fatal, only in severe cases

# Second turning point – the change for a better

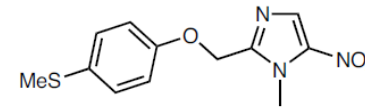


DRC: Overview of new HAT cases from 1926-2018

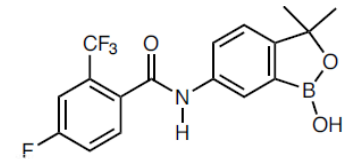


## New treatment:

- NECT – combinatory therapy, IV
- Fexinidazole – 10 tablets, orally, active for the 2<sup>nd</sup> stage
- Acoziboroles – 1 tablet



**Fexinidazole**  
General toxin activated by parasite nitroreductase



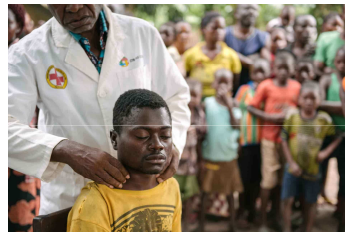
**Acoziborole**  
CPSF3 inhibitor

## Putting sleeping sickness to sleep forever

### Diagnostics



### Surveillance



### Treatment



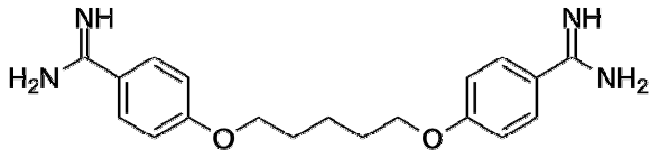
### Vector control



# Pentamidine and Melarsoprol -cross resistance

## Pentamidine

- Diamidines, accumulate in mt
- Binds DNA
- Pleiotropic effect on various cell fce

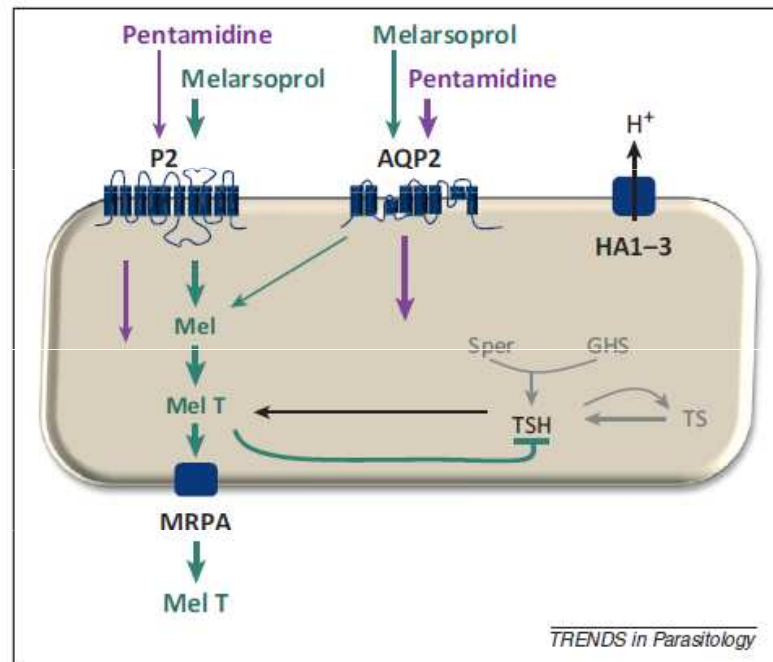
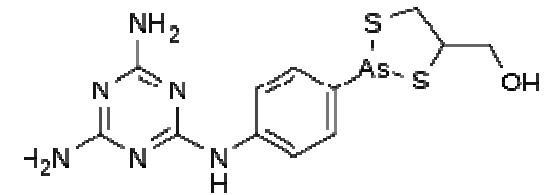


## Pentamidine Injection



## Melarsoprol

- Generates a toxic adduct with trypanothione (MeIT)



*TRENDS in Parasitology*

# Eflornithine

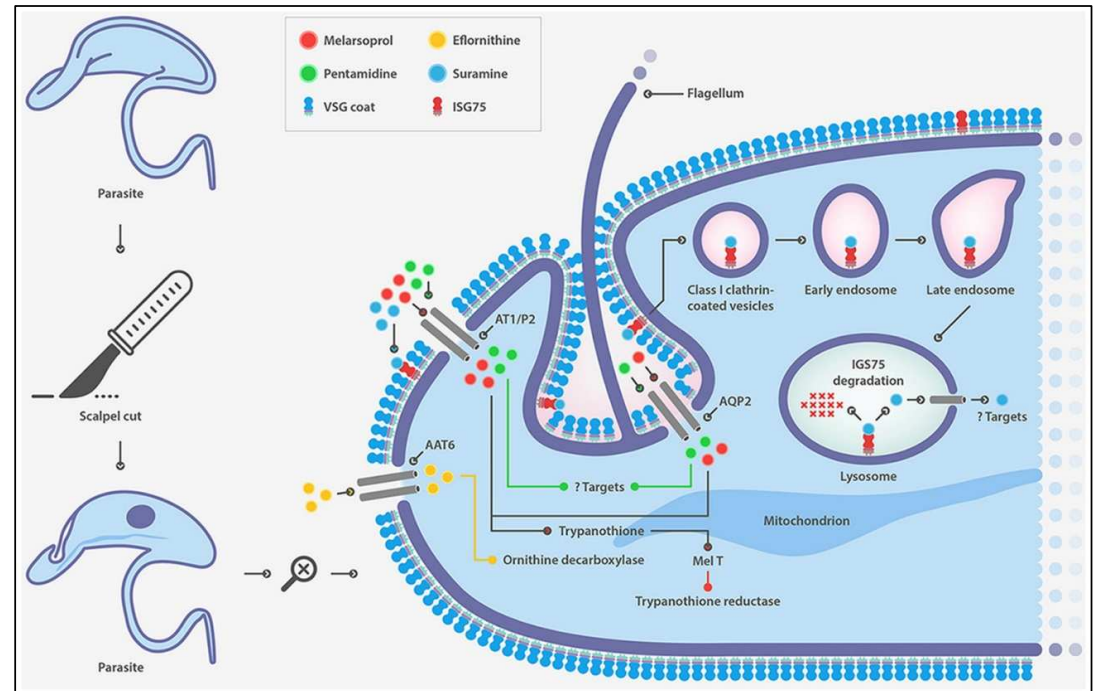
## Nifurtimox-eflornithine combination treatment (NECT)

### Eflornithine

- › Failed cancer drug
- › polyamine synthesis disruption
- › irreversibly binding to **ornithine decarboxylase**
- › preventing the natural substrate ornithine from accessing the active site

### Nifurtimox

- › Originally for *T. cruzi*
- › forms a **nitro-anion radical** metabolite
- › causing significant **breakdown of DNA**
- › mechanism is similar to action of metronidazole



Open Access Review

### The Drugs of Sleeping Sickness: Their Mechanisms of Action and Resistance, and a Brief History

by [Harry P. De Koning](#)

Institute of Infection, Immunity and Inflammation, University of Glasgow, Glasgow G12 8TA, UK



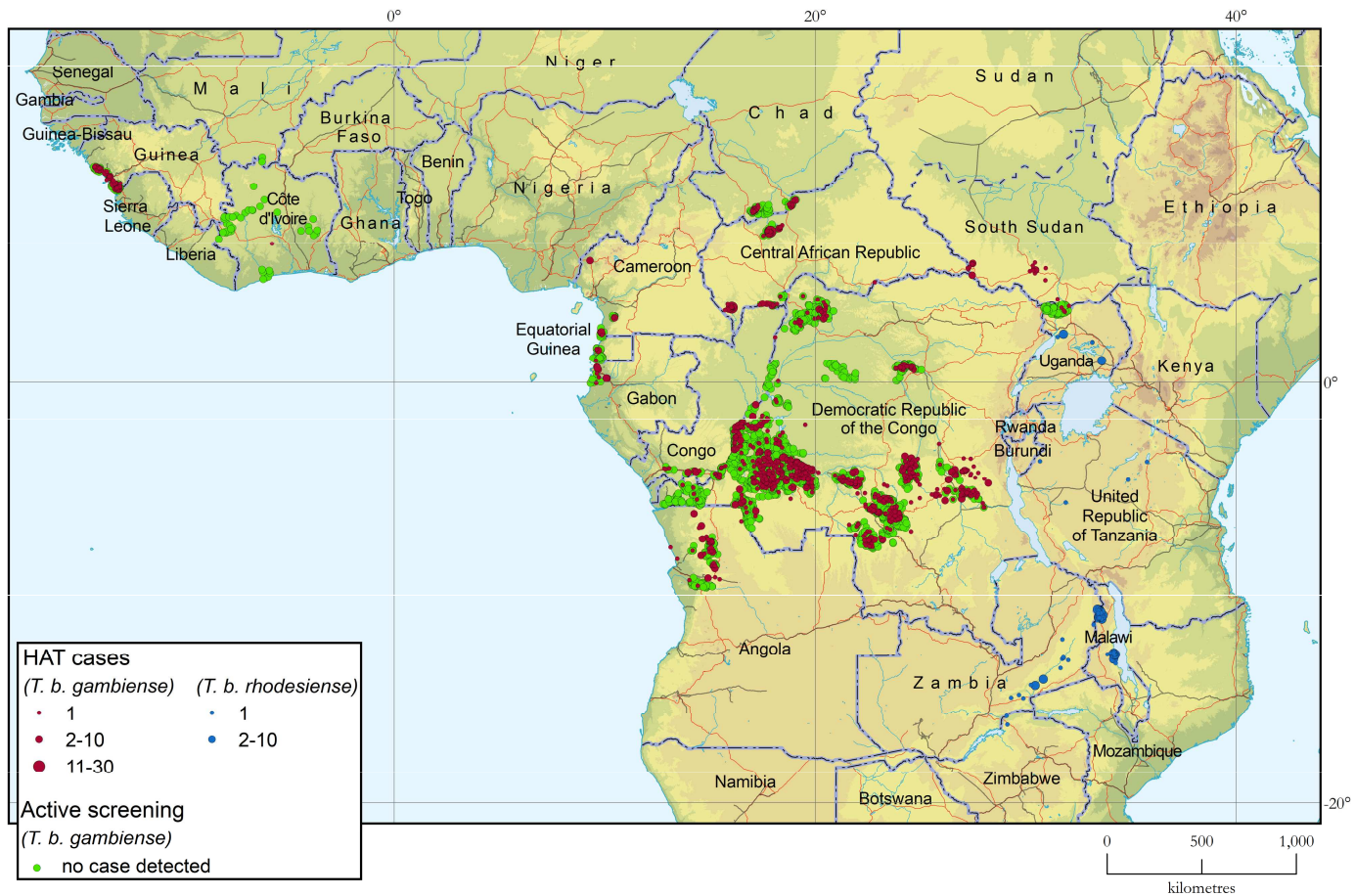


# WHO bold targets

## Elimination of transmission of gambiense HAT

### Elimination as a public health problem of rhodesiense HAT

### by 2030





**African Sleeping Sickness** is a  
parasitic disease spread  
by tsetse flies.

La maladie africaine du sommeil est une maladie parasitaire transmise par la mouche tsé-tsé.