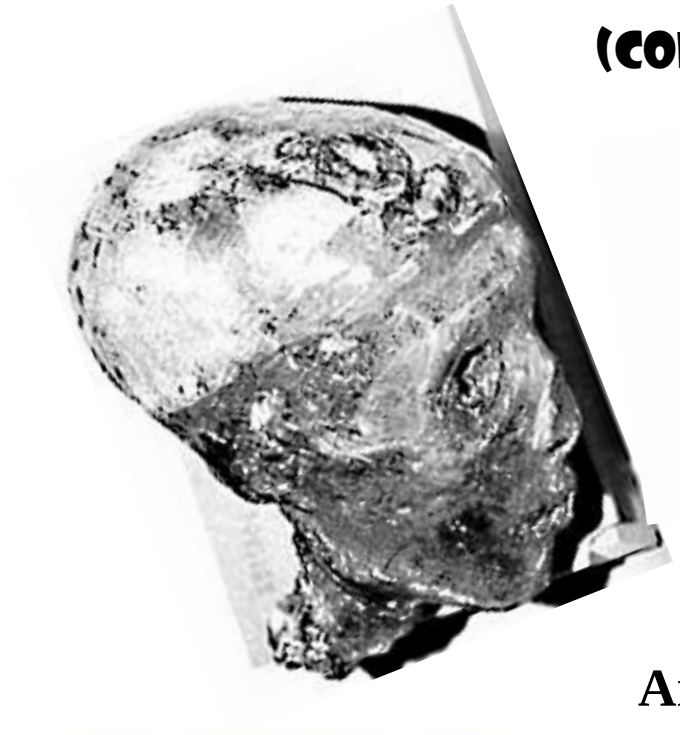
THE HUMAN SCOURGE THAT REFUSES TO GO AWAY

MALARIA UPDATE 2011

(COMING TO A THEATER NEAR YOU?)



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What is Malaria

- ***Mal'aria*: literally "bad air"; reflects the ancient idea that many diseases were caused by miasmas or bad vapors from swamps and marshes.**

- **1880: Dr. Charles Laveran first to attribute a parasite as the cause for malaria. He observed and described what would later be classified as *Plasmodium malariae* in the blood of sick French soldiers stationed in Algeria.**

- **1890-1922: three additional human plasmodia were identified.**

- **1990s: a fifth species, long recognized as a simian form, was found to be capable of producing illness in humans.**

Types of Human Plasmodia - Malaria

- *Plasmodium falciparum* - Falciparum malaria (Welch 1897)
- *P. malariae* - Quartan Malaria (Laveran 1881)
- *P. ovale* - Ovale malaria (Stephens 1922)
- *P. vivax* - Vivax malaria (Grassi and Feletti 1890)
- *P. knowlesi* *new* - Knowlesi malaria (Knowles and Das Gupta 1932)

What is Malaria (cont)

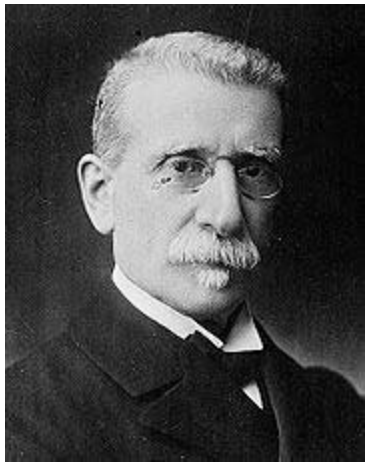
- Today nearly 120 species of plasmodia, including 22 species found in primate hosts, are known.
- There are species that infected birds, reptiles, rodent, bats and many other animals. But these have nothing to do with human morbidity.
- 1898: Sir Rondald Ross described the complete transmission cycle of avian malaria in culicine mosquitoes & birds. His work led to the mosquito being acknowledged as the vector of malaria.

- 1898: Anopheles mosquitoes established as the sole vector of human malaria.

Grassi

Conquerors of Malaria

Marchiafava



Giovanni Battisa Grassi (1854-1925)

Ettore Marchiafava (1847-1935)

Amico Bignami (1862-1919)

Giuseppe Bastianelli (1862-1959)

Angeolo Celli (1857-1914)

Camillo Golgi (1843-1926)

Celli

Golgi

Discerned the complete transmission cycle of human malaria in anopheline mosquitoes & humans between 1898 & 1900.

Malaria Today

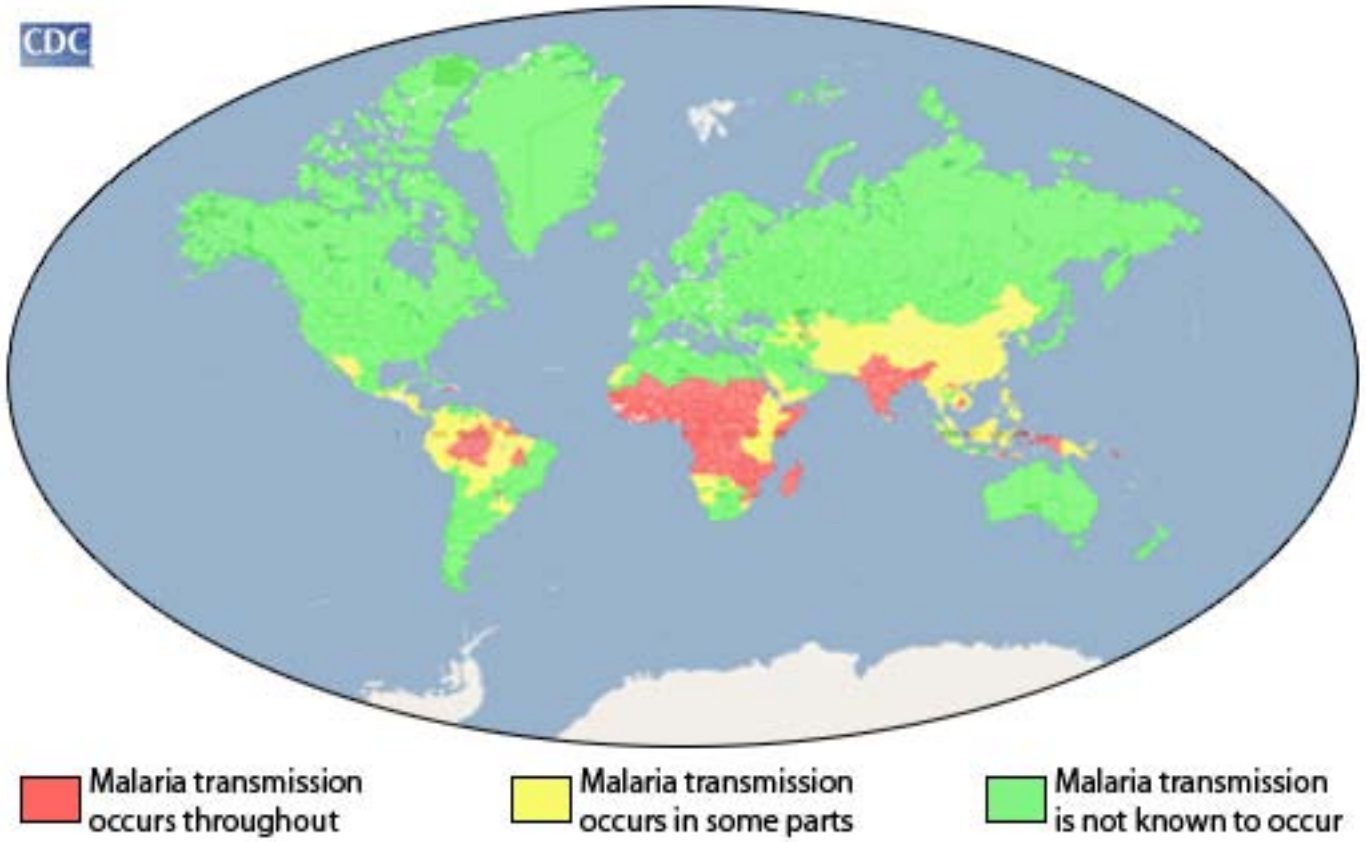
- Malaria is no longer endemic in the U.S., Canada and many parts of Europe.

- BUT….41% of the world's population live in areas where the disease still prevails in an endemic state.

- Each year 350-500 million cases are contracted, with 1 million associated deaths (mostly in children).

- CDC illustration: the 990,000 estimated deaths occurring in 1995 translates to 2,700 deaths per day, 2 deaths per minute!

Current World Wide Distribution of Malaria



THE MONSTROUS EQUATION

COMPETENT ANOPHELES VECTOR

(and therefore good mosquito breeding areas)

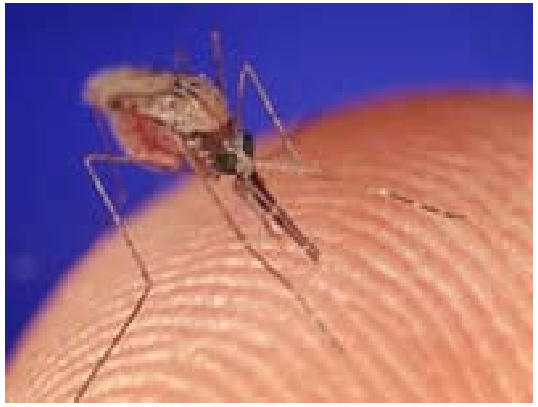
+

A HUMAN RESERVOIR

HUMAN MALARIA

Human Malaria is Transmitted Only by Anopheles Mosquitoes

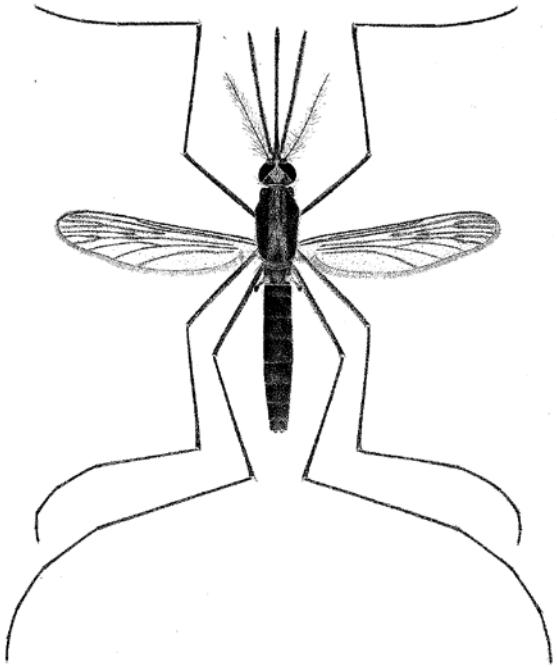
- Around 3,500 mosquito species worldwide.
- About 430 recognized *Anopheles* species worldwide.
- But only around 70 *An*. species capable (16%) of transmitting malaria; about 30-40 common or competent vectors, others occasional or secondary transmitters.



An. gambiae

- Competence only partially understood:
  - **biochemical compatibility with plasmodia**
  - **willing/frequent feeder on humans (anthropophilic / phagic)**
  - **willing to enter human domiciles (endophilic)**
  - **longevity of species & its density in relation to humans**

Residual Anophelism in Arizona



Anopheles hermsi

(formerly *An. freeborni*)

Known competent vector:

- wide distribution in AZ and the western U.S.
- endophilic and anthropophilic
- found infected in nature

Residual Anophelism in the Verde Valley, Yavapai County, AZ.*
Anopheles hermsi Collected 2004-2010

Year	No. Specimens
2004	362
2005	432
2006	681
2007	112
2008	73
2009	14
2010	550
Total	**2,224**

*Collection sites: Camp Verde, Clarkdale, Cornville, Cottonwood, Lake Montezuma and Rimrock

Residual Anophelism in Arizona

An. franciscanus (secondary vector?)

- ubiquitous, but exophilic and zoophilic
- will feed on humans when need arises
- no data on infected in nature, but has been infected with *P. vivax* in the laboratory

An. judithea*, formerly *An. barberi (secondary vector??)

- treehole species w/ limited distribution
- exophilic and zoophilic
- no data on infection in nature; laboratory study shows *An barberi* can be infected with *P. vivax* and later transmit malaria to a human

Malaria in Arizona

- Like most of the U.S. in the 19th century, malaria was endemic in the state.
- The last endemic cases occurred in the 1930s, early 1940s (prior to WWII).
- Endemic malaria in the state and the U.S. declined due to a combination of factors: damming of rivers, draining of marsh areas, greater use of screening, extensive mosquito control efforts and improved medical treatment and availability of quinine.

The Arizona Experience

Old song, sung to the tune chorus of *Old Dan Tucker*.

The people here in Arizony
All look very pale and bony.
They shake and ache and burn and shiver
Up and down the Gila River.
I'm freezing in the heat of day,
I feel like winter's here to stay.
I'm too cool for the month of June,
So bring me quinine and a spoon…

As presented in *Arizona's Changing Rivers: How People Have Affected the Rivers*, B. Tellman, R. Yarde & M.G. Wallace, 1997.

Malaria in Arizona, 1934-2009*

Ten Year Period	No. of Cases
1930 – 1939†	205
1940 – 1949	794
1950 – 1959	154
1960 – 1969	36
1970 – 1979	52
1980 – 1989	127
1990 – 1999	110
2000 – 2009	160

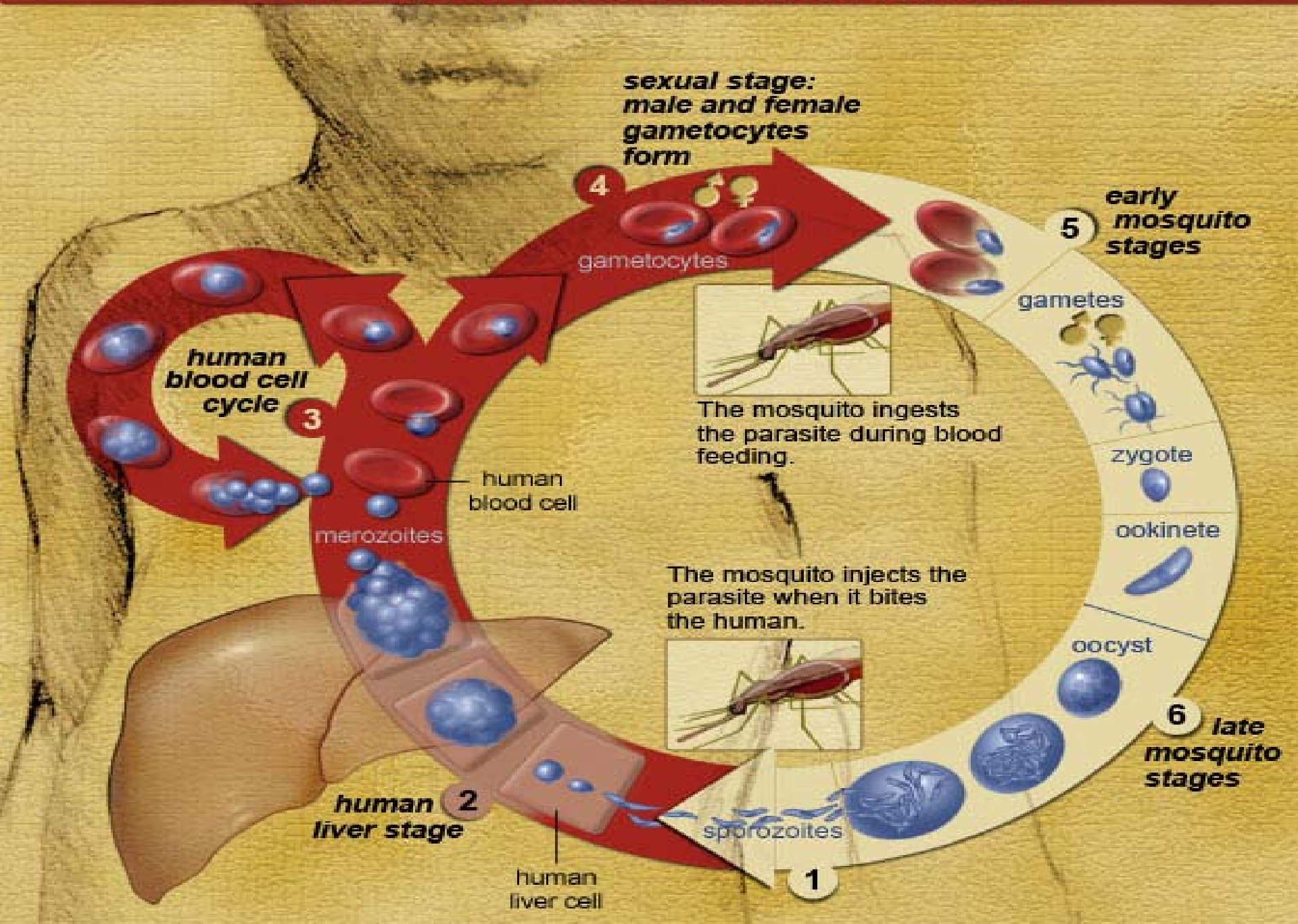
- Cases imported except for some from the 1930s and early 1940s that probably represent the last of the state's endemic cases.

† No records available for 1930 – 1933.

Malaria in the U.S.

- Mosquito control activity in the U.S. was greatly increased during WWII to protect training bases.
- The fight was lead between 1942-1945 by the Office of Malaria Control in War Areas (MCWA), headquartered in Atlanta, GA.
- This federal agency later became the Communicable Disease Center and today is known as the Centers for Disease Control and Prevention.

Life Cycle of the Malaria Parasite



Malaria Transmission 101 – THE MOSQUITO

- A female *Anopheles* mosquito ingests blood containing male and female **gametocytes** while taking a human blood meal (immature or asexual forms are digested along with red blood cells).

- Inside the lumen of the mosquito gut the **gametocytes** further mature into male and female **gametes:**

  Male — nucleus divides into 4-8 new nuclei
  each nuclei forms tail-like **flagellum** which extends out of the original cell (**exflagellation**)
  flagella break free → **male gamete** or **microgamete**
  Microgamete seeks out female parasite and enters → fertilization

  Female — go through general maturation process → **female gamete** or **macrogamete**
  Macrogamete forms small projection for **microgamete** to enter → fertilization

Malaria Transmission 101 – THE MOSQUITO (cont)

- Microgamete + macrogamete → **zygote.**
- **Zygote** is motionless for while and then elongates, develops a cytoskeleton and becomes mobile → **ookinete.**
- The **sporgony** process is now initiated.
- The **ookinete** penetrates the gut wall → **oocyst.**
- The **oocyst** becomes round and remains on the outside surface of gut where it increases in size. This causes it to rupture. Inside, it's nucleus and cytoplasm repeatedly divide → **sporozoites**.
- **Sporozoites** are motile and burst out of the weaken outer wall of the **oocyst**, and into the body of the mosquito making their way to the salivary glands.
- **THE MOSQUITO IS NOW INFECTIVE - SHE IS LOCKED AND LOADED!**

Malaria Transmission 101 – THE HUMAN

- Female anopheles mosquito injects **sporozoites** into a human. Some destroyed by phagoctes while some eventually invade parenchymal cells of the liver (**hepatocytes**).

- Each **sporozoite** begins asexual multiplication (**pre-** or **exo-erythrocytic schizogony**) → single **schizont** in a liver cell → multiple uninucleate **merozoites** in each **schizont. Hepatocyte** and **schizont** rupture spilling **merozoites** into the blood → **i**nvade red blood cells (**erythrocytes**).

- **Special Note**: In *P. vivax* and *P. ovale* infections, some **sporozoites** → **hypnozoites**. These are basically **schizonts** that remain dormant for considerable periods of time until they undergo **exo-erythrocytic schizogony.** This causes relapse.

Malaria Transmission 101 – THE HUMAN (cont)

- The **merozoites** undergo 2nd phase of asexual multiplication in the erythrocytes (**erythrocytic schizogony**) → **trophozoite** → **schizont** → **merozoites** → burst forth to invade additional fresh red blood cells.

- This process is repeated over and over again raise the level of parasitemia until the immune system kicks in slowing the process down.

- The **erythrocytic cyle of schizogony** becomes synchronized producing the classic 24, 48 and 72 febrile paroxysms of malaria.

- A few young **merozoites** develop into male and female **gametocytes** that circulate in the peripheral blood until a female *Anopheles* mosquito comes along and takes a blood meal.

Prodrome
2-3 days before first paroxysm

Symptoms

- Malaise, fatigue, & lassitude, with dire to stretch the limbs & yawn
- Headache
- Dizziness
- Pain or aching in the chest, back, abdomen, joints & bones (so-called ‘break bone’ fever affect)
- Anorexia
- Nausea
- Vomiting
- Sensation of cold water trickling down the back
- Slight fever

Physical Presentation

- Patient looks weak and ill
- Clinically anemic
- Mildly jaundiced with tender enlargement of the liver & spleen
- Conjunctivae suffused
- Perspiration

Many of these symptoms may continue through the febrile paroxysmal cycle

Variability in the Febrile Paroxysm Cycle

- In early stages of schizogonic periodicity there are multiple ‘broods’ of parasites developing at different times.
- As a result the initial cycle of febrile paroxysms will vary and exhibit no specific periodicity.
- Schizogonic periodicity eventually becomes synchronized reflecting the classic 24, 48 or 72 febrile cycle.
- Febrile variability in the early stages is why it is important to submit smears to identify malaria type.

Classic Paroxysmal Cycles

- Synchronized Cycles:
  Tertian: occurring every 48 hrs or every 2nd day.
  Quartan: occurring every 72 hrs or every 3rd day.
  Quoditian: 24 hr febrile periodicity (mixed infections).

- Regardless of cycle duration, cases start with:
  Cold Stage (shakes)
  Hot Stage (fever)
  Sweating Stage (profuse perspiration)

- Onset is in the afternoon or early evening

Why the Terms 'Tertian' and 'Quartan'

- These are ancient Roman classifications for intermittent febrile events.
- The Roman system measures from the beginning of the first paroxysm to the end of second.

Example:

- If you have a first bout on Monday and have your second on Wednesday – that's 'tertian'.
- If, on the other hand, you have a first bout on Monday and your second on Thursday – that's 'quartan'.

Terminology

Relapse:

follows a variable interval of up to 3 years or more after the primary infection (caused by exoerythrocytic parasites, i.e., hypnozoites of the liver)

Recrudescence:

renewal of activity of the disease after a few weeks following incomplete treatment/cure (caused by erythrocytic parasites)

Falciparum Malaria*

pernicious, aestivo-autumnal, malaria tropica

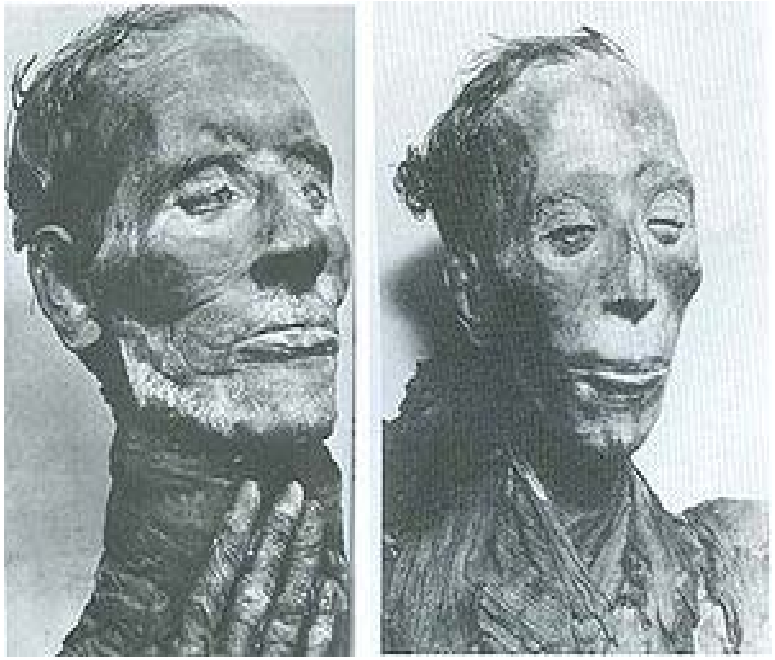
- **Incubation period: 9-14 (12) days**
- **Erythrocytic (paroxymal) cycle: traditionally 48 hrs (malignant tertian), but 24 and 36 hrs cycles can occur; sometimes twice every 3 days (sub-tertian). More often fever is continuous or remittent.**
- **Febrile paroxysm: 16-36 hrs or longer**
- **Parasitemia (per µl): Average - 20,000 to 500,000**
  Maximum - 2,000,000
- **Primary attack: severe in non-immunes (often fatal)**
- **Duration of untreated infection: 1-2 yrs**
- **Relapses: no**
- **Recrudesent: yes**

* Based on Gilles and Warrell (1993)

FALCIPARIUM MALARIA

The Real Mummies Curse

Late 18th Dynasty Egyptian Royalty DNA+ for *P. falciparum*



Yuya and Thuya
Great-Grandparents of Tut

Tutankhamun
'King Tut the Boy King'

Vivax Malaria*

- Incubation period: 12-17 (15) days or up to 6-12 months
- Erythrocytic (paroxymal) cycle: 48 hrs (benign tertian)
- Febrile paroxysm: 8-12 hrs
- Parasitemia (per µl): Average - 20,000
  Maximum - 50,000
- Primary attack: mild to severe
- Duration of untreated infection: 1.5-5 yrs
- Relapse: yes
- Recrudescent: no

* based on Gilles and Warrell (1993)

Ovale Malaria*

- Incubation period: 16-18 (17) days or longer
- Erythrocytic (paroxymal) cycle: 50 hrs (tertian)
- Febrile paroxysm: 8-12 hrs
- Parasitemia (per µl): Average - 9,000
  Maximum - 30,000
- Primary attack: mild
- Duration of untreated infection: 1.5-5 yrs?
- Relapse: yes
- Recrudescent: no

* based Gilles and Warrell (1993)

Quartan (malariae) Malaria

- Incubation period: 18-40 (28) days or longer
- Erythrocytic (paroxymal) cycle: 72 hrs
- Febrile paroxysm: 8-10 hrs or longer
- Parasitemia (per µl): Average - 6,000
  Maximum - 20,000
- Primary attack: mild
- Duration of untreated infection: 3-50 yrs
- Relapses: no
- Recrudesent: yes

* based on Gilles and Warrell (1993)

THE NEW KID ON THE BLOCK

Knowlesi Malaria (*Plasmodium knowlesi*)

- Simian malaria common in macaques and other monkeys in Southeast Asia.
- 1965: first recorded naturally acquired case in a human.
- Since then examples of natural infected humans (both individual and group cases) have been identified in southern China, Indonesia, the Philippines, Malaysia, Myanmar (formerly Burma), Singapore, Thailand and Vietnam.
- Acrodendrophilic anopheles mosquitoes (e.g., *An. leucosphrus* complex, especially *An. latens*) feeding on monkeys will come closer to the ground and feed on humans when the opportunity arises.

THE NEW KID ON THE BLOCK

- Human infections appear to be occurring while people are tending their farm plots at the edge of the jungle (ectophily) and possibly when in their domiciles in nearby villages (endophily).
- This ‘new’ phenomenon has been attributed to increased encroachment by humans on the natural anopheles-simian cycle of *P. knowlesi* infection.
- Anopheles vectors are capable of:

  (1) monkey-to-monkey transmission

  (2) monkey-to-human transmission (zoonosis)

  (3) human-to-human transmission

  (4) human-to-monkey transmission (anthroponosis)

Knowlesi Malaria*

- Incubation period: 10-12 (11) days or longer
- Erythrocytic (paroxymal) cycle: 24 hrs (quoditian)
- Febrile paroxysm: 12-31 (20) hrs
- Parasitemia (per µl): generally low to moderate but vary considerably and may be as high as 150,000 to 200,000+
- Primary attack: mild to very severe, but can be fatal
- Duration of untreated infection: not yet defined
- Relapse: no
- Recrudescent: no

* Data provisional based on available information. and subject to change when this form of malaria is better understood.

The Mosquito is little

But Has bugs in her spittle

Repellents and spray

Will keep her away