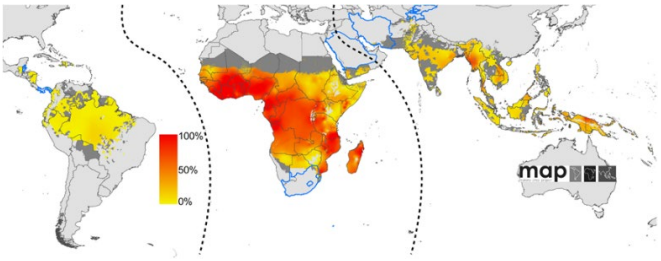
STANDARD DEVIATIONS: March Madness – Cerebral Malaria

Greetings,

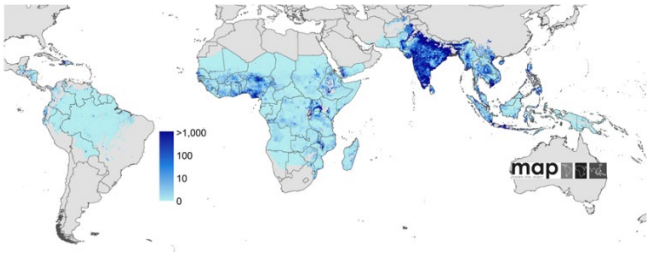
Encephalopathy from *Plasmodium falciparum*. It rolls off the tongue like a spell from Harry Potter's Hogwarts' homework.

But **Cerebral Malaria (CM)** is not fiction, it doesn't have happy endings, and its story is still being written.

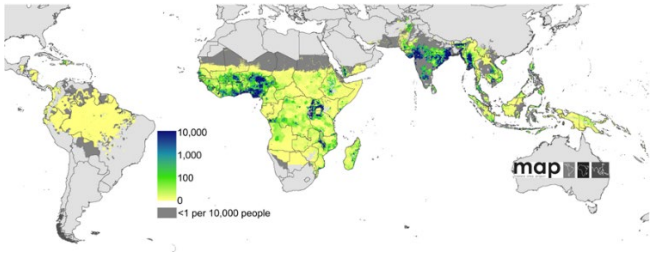
Over 3.5 billion humans are at risk from several different *Plasmodium* species. Cerebral malaria is the most severe neurological complication of *P falciparum*, with over 575,000 cases annually.



{A. Infected *Anopheles* mosquitoes}



{B. Population density}



{A + B = Malaria}

Today, that burden is mainly in Sub-Saharan Africa and Eurasia. But we're closer to malaria here in the US, than most realize, understand, or remember.

Between 1957 and 2011, there have been 63 reported outbreaks, and there are approximately 1,500 – 2,000 cases of malaria reported every year, right here, in America. Every state in America except Alaska has been endemic for malaria at some time.

Columbus and crew had malaria. Jamestown was epidemic in 1607. George Washington had malaria. Abraham Lincoln had malaria. Ulysses S. Grant did too; so did JFK. During the Panama Canal construction, 21,000 of 26,000 workers were affected by malaria. Ten thousand soldiers died of malaria in the Civil War and 60,000 WWII American soldiers died from malarial disease.

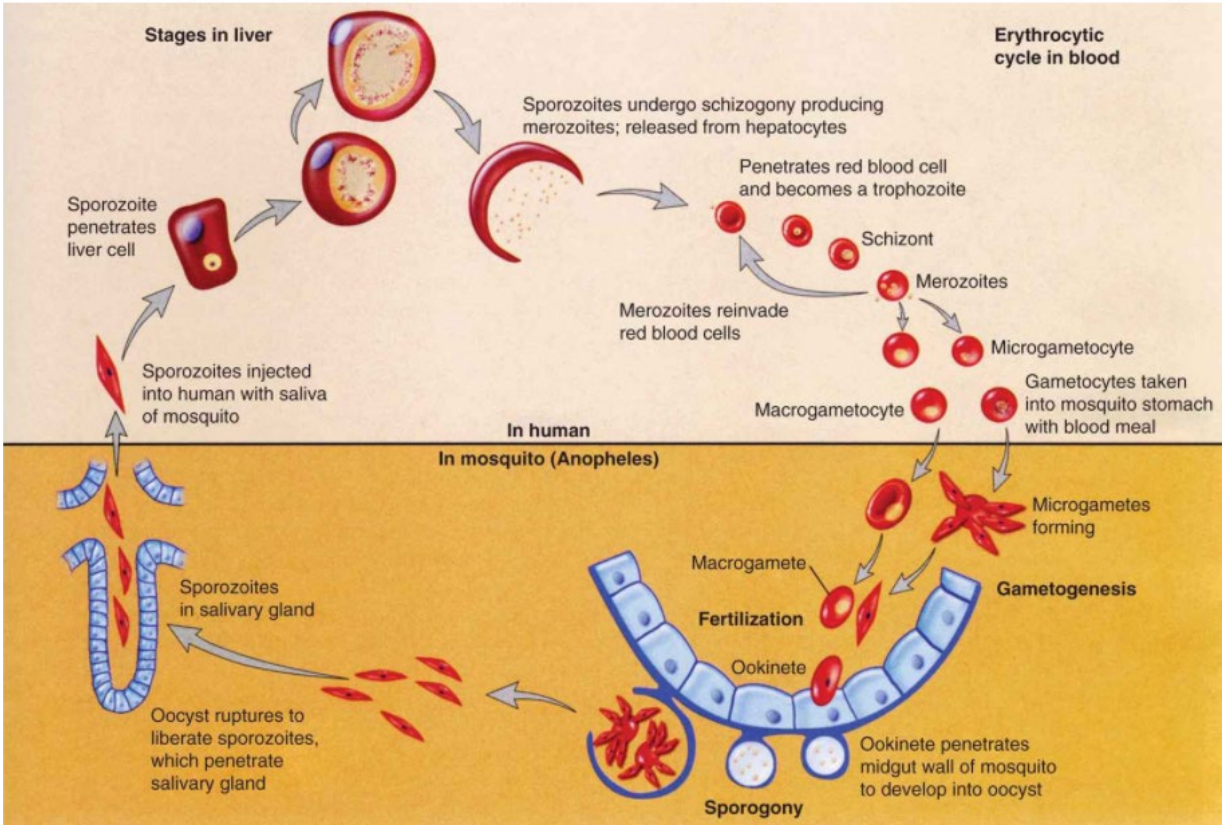
The CDC evolved directly from a malaria control program. The original WWII program, Malaria Control in War Areas until 1946, was located in Savannah, GA. This is why the CDC is in Atlanta.

{Originally just mosquito entomologists fighting malaria.}

***Falciparum* malaria is the most important parasitic disease globally.** Cerebral malaria (CM) is the presenting syndrome in around half of the patients with severe malaria, both in children and adults. **CM leads to neurological dysfunctions** including seizures and impaired consciousness **and has a fatality rate up to 30%** in treated patients.

The pathogenesis of fatal CM is poorly understood, but we can point a finger at red blood cells and how *Plasmodia* affects them. Infected RBCs (**pRBC**) clog the vascular network of the brain, starving it of oxygen and causing edema; the brain swells up and suffocates. Children die of brain hypoxia, and adults do too, but adult brains tolerate infection better.

Here's the classic life cycle schematic:

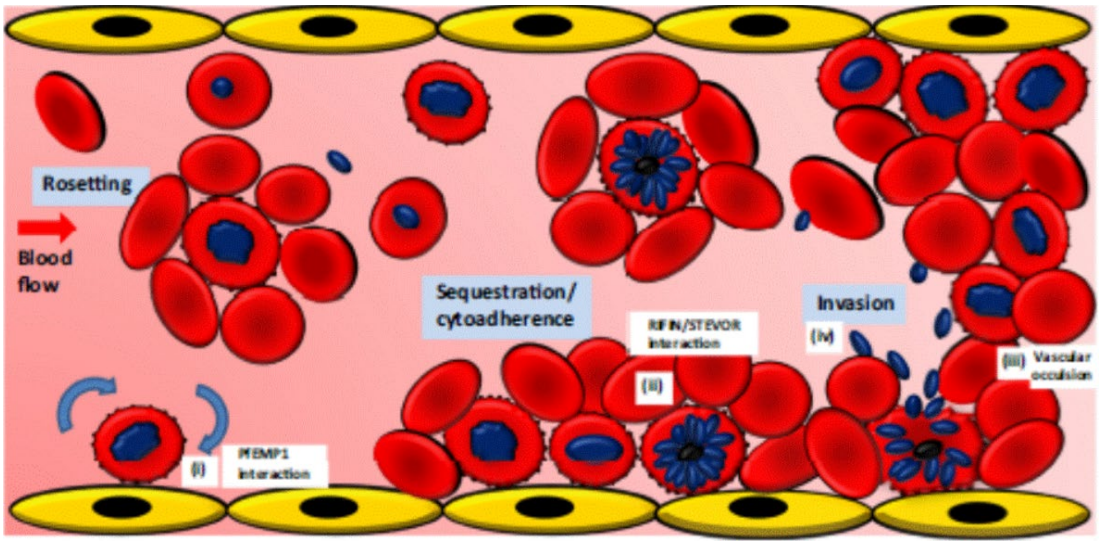


{There is often more than one parasite per cell.}

The cycle is pretty uniform for all species. **So, why does *P falciparum* cause CM and the other *Plasmodium sp*. don't?**

Other species are not as invasive. *P vivax* and *P ovale* only attack young reticulocytes; and *P malariae* prefer old, senescent erythrocytes. With these guys, only 1-2% of all RBCs are in play. ***P falciparum* isn't nearly as picky and produces high levels of parasitemia because it invades <u>any</u> RBC**, regardless of its age. When a bunch of cells have problems, the problems are bad.

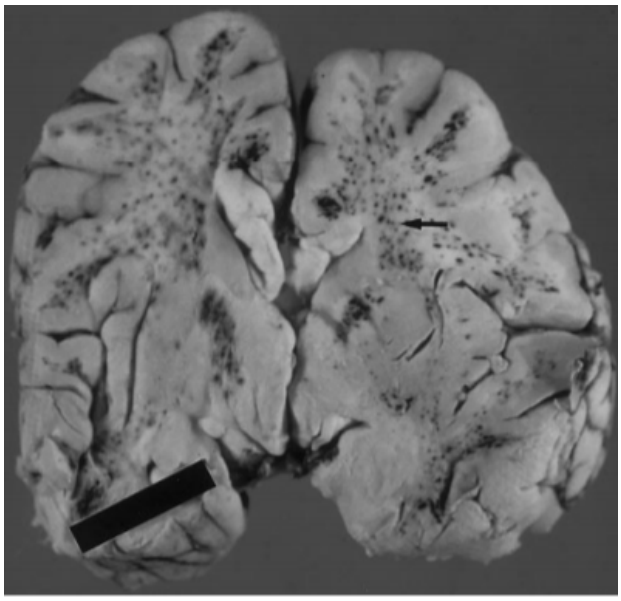
And **the problem with pRBCs is a change in cell membrane antigens**. Infected RBCs have a sudden and strong affinity for each other (<u>rosettes</u>) and they now bind to the specific endothelial cells that line the brain capillary (<u>adhesion and occlusion</u>). Rosettes and pRBCs adhere to the capillary lining, blocking the flow of oxygen. Downstream effects cause platelet changes and an immune response that pile on with problems of their own.



{Rosette formation and adhesion/occlusion of neural endothelial lining.}

That **conformational change in the surface of the infected RBC**, making it sticky to brain capillaries, **causes the fatal cascade** of metabolic and immunity related symptoms. The changes are related to glycoproteins of the malaria gamete but also to changes that happen to antigens already present on the red blood cell surface, the ABO group (and Duffy antigens in other malarias).

All RBCs are culprits, but "A" blood type antigens show higher incidence and severity of CM.



{Diffuse hemorrhage in CM}

The pRBC blockage accumulates, fresh oxygen is cut off, and hypoxia sets in. A coagulation and immune response is initiated. This alters fluid dynamics and sets off a cytokine storm that floods the region. The metabolic, coagulation and immunity problems result in edema. Brain hypoxia and cerebral herniation that result often lead to death, especially in the young.

The crazy thing about this story is that these same dynamics are playing out in COVID-19. Changes in membrane glycoproteins result in the effusion and cytokine storm cascades that typify severe coronavirus infection. In this case, the endothelium of the lung (and less the kidney, and heart, and brain, etc.) are affected.

With SARS-CoV2, some studies show A blood type bias and others refute this. Who knows? We just don't have the centuries of data to examine, like we do with malaria.

Next week, more March Madness.

Have a great week and be safe,

Bryan

p.s. (The protective anomaly of hemoglobinopathy in malaria is fodder for another newsletter barrage… someday.)