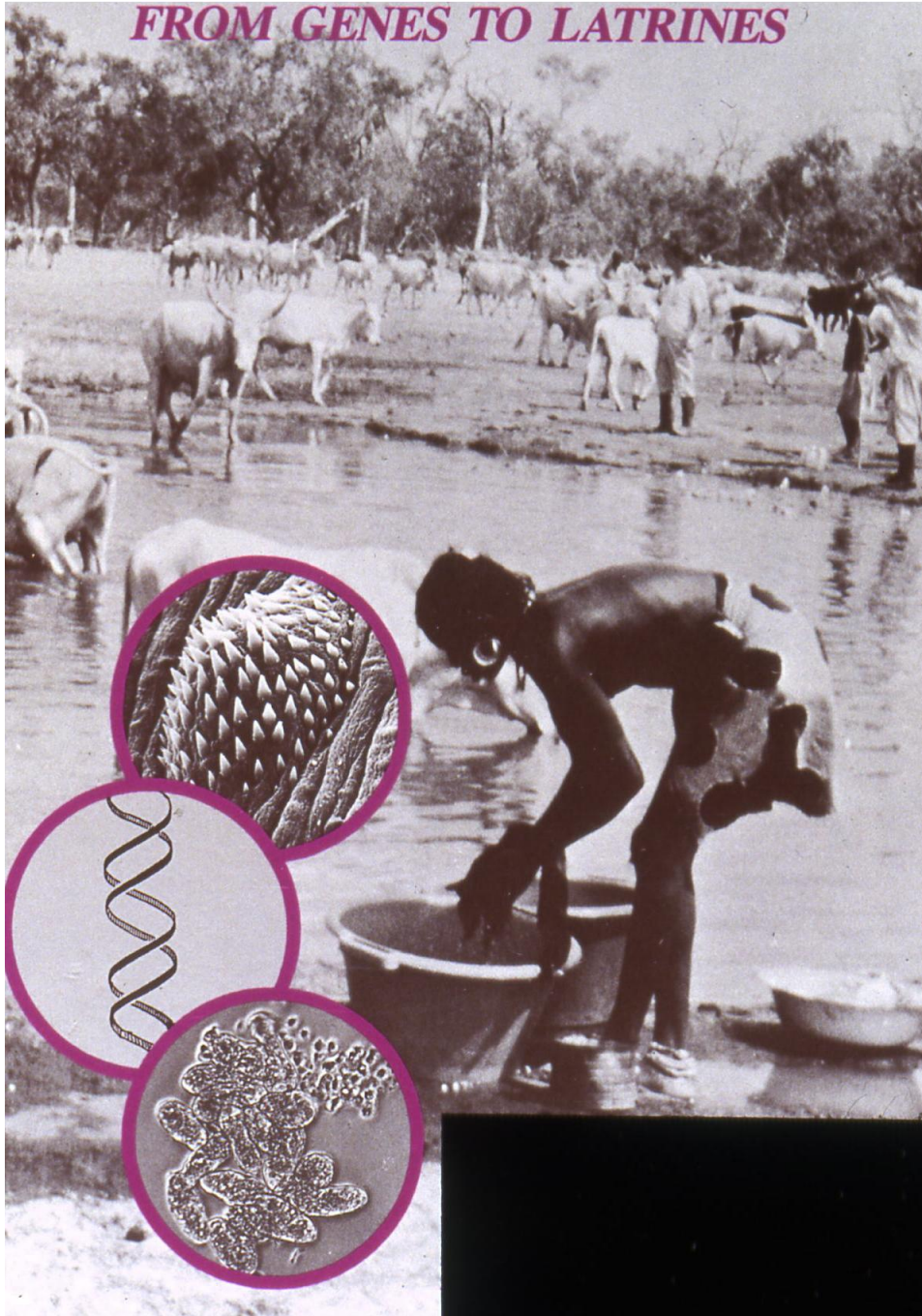


FROM GENES TO LATRINES



Schistosomiasis

Originally named bilharzia in honor of Theodor Bilharz who first described the disease in 1851 in Cairo, Egypt.

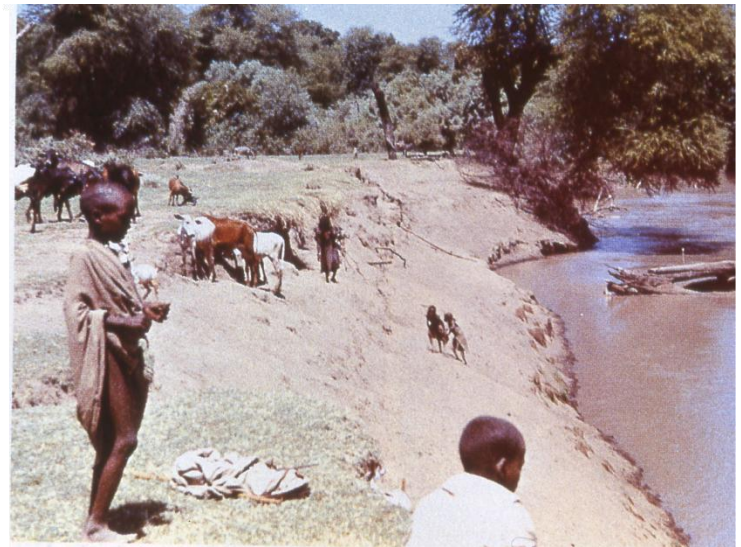
“Make you no piss for water. If you wan piss go piss for dry ground.”

--Bilharzia Notice Board,
Cameroon, 1972.



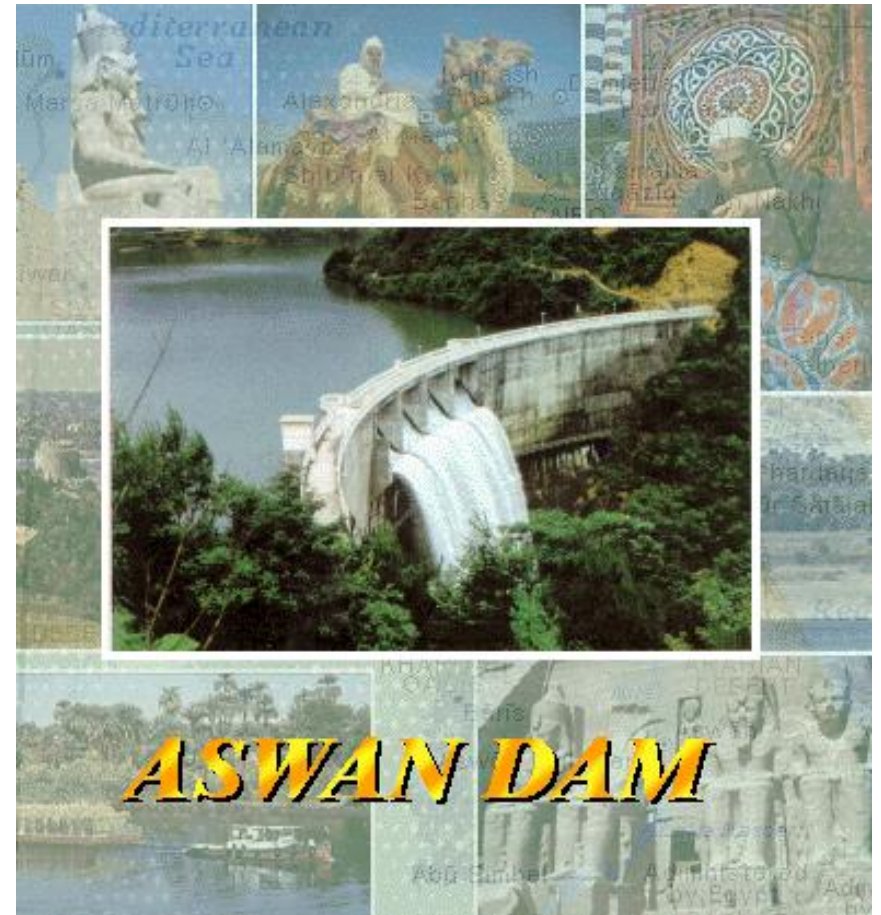
Schistosomiasis-Introduction

- **Affected humans for many millennia.**
 - **Calcified ova in Egyptian mummies.**
- **Because so many of Napoleon's soldiers suffered from the effects of urinary schistosomiasis during his Egyptian campaign, the country was referred to as the 'the land of menstruating men.'**



Schistosomiasis-Introduction

- Prevalence of infection increasing in many countries due to introduction of agricultural programs and the development of man-made water systems.

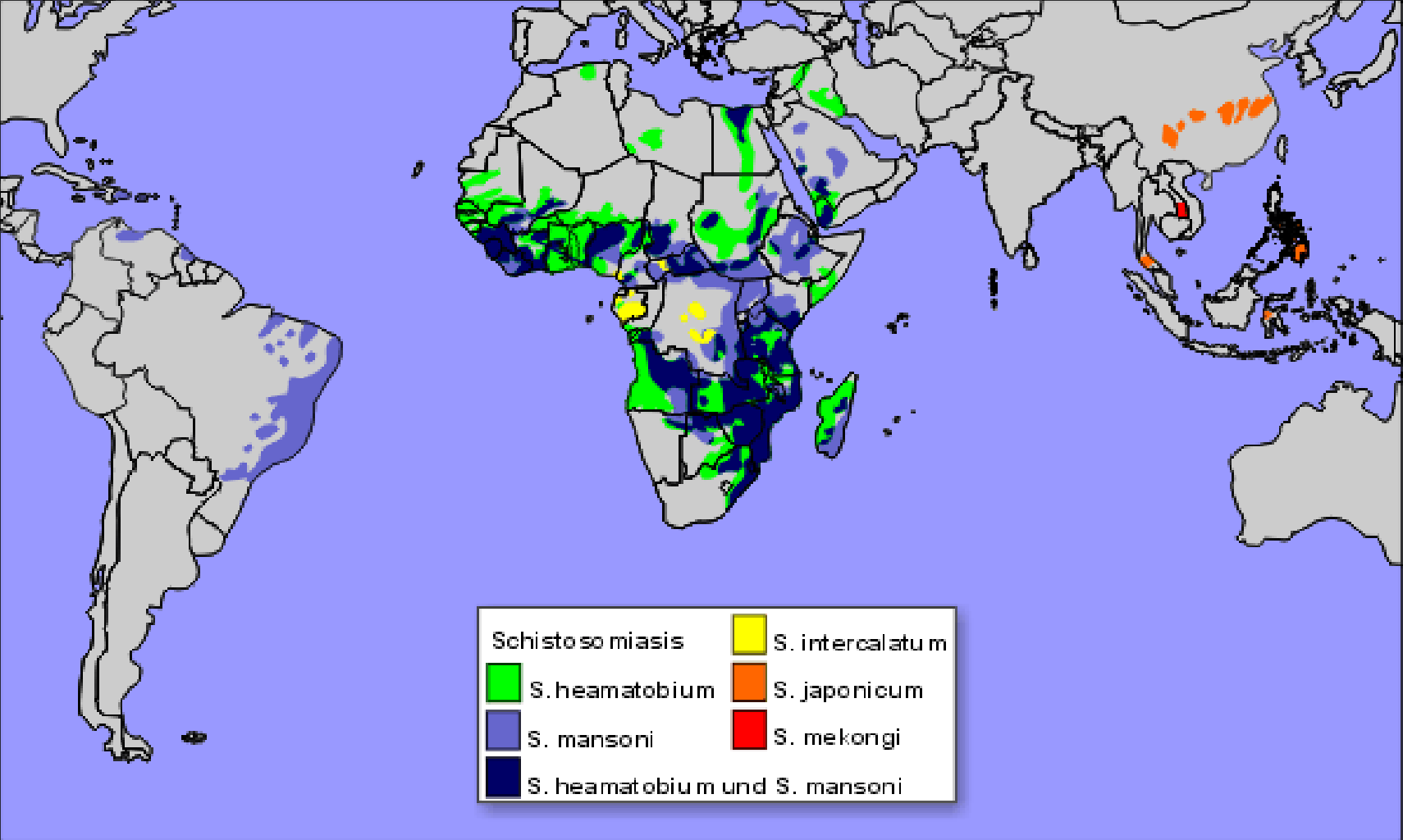




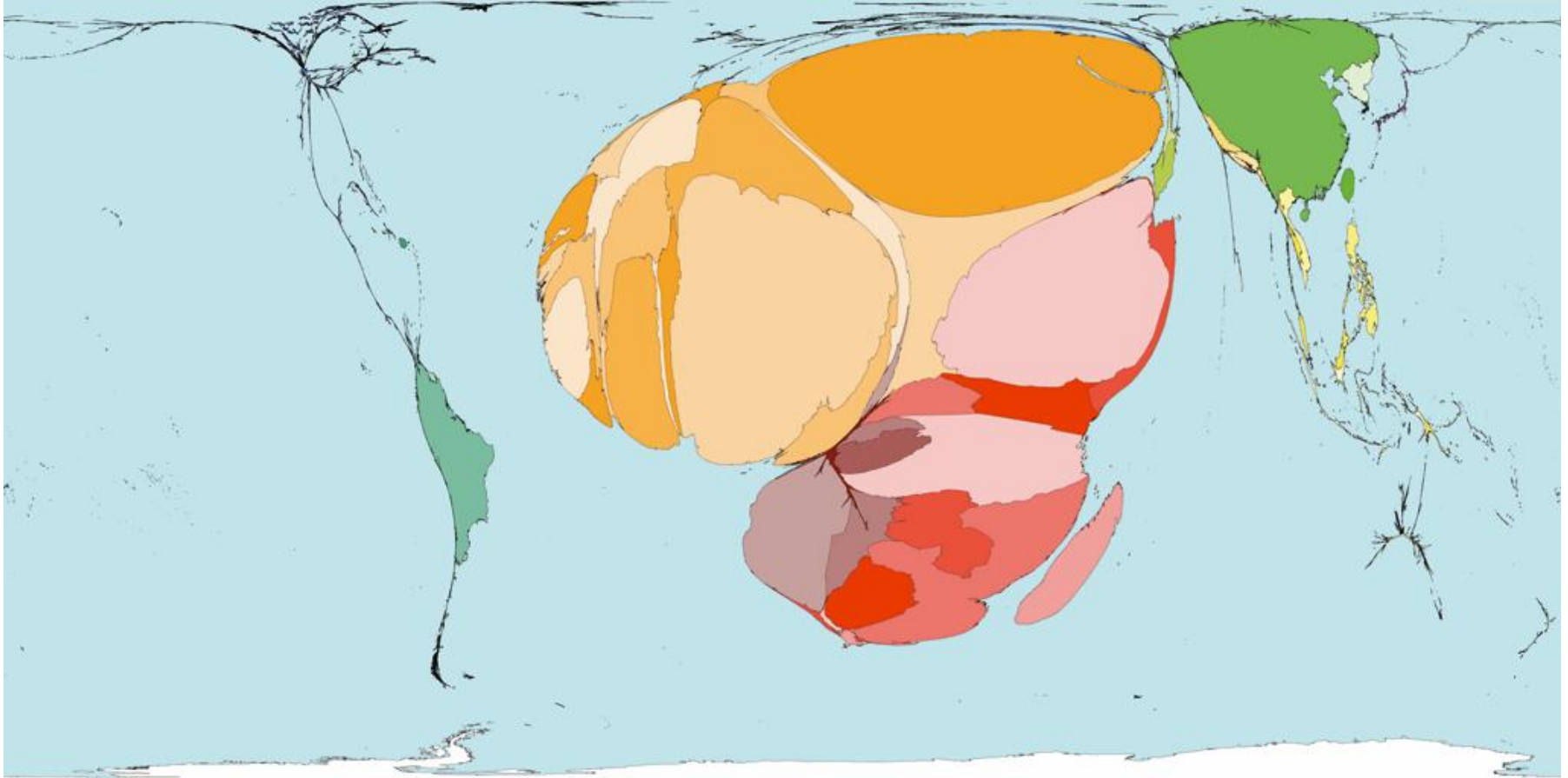
Schistosomiasis: World-wide

- **Schistosoma is a genus of parasitic DIGENETIC TREMATODES that chronically infect more than 200 million people.**
- **Mortality from *S. mansoni* and *S. haematobium* in sub-Saharan Africa is infections 280,000 per year.**
- **Mortality world-wide: 800,000.**
- **After malaria it is the most prevalent serious parasitic disease.**
- **20 million suffer severe consequences.**
- **74 countries.**
- **500-600 million at risk for infection.**

Schistosomiasis World-Wide



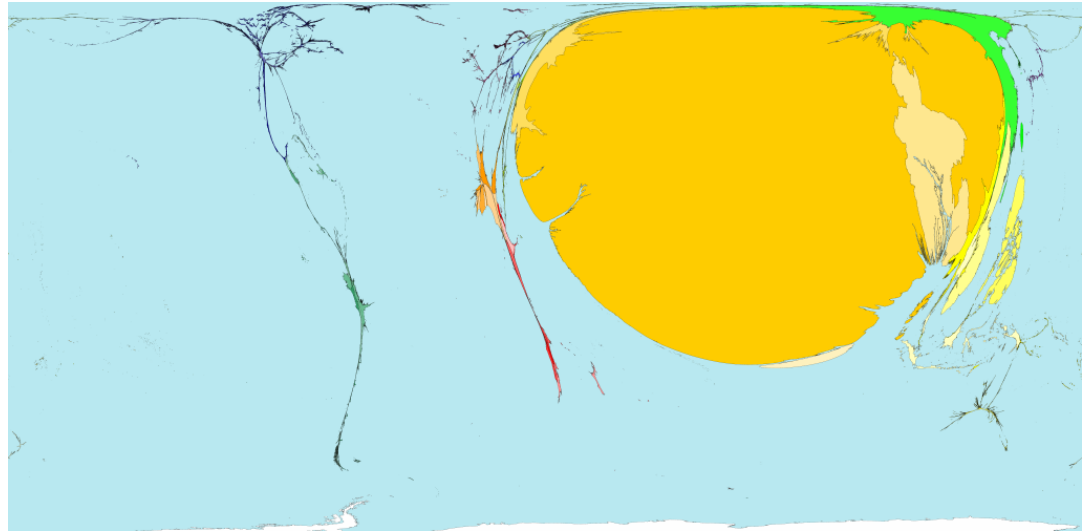
Territories are sized in proportion to the absolute number of people who died from schistosomiasis (bilharzia) in one year (2002).



<http://www.worldmapper.org/index.html>

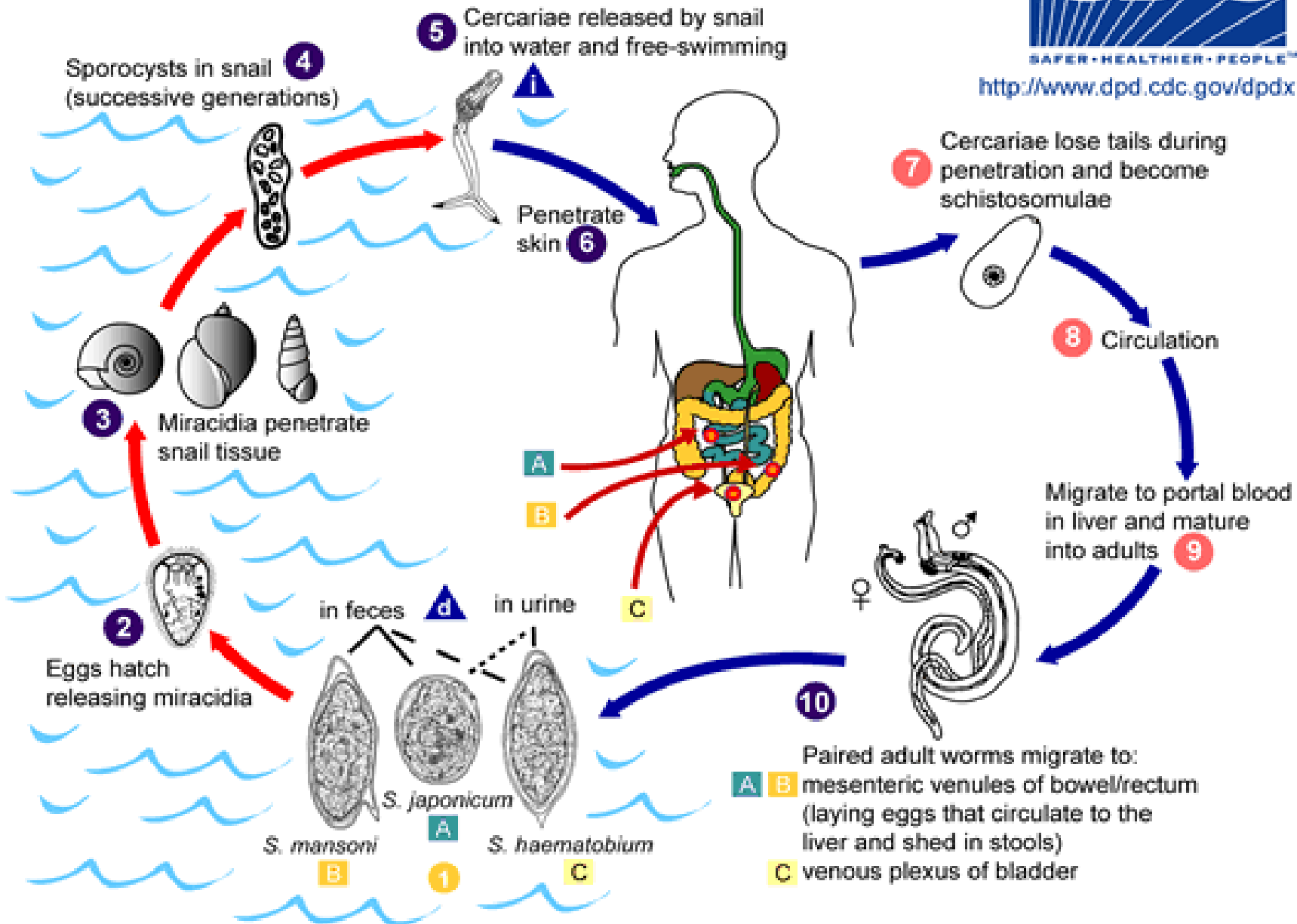
Territory size shows the proportion of human deaths from rabies worldwide that occurred there between 1995 and 2004.

"About 3.5 million dog bites are registered every year in India. The Government cannot give vaccine free of cost to all people. By 2006, the price of vaccine is expected to increase ..." K. Sandeep, 2002



<http://www.worldmapper.org/index.html>

i = Infective Stage
d = Diagnostic Stage



T/F _____

**T/F _____ Can you be infected
with Schistosomiasis?**

The superfamily Schistosomatidae

- **Members of the family Schistosomatidae are dioecious Digenea.**
 - Digenea (Gr. Dis - double, Genos - race) is a subclass within the **Platyhelminthes** consisting of parasitic flatworms with **a syncytial tegument** and, usually, two suckers, one ventral and one oral. They are particularly common in the digestive tract, but occur throughout the organ systems of all classes of vertebrates.
- **The family can be divided into **three** subfamilies (12 genera total):**
 - **Schistosomatinae**
 - **Bilharzeillinae**
 - **Gigantobilharziinae**

The superfamily Schistosomatidae

- 7 are confined to birds and 5 to mammals, but **only the genus *Schistosoma*** is associated with human infections.
- Of the mammalian blood flukes, the genus *Schistosoma* has achieved the greatest geographical distribution and diversification in terms of numbers of recognized species and different hosts parasitized.

The *Schistosoma* Species...

• <u><i>S. haematobium</i></u>	<i>Bulinus</i>	Primates
• <i>S. intercalatum</i>	<i>Bulinus</i>	Primates
• <i>S. mattheei</i>	<i>Bulinus</i>	Artiodactyla
• <i>S. bovis</i>	<i>Bulinus</i>	Artiodactyla
• <i>S. curassoni</i>	<i>Bulinus</i>	Artiodactyla
• <i>S. margrebowiei</i>	<i>Bulinus</i>	Artiodactyla
• <i>S. leiperi</i>	<i>Bulinus</i>	Artiodactyla
• <u><i>S. mansoni</i></u>	<i>Biomphalaria</i>	Primates
• <i>S. rodhaini</i>	<i>Biomphalaria</i>	Rodentia/Carnivora
• <i>S. edwardiense</i>	<i>Biomphalaria</i>	Artiodactyla
• <i>S. hippopotami</i>	?	Artiodactyla
• <i>S. indicum</i>	<i>Indoplanorbis</i>	Artiodactyla
• <i>S. spindale</i>	<i>Indoplanorbis</i>	Artiodactyla
• <i>S. nasale</i>	<i>Indoplanorbis</i>	Artiodactyla
• <i>S. incognitum</i>	<i>Lymnaea/Radix</i>	Rodentia/Carnivora
• <u><i>S. japonicum</i></u>	<i>Oncomelania</i>	Primates/Rodentia/Carnivora/Artiodactyla
• <i>S. mekongi</i>	<i>Tricula</i>	Primates/Carnivora
• <i>S. sinensium</i>	<i>Tricula</i>	Rodentia

The *Schistosoma* Species...

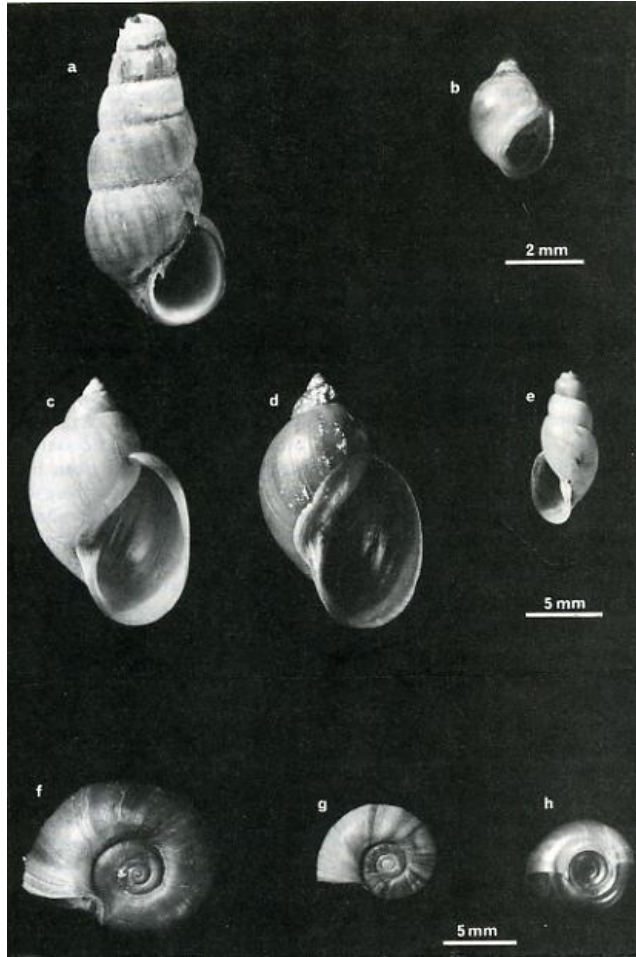
• <u><i>S. haematobium</i></u>	<i>Bulinus</i>	Primates
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• <u><i>S. japonicum</i></u>	<i>Oncomelania</i>	Primates/Rodentia/Carnivora/Artiodactyla
• <i>S. mekongi</i>	<i>Tricula</i>	Primates/Carnivora
• <i>S. sinensium</i>	<i>Tricula</i>	Rodentia

Swimmer's Itch (Cercarial Dermatitis)

- **Dermal rash resulting from Schistosome infections with species not infectious to humans.**



Representative shells of the intermediate snail host genera



a-*Oncomelania hupensis*-Japan

b-*Tricula aperta*-Laos

c-*Lymnaea luteola*-India

d-*Radix rubigniosa*-Indonesia

e-*Bulinus senegalensis*-Gambia

f-*Planorbarius metidjensis*-Portugal

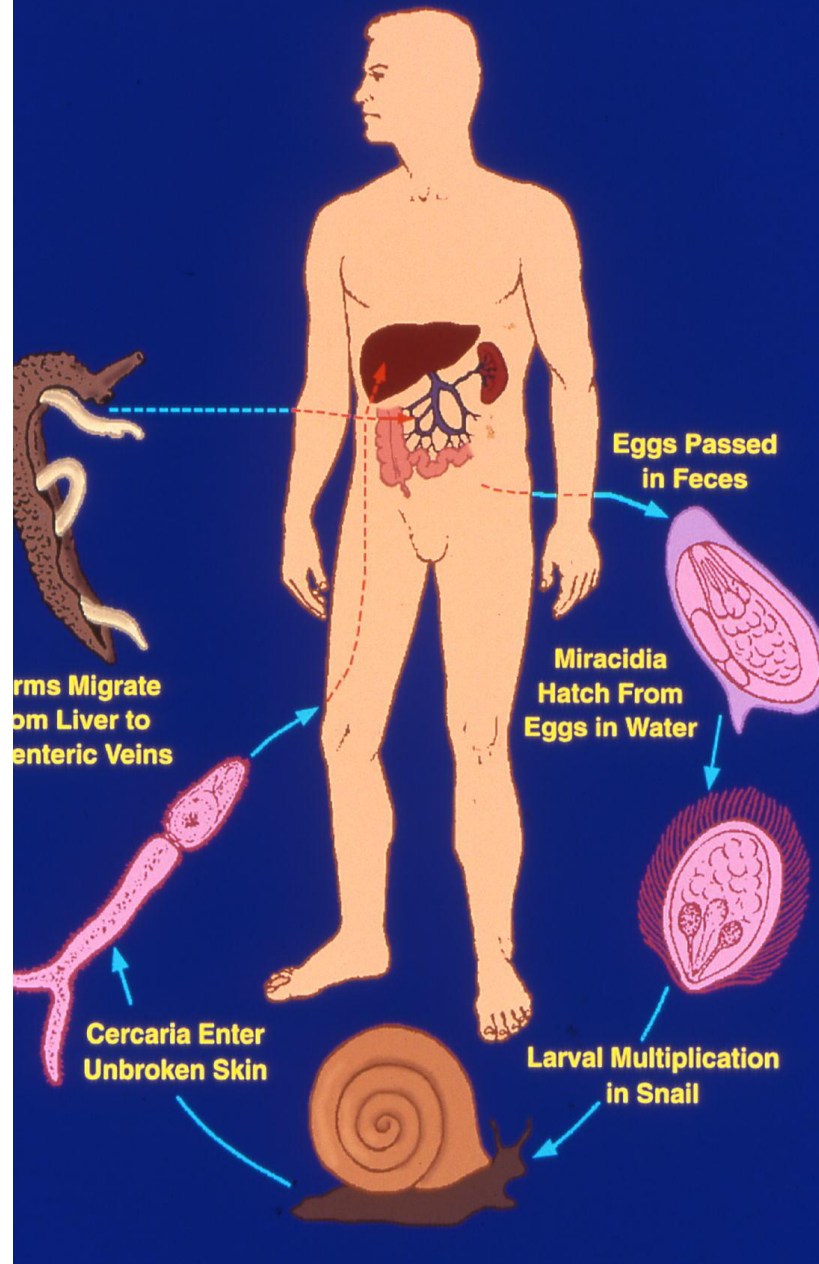
g-*Indoplanorbis exustus*-India

h-*Biomphalaria pfeifferi*-Burundi

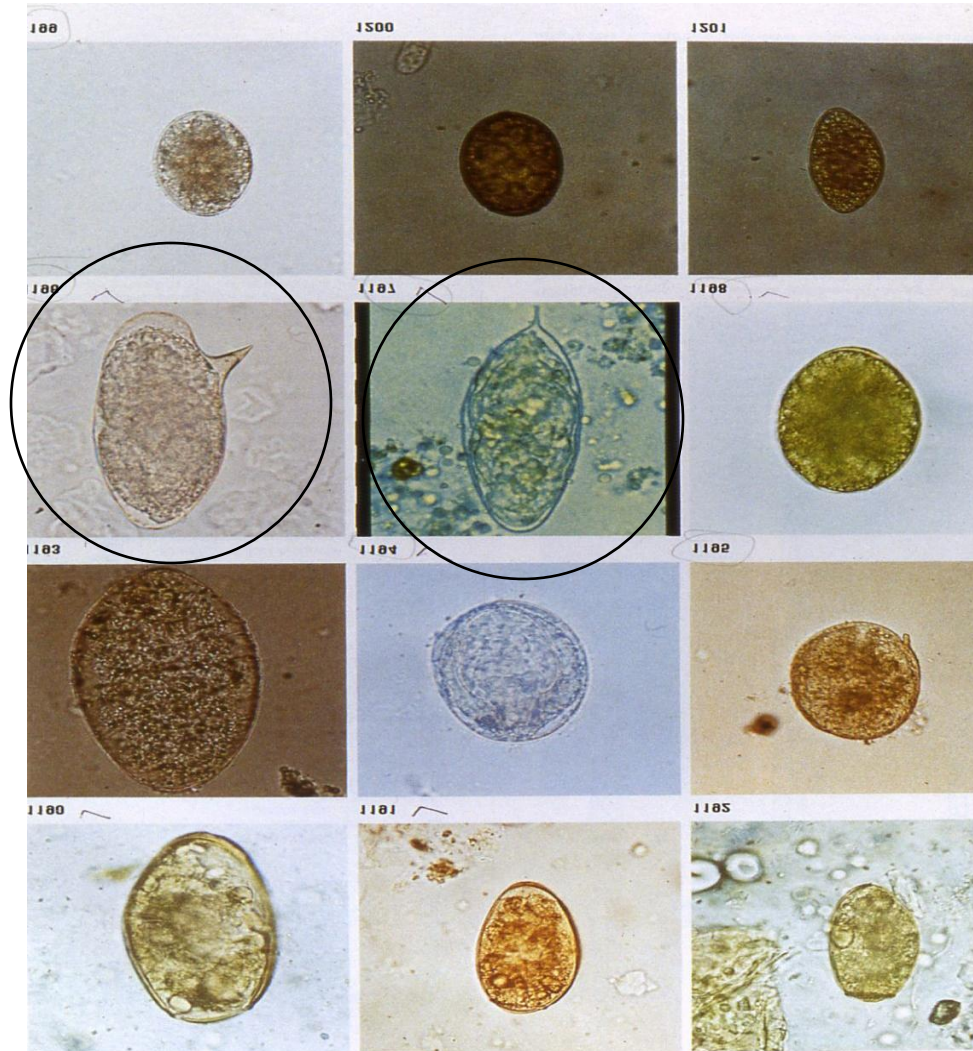
Schistosomatidae

- **Of the approximately 2700 genera of Digenian parasites, the 12 that comprise the Schistosomatidae are unusual in 4 ways:**
 - a) **2 rather than 3 hosts**
 - b) **they are dioceious**
 - c) **they infect their host by direct contact**
 - d) **they parasitize the intravascular niche**

Life Cycle of *Schistosoma mansoni*



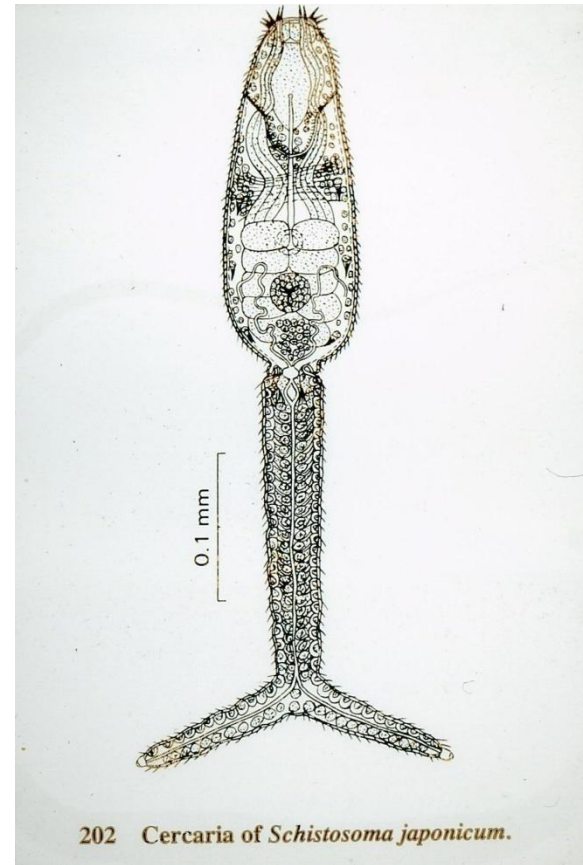
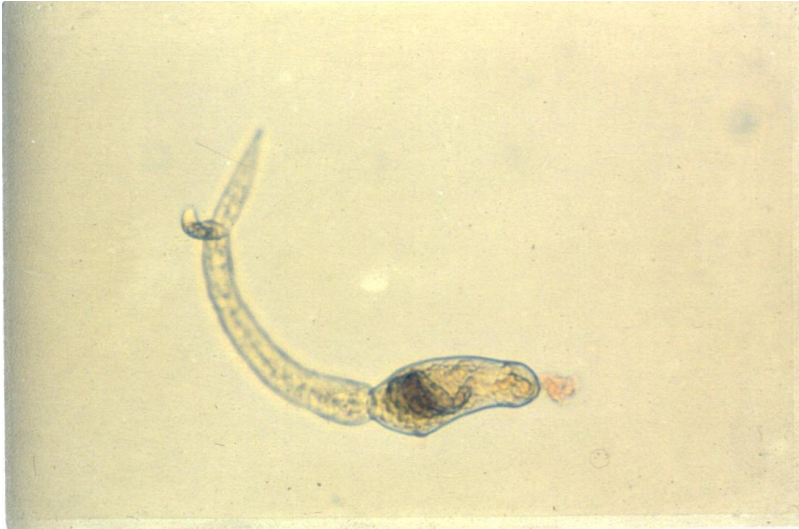
Eggs → Miracidia



From mollusks to man...

- The schistosome cercaria have only a brief period in which to locate and penetrate its mammalian (or avian) host.
- Energy reserve of free-swimming cercaria is glycogen.
- Stored in both the body and tail.
- These stores last roughly 8 hours (need up to **22-35% of stores for skin penetration.**

Cercaria



How cercariae find their host...

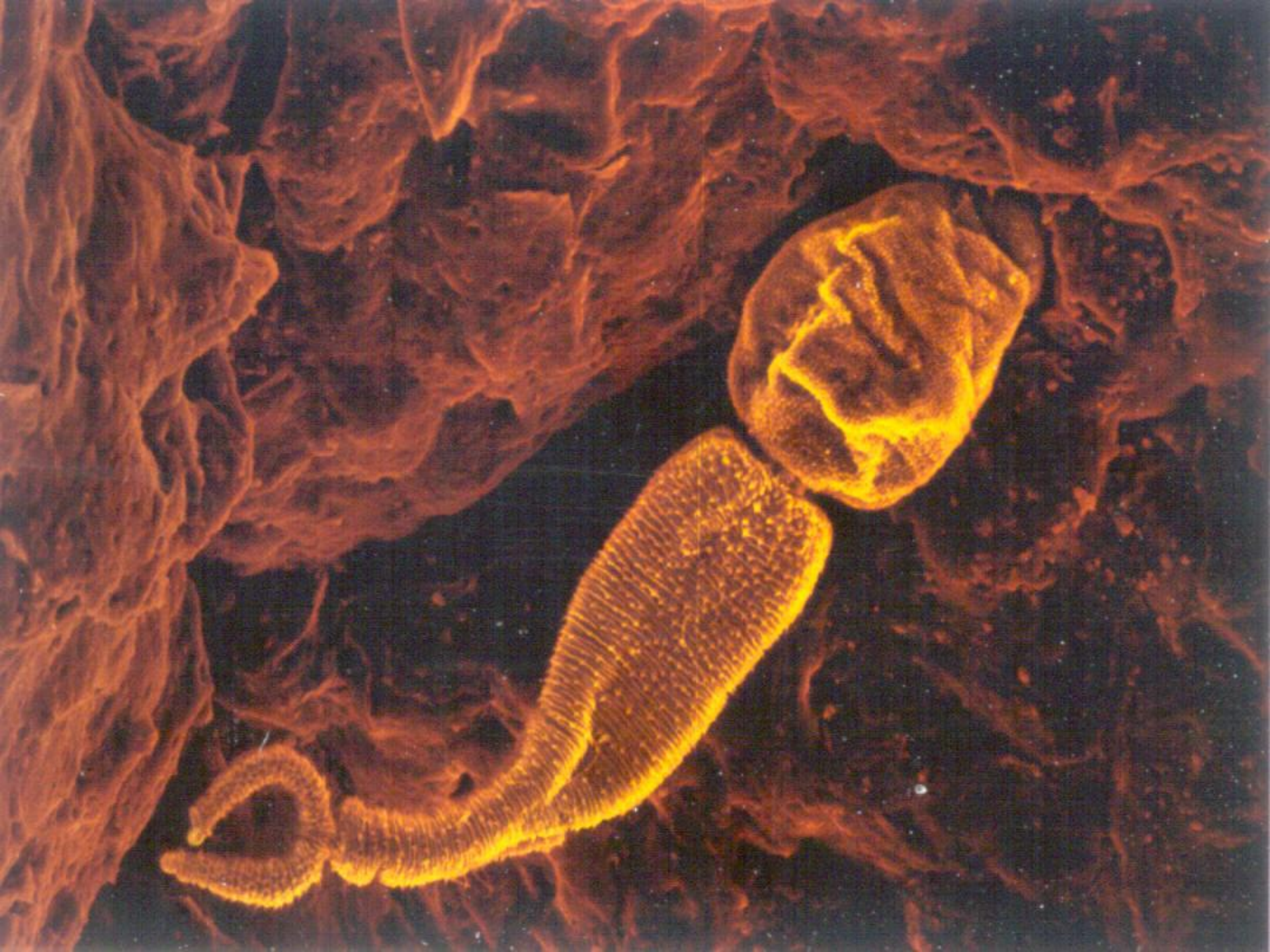
- Bursts of active upward swimming alternates with passive downward sinking.
- This strategy keeps the cercariae just below the water surface.
- As they 'age' the period of passive sinking comes to exceed that of upward swimming.
- Cercaria can be induced to increase their activity as a result of water turbulence (**wading**), shadows, human skin substances and **light**.
- No suggestion of directed movement (taxis).

Penetration into the host skin...

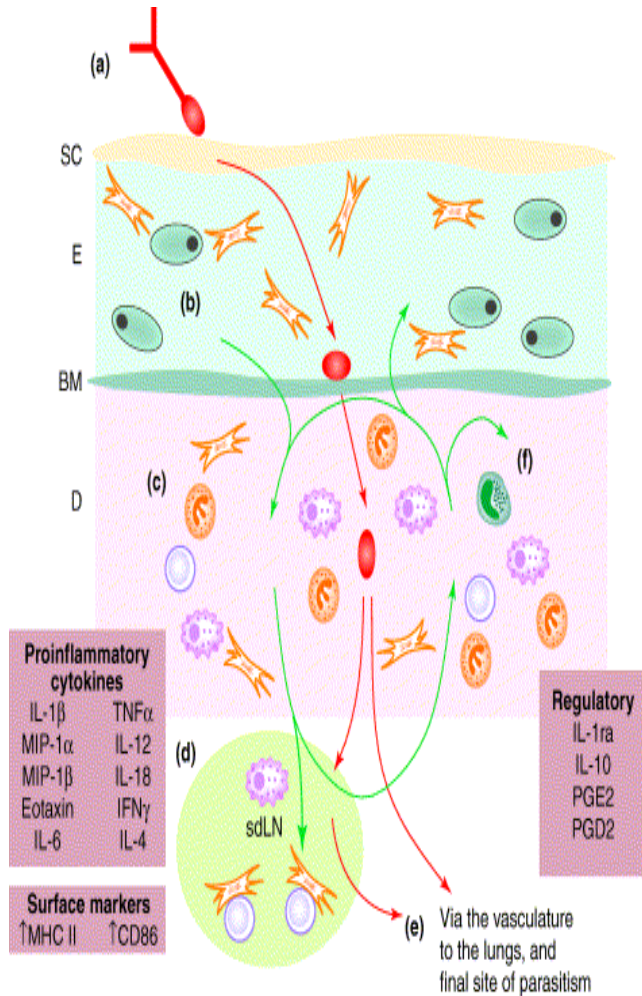
- **Described as a 3-step process:**
 - **1-Attachment.**
 - **2-Creeping over the surface exploring for an entry site.**
 - **3-Penetration into the epidermis.**
- **Phases 1 & 2 can be triggered by thermal and chemical stimuli.**
- **Phase 3 triggered by chemical stimuli alone.**

Penetration into the host skin...

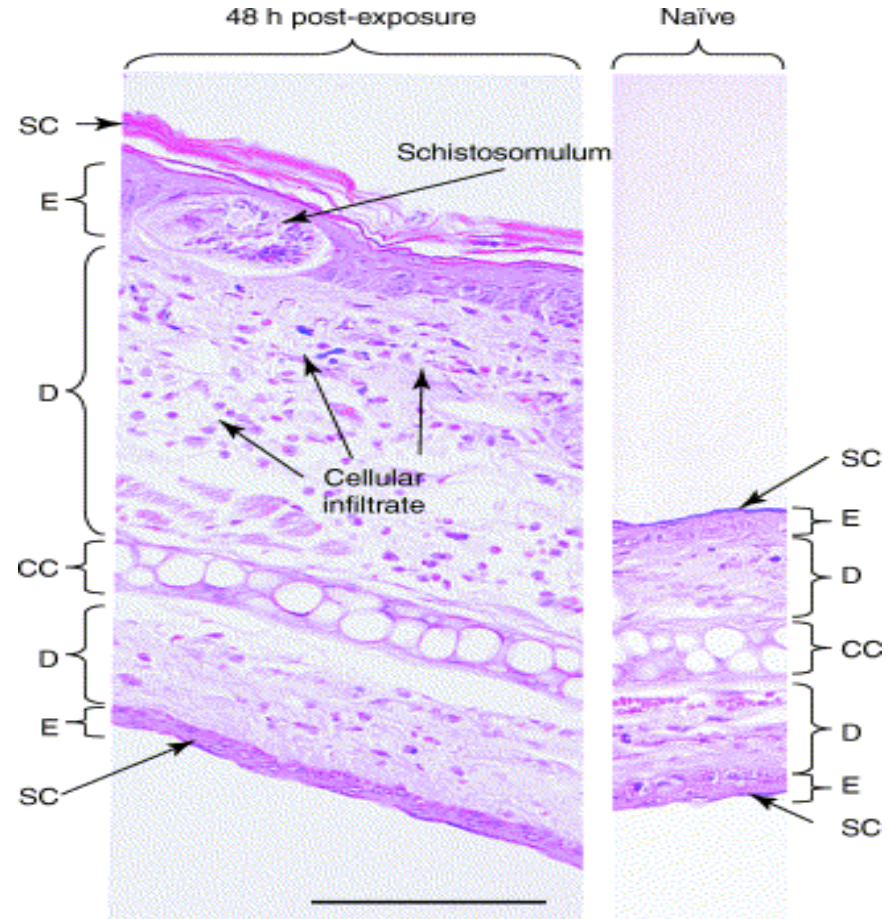
- Skin penetration takes approximately 1 h and involves coordinated musculature and secretory processes.
- The cercarial glycoalyx and tail are lost during penetration which is facilitated by various **proteases** and **mucin** secretions.
- Following penetration (and numerous physiologic changes) the cercaria becomes what is called a **schistosomulum**.



Inflammation in the Skin



- Key:
- Lymphocyte
 - Langerhans and/or dendritic cell
 - Neutrophil
 - Macrophage
 - Mast cell
 - Keratinocyte
 - Parasite movement
 - Cell movement

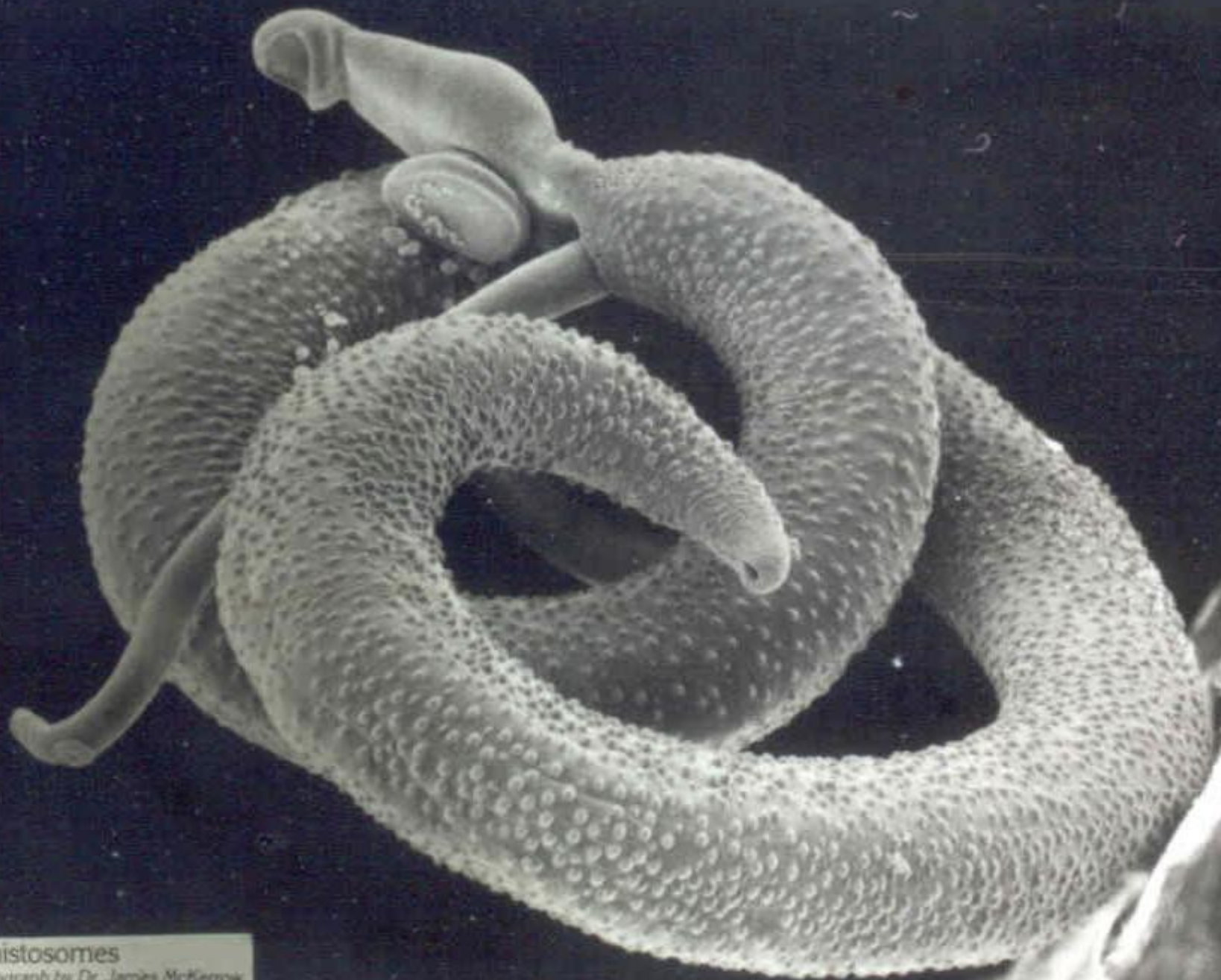


Cercaria vs. Schistosomulum

- **There is a significant change in surface protein expression following skin penetration.**
- **One of the most antigenic proteins found on the schistosomulum surface is actually mollusk in origin.**
 - **NOTE: Immune response is initially to mollusk antigens; then it is too late.**

Schistosomulum migration...

- Following penetration, migration from the epidermis to the dermis can take from 30 min to 40 h.
- From the skin, the schistosomula migrate to the lungs (primarily via the circulation).
- Between 48-63% of the infecting schistosomula reach the **lungs by day 3-5**.
- Majority of the schistosomula migrate to the liver by **day 10** where they develop into adult worms.



Schistosomes

Photograph by Dr. James McKierrow



The Schistosomatidae...

GENUS	Pre-patent period in definitive host (days)
• <i>S. haematobium</i>	56
• <i>S. intercalatum</i>	41
• <i>S. mattheei</i>	42
• <i>S. bovis</i>	41
• <i>S. curassoni</i>	40
• <i>S. margrebowiei</i>	33
• <i>S. leiperi</i>	49
• <i>S. mansoni</i>	34
• <i>S. rodhaini</i>	30
• <i>S. edwardiense</i>	?
• <i>S. hippopotami</i>	?
• <i>S. indicum</i>	52
• <i>S. spindale</i>	46
• <i>S. nasale</i>	77
• <i>S. incognitum</i>	35
• <i>S. japonicum</i>	34
• <i>S. mekongi</i>	43
• <i>S. sinensium</i>	?

Number of eggs/day...

Difficult to estimate; regardless, it varies *e.g.*, *S. bovis*, 81/day compared to *S. japonicum* 2157/day (x number of worm pairs).

Consequences of Infections with Schistosomes

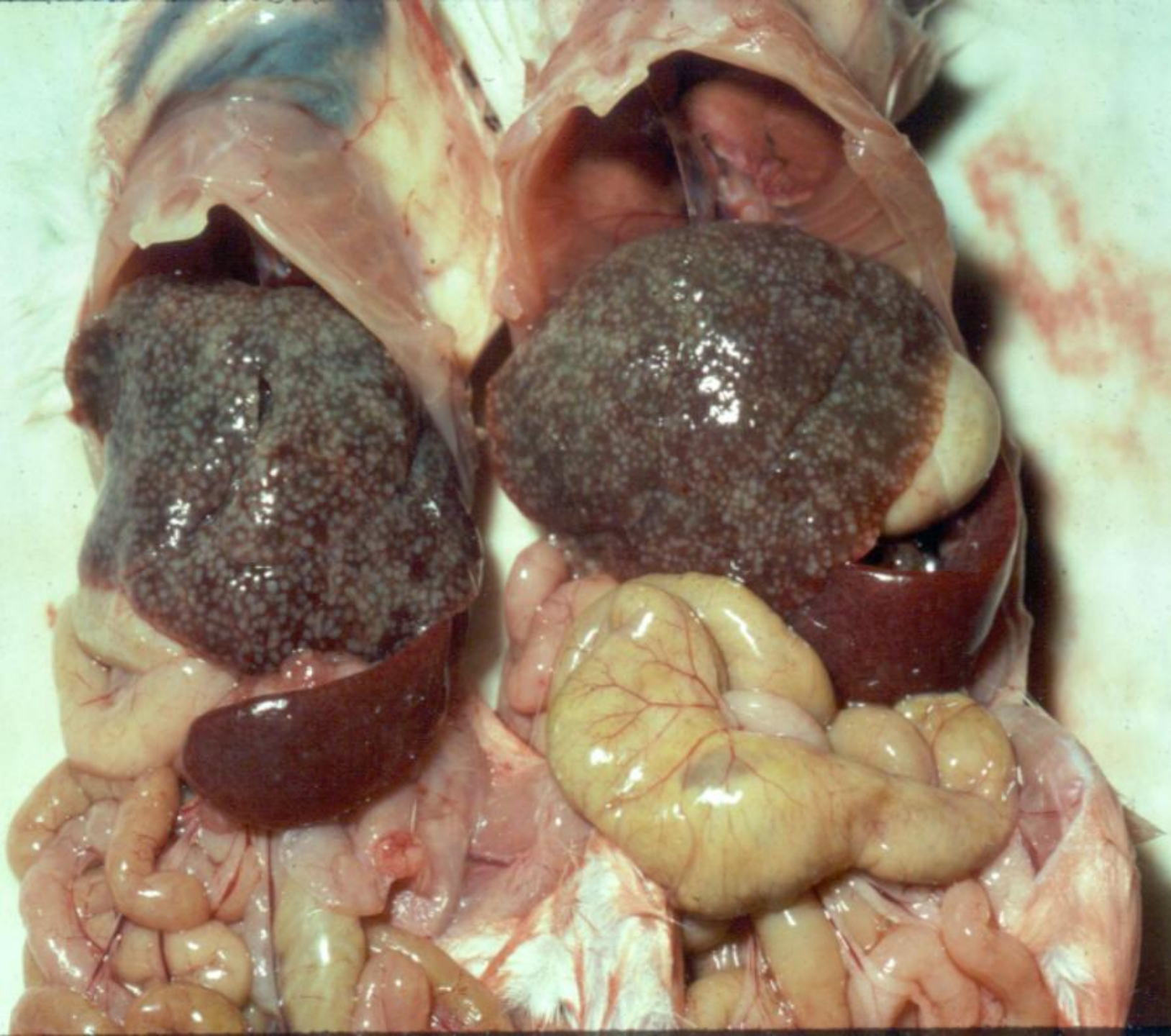
- Schistosome worm pairs take up residence in their definitive venous habitat and engage in permanent copula and egg-laying for many years.
- Life-span in humans has been estimated to average 3.5-12 years, **with some worms surviving 30 years or longer!**

Consequences of Infections with Schistosomes

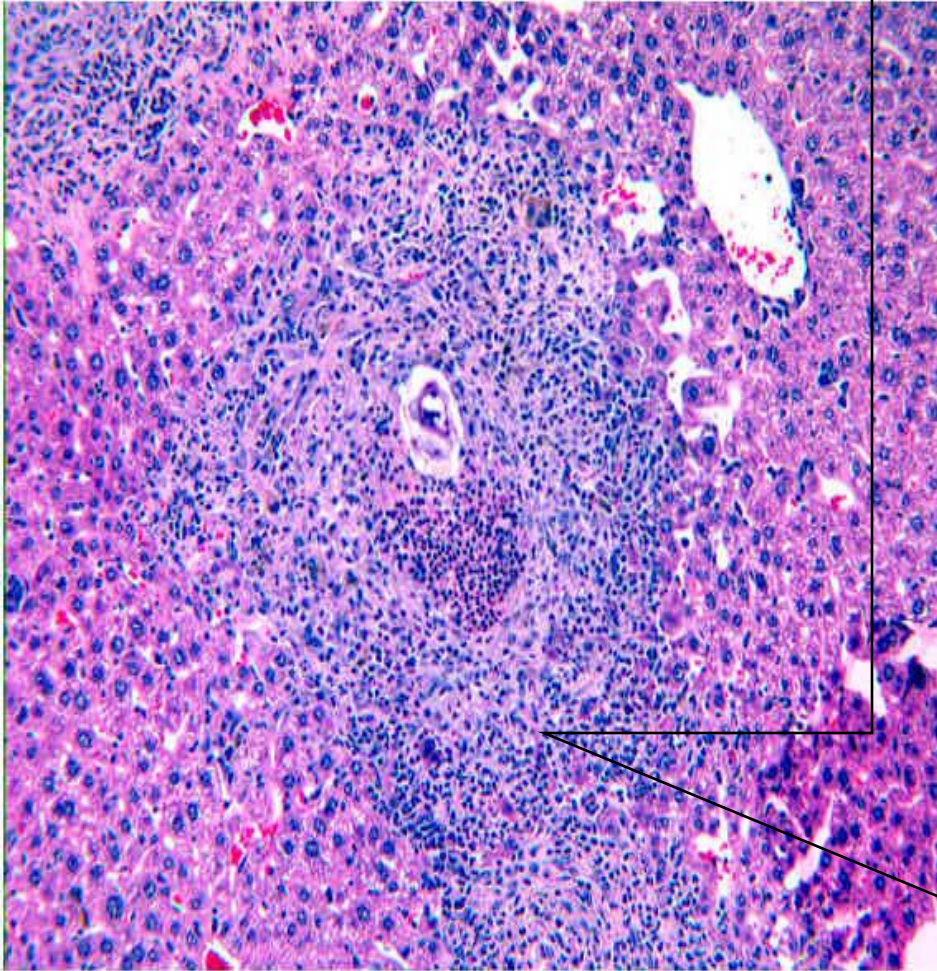
- Coinciding with maturation and early egg output, the host must adjust to a heavy, new antigen burden, yet...
- Only a few infected persons develop an acute febrile illness at that time (*i.e.*, infection time).
- This self-terminating phase which begins one or two months after first cercarial exposure, is referred to “**toxemic schistosomiasis**” (in Brasil) or “**Katayama fever**” (in Japan).

Consequences of Infections with Schistosomes

- **5 or more years into infection, individuals with heavy parasite burdens begin to suffer advanced fibrovascular lesions.**
- **The lesions which ensue during this time are largely caused by schistosome eggs, rather than worms.**



Schistosome granulomas



- Eosinophils
- Macrophages
- Fibroblasts
- Lymphocytes
- Neutrophils
- Plasma cells
- Mast cells

In order of descending concentration.

Chronic lesions

- Schistosome eggs measure up to 70 μm in width (**Compared to 370 μm and greater when granuloma is formed**).
- Less than $\frac{1}{2}$ of the eggs laid will reach the lumen of the gut or urinary tract; the remainder are either trapped primarily in the liver (but also lungs, kidneys, spleen, brain).

Summary of Principal Clinical Manifestations

Time	Disease	Sm, Sj	Sh
1-4 Months	ACUTE	Toxaemic stage Katayama fever	-----
Indefinite Duration	Chronic subclinical	No organomegaly Hepatomegaly Hepatosplenomegaly	Haematuria- (no obstruction) Microhaematuria (with obstruction)
5+ years Post infection	Severe symptomatic	Portal hypertension, liver failure	Pylonephritic renal failure

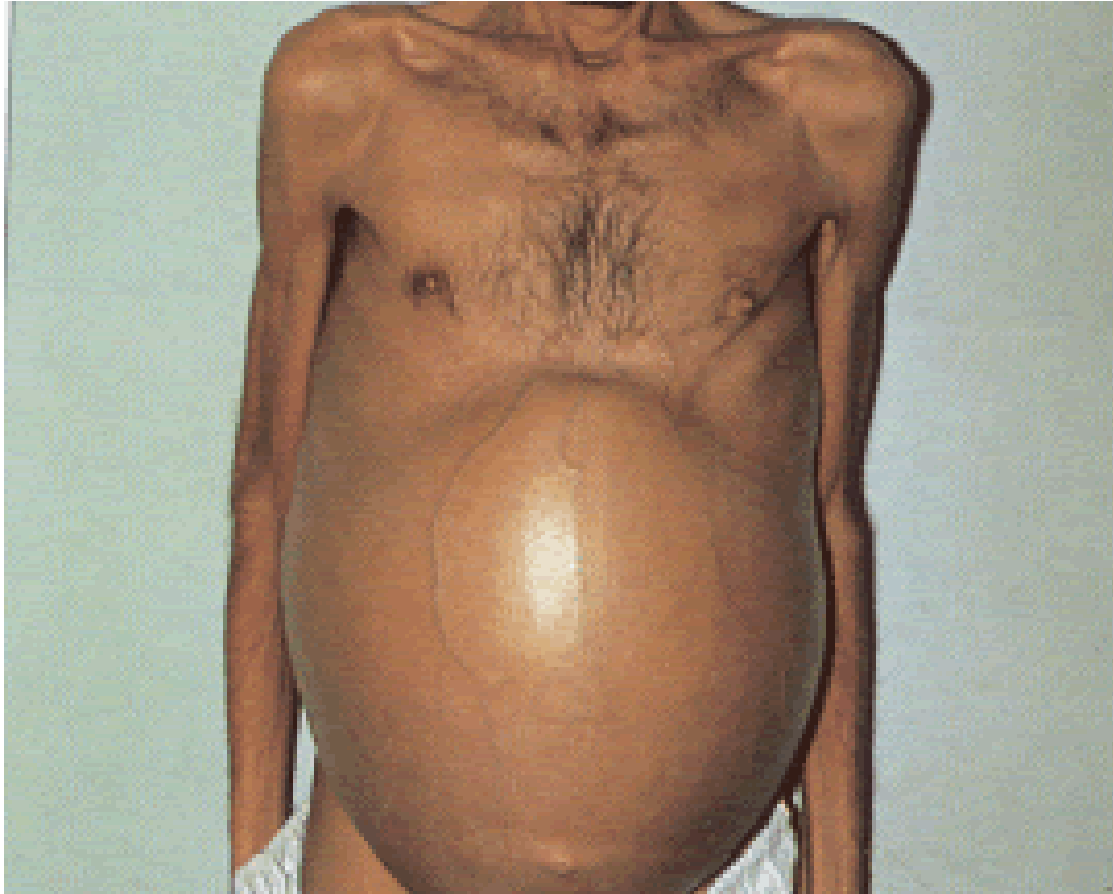
Sm=*S. mansoni*, Sj=*S. japonicum*, Sh=*S. haematobium*

Schistosomiasis-GU tract

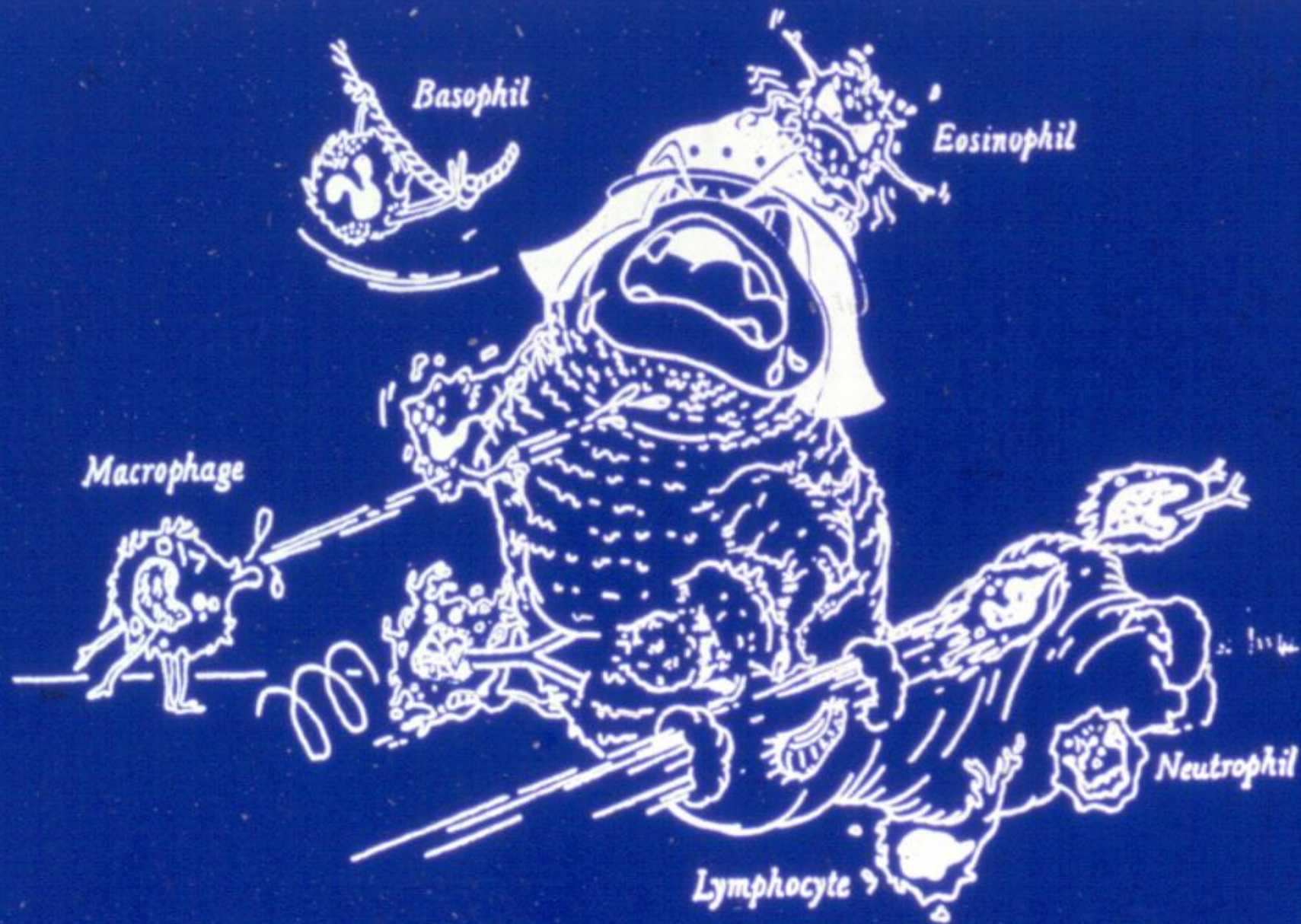
- **1. Calcification of the distal two thirds of both ureters.**
- **2. Bladder calcifications.**
- **3. Seminal vesicle calcifications superimposed on bladder calcifications.**



Hepatosplenomegaly

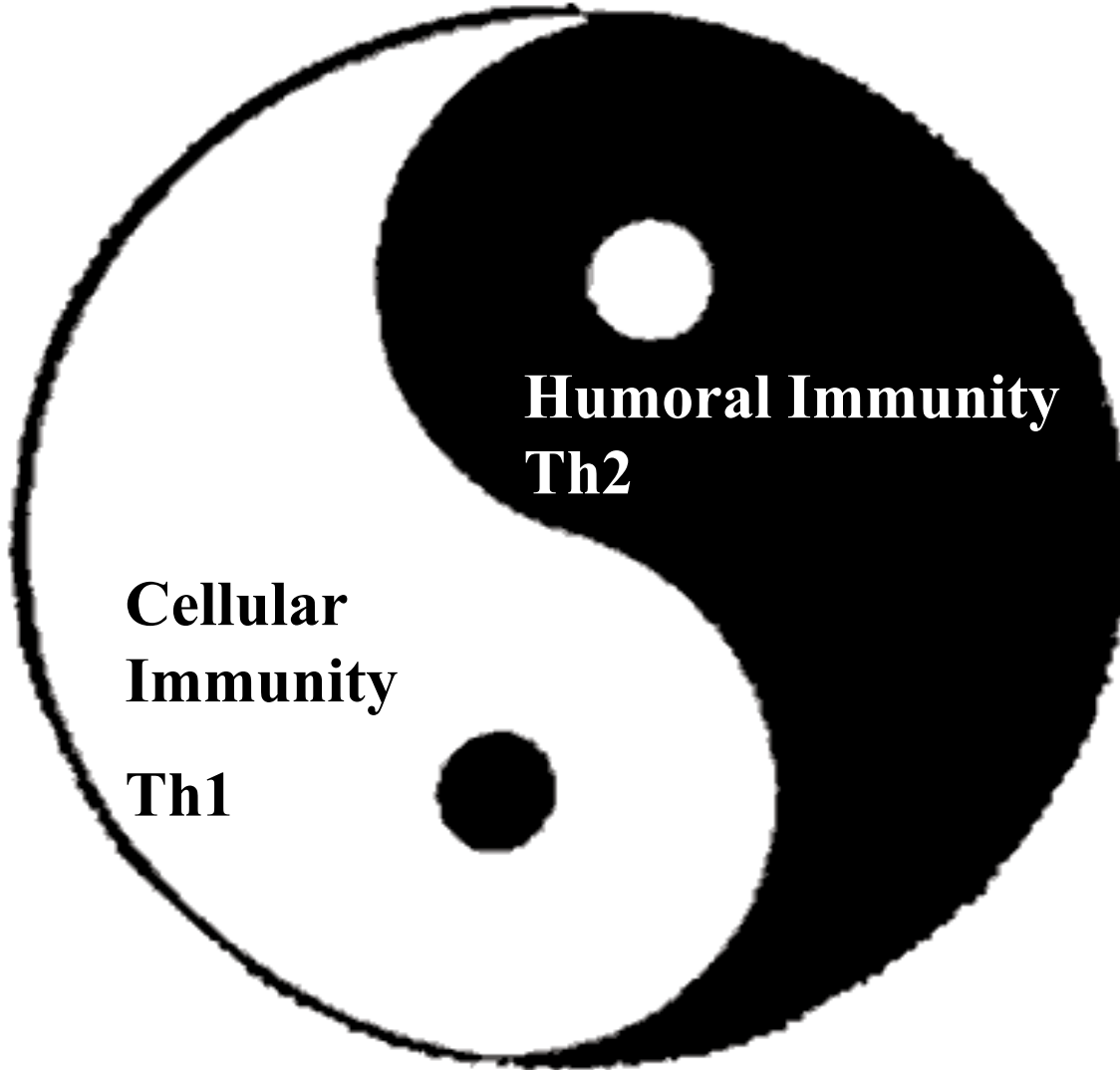


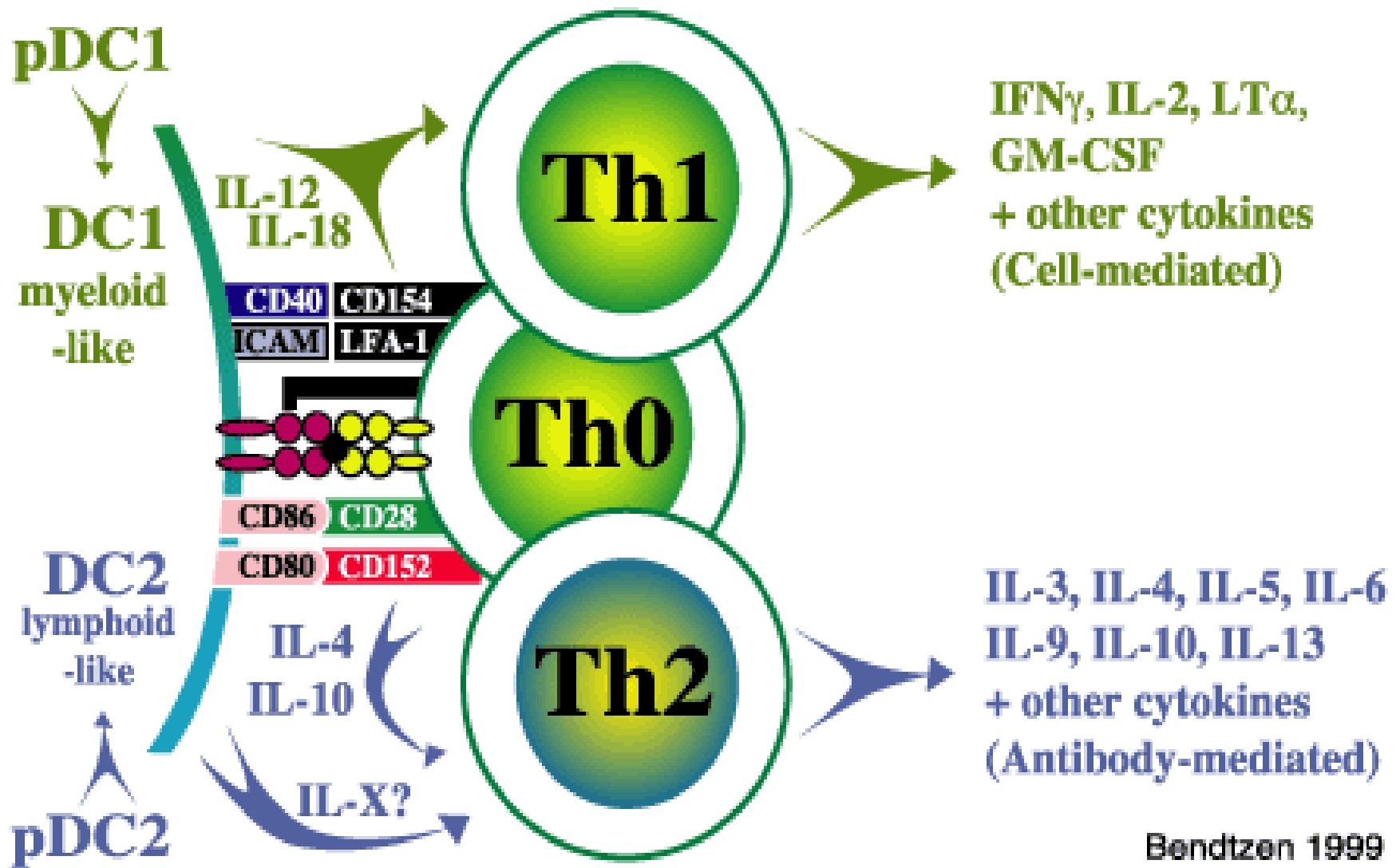
Immunity to Schistosomes...



ELLNER AND MAHMOUD. REV INF DIS 4:698, 1982.

Immune System Dynamics



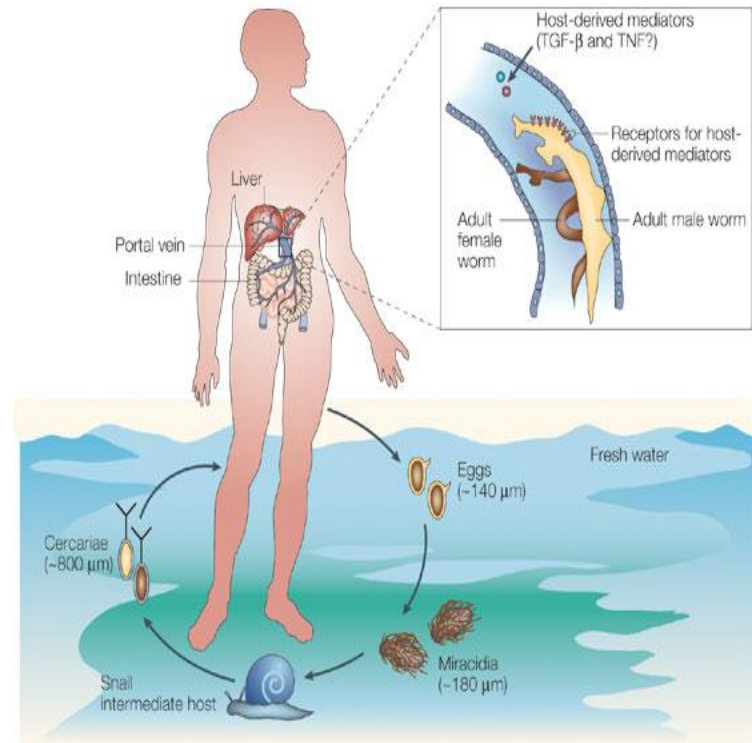


Immunity to Schistosomes

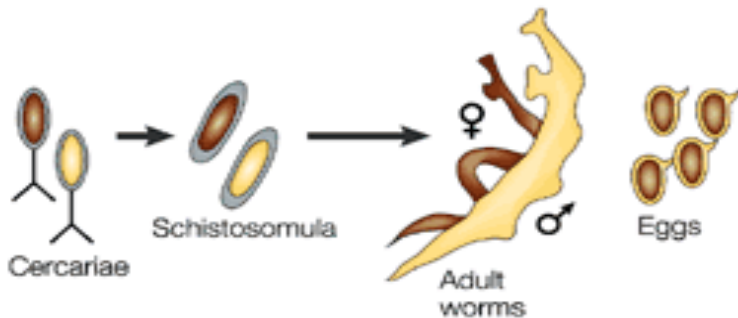
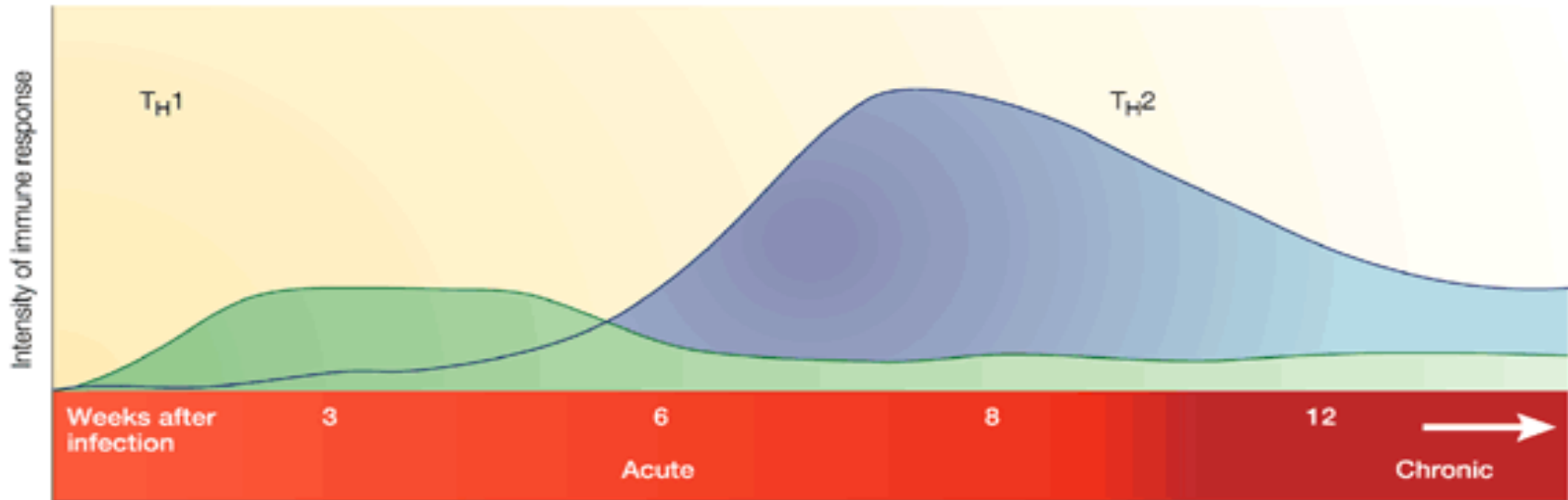
- The immune response is intimately involved in the development of many of the pathological changes that accompany infection.
 - Infected individuals have resistance to **superinfection**.
 - Schistosomes survive for years in the host despite a strong immune response.
 - Schistosome maturation and fecundity are, in some way, **dependent on the host immune response**.

Immunity & Infection

- **Immune component needed for egg excretion.**
 - **Egg excretion is minimal in immunocompromised mice.**
 - **Excretion can be increased with the passive transfer of immune cells/serum from infected mice.**
 - **HIV⁺ individuals infected with Schistosomes have decreased egg excretion when their CD4⁺ counts go down.**

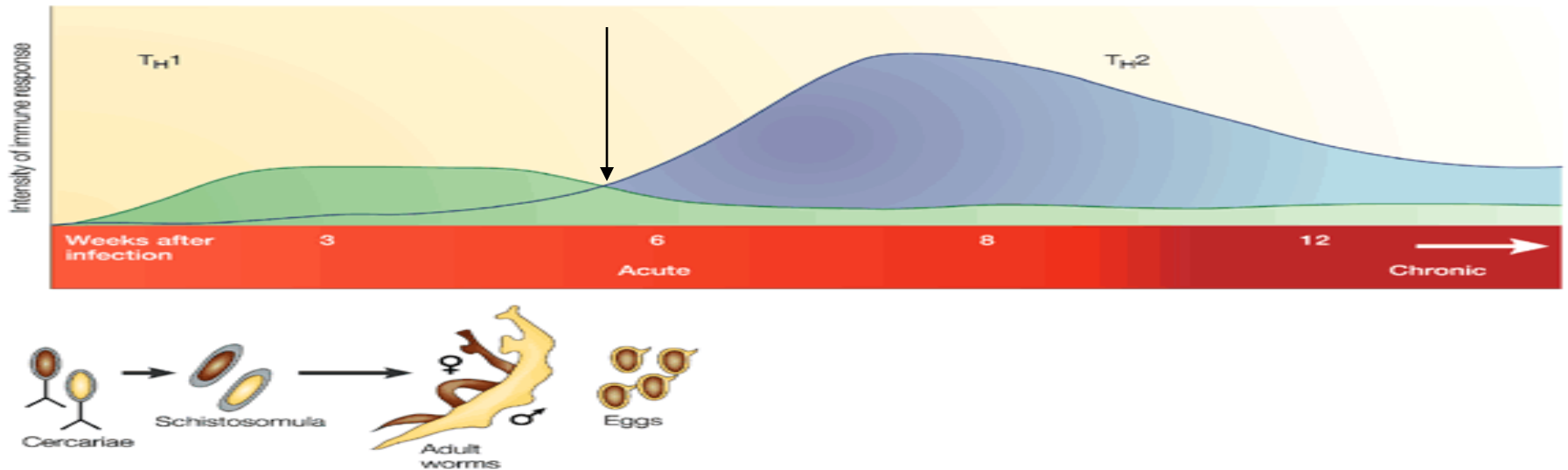


Development of the Immune Response During Infection



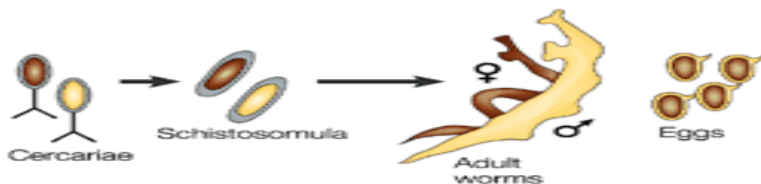
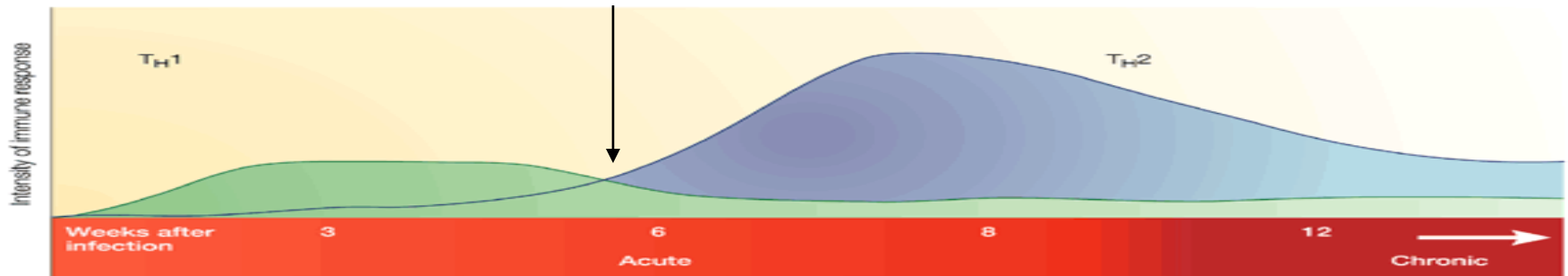
Is Acute Schistosomiasis a Th1 Disease?

- **Acute** schistosomiasis is a debilitating febrile illness.
- During acute illness there are measurable levels of tumor–necrosis factor (**TNF**) in the plasma and peripheral blood mononuclear cells (PBMCs) produce large quantities of TNF, **IL-1 and IL-6** (inflammatory).
- Following egg production, the response changes towards a Th2 response as is characterized by IL-10 production (anti-inflammatory).



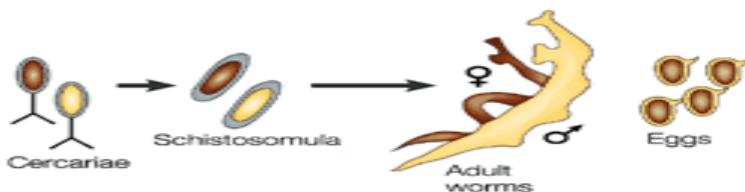
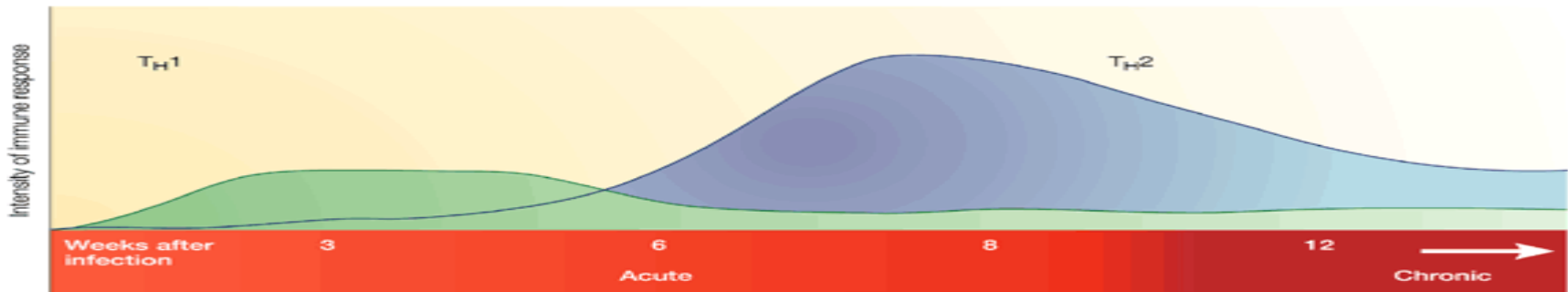
Is Acute Schistosomiasis a Th1 Disease?

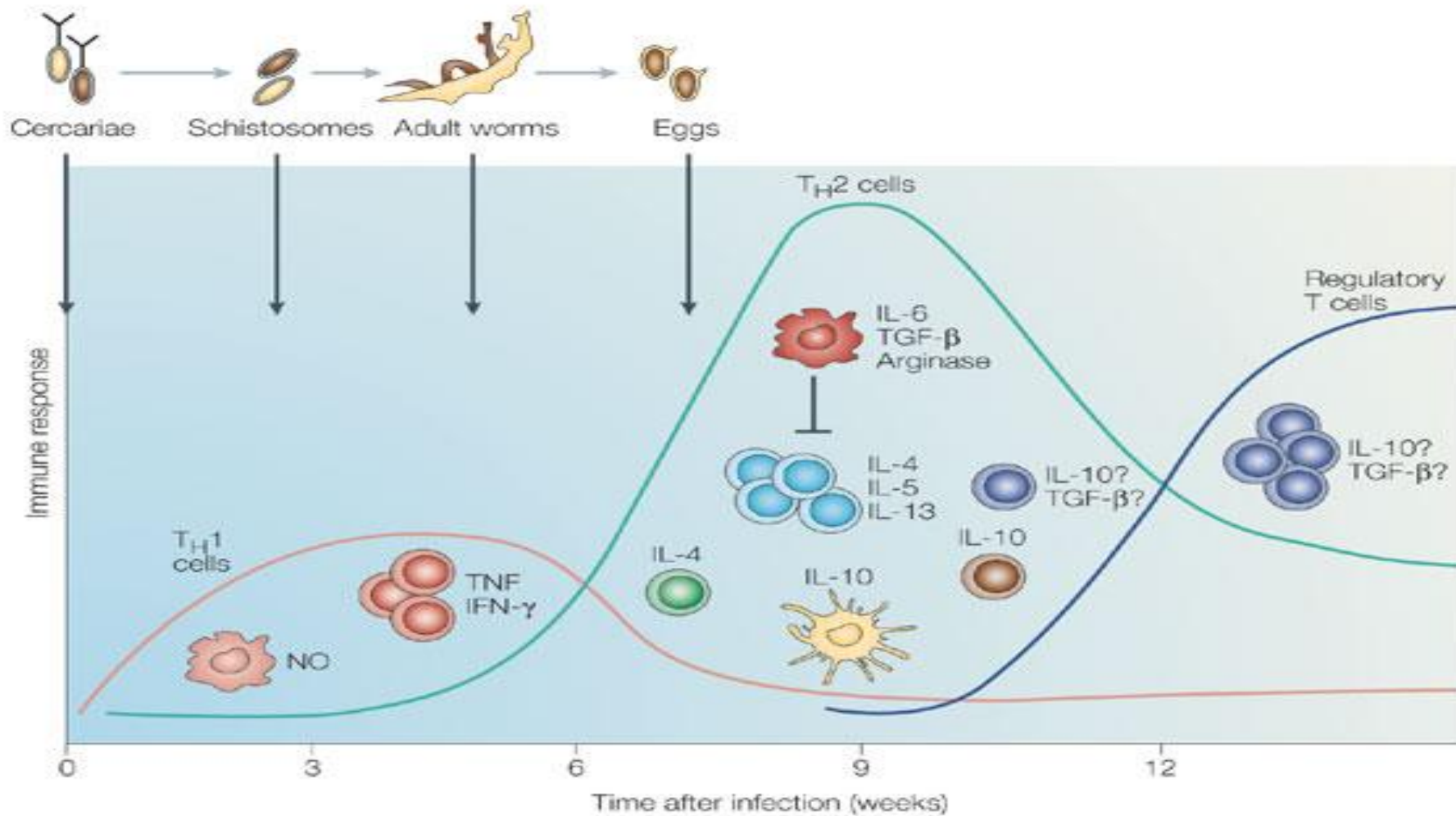
- Anomalously, the febrile illness that is associated with the initial stages of schistosome infection seems to be uncommon in individuals who live in areas that are endemic for schistosomiasis.
- It occurs, instead, in individuals who have no previous history of exposure.
- Sensitization *in utero*? Different immune response? Pre-existing Th2? **Existing infection?**



Is Chronic Schistosomiasis a Th2 Disease?

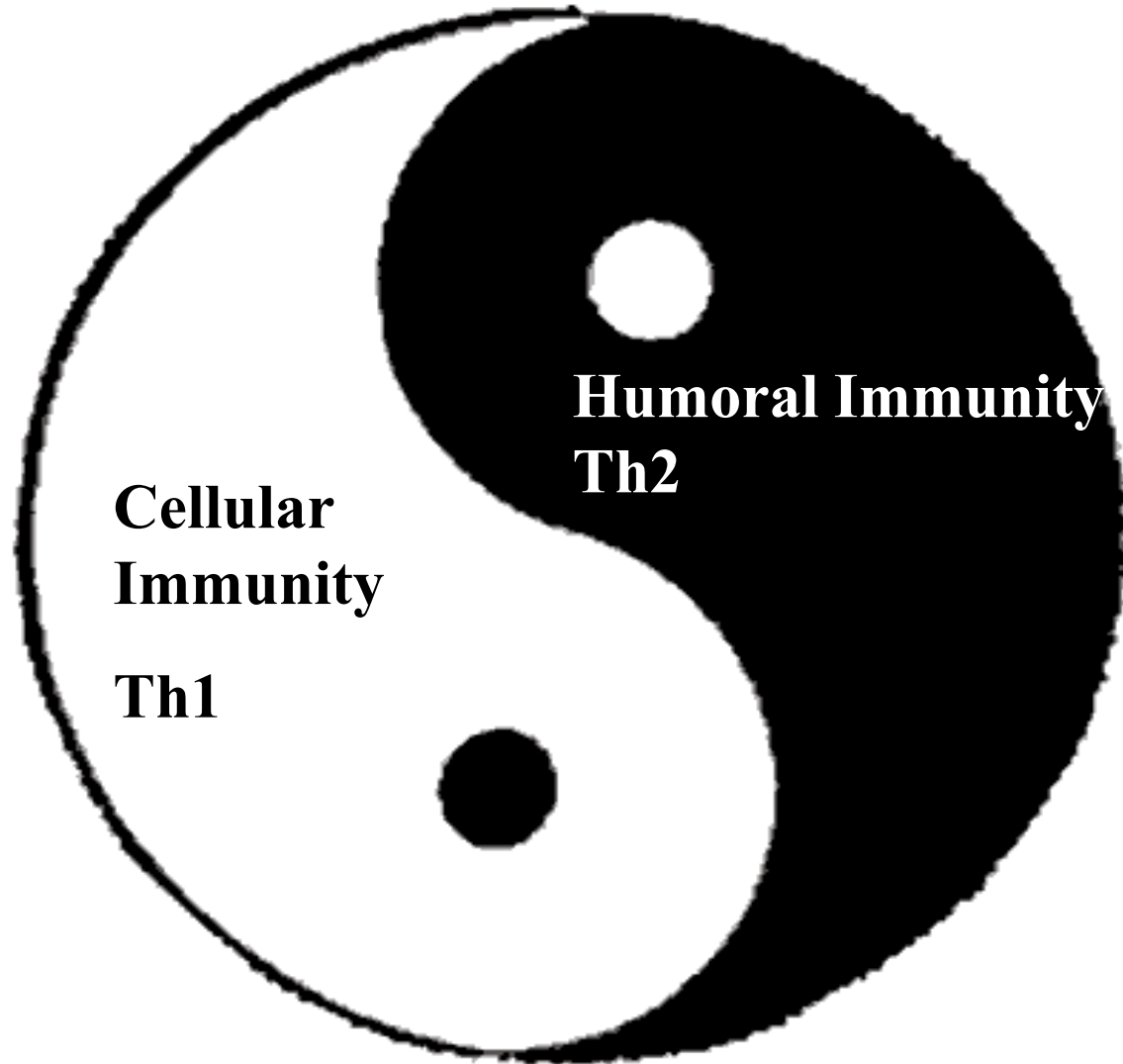
- Chronic disease is graded according to severity and fibrosis can be ranked on the basis of ultrasound patterns.
- Although a Th2 response is needed to dampen the potent Th1 response (if not it is lethal), it is the Th2 environment which leads to chronic morbidity.
- The primary Th2 cytokine involved in this process is IL-10 and IL-13.
- Th1 mediators INF- γ , IL-12, TNF prevent IL-13-mediated fibrosis.





Other considerations...

Schistosomiasis: effects on concurrent disease



Schistosomiasis: effects on concurrent disease

- **IL-4, a Th2 polarizing cytokine is present at high levels as a result of *S. mansoni* infection.**
- **Therefore, elevated levels of IL-4 might be expected to influence the outcome of immune responses to other antigens (infections).**

Schistosomiasis: effects on concurrent disease

- **Vaccination of Schistosome infected adults and the babies of infected mothers had impaired Th1 immune response to vaccines that normally induce Th1 responses.**
- **Mice infected with schistosomes are less able to mount anti viral responses, have greater susceptibility to malaria and are extremely susceptible to infection with *T. gondii*.**

Schistosomiasis: effects on concurrent disease

- **In clinical settings: co-infection with hepatitis B or C is common.**
- **The opposite requirements for anti-viral immunity (Th1) and the observed dominant Th2 response to schistosomiasis is an explanation for the occurrence of chronic hepatitis-virus infection in schistosomiasis patients.**

Further evidence for association of hepatitis C infection with parenteral schistosomiasis treatment in Egypt (2002)

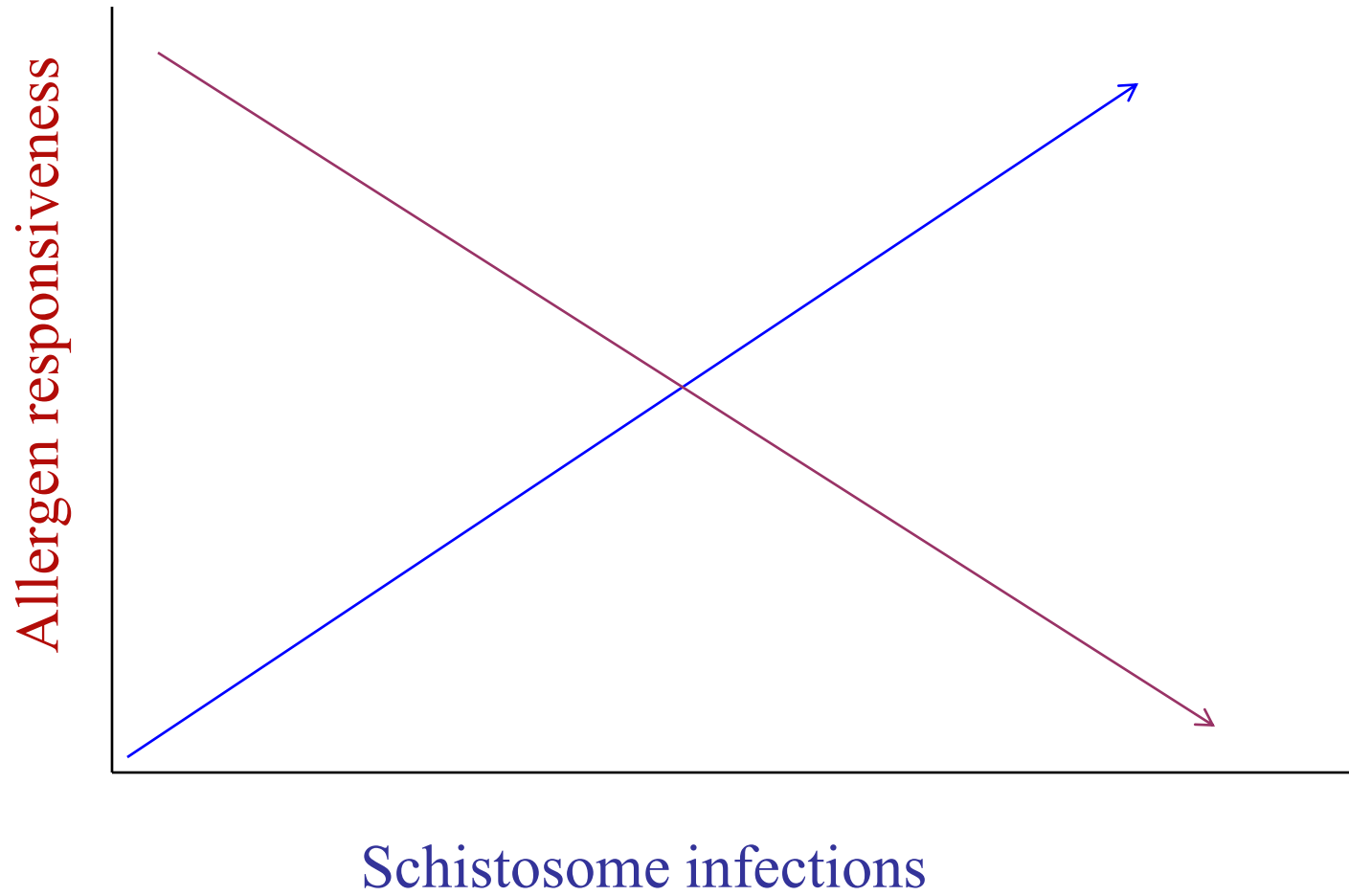
Rao et al. **BMC Infect Dis.** 2002; 2: 29.

- Hepatitis C virus (HCV) infection and schistosomiasis are major public health problems in the Nile Delta of Egypt.
- To control schistosomiasis, mass treatment campaigns using tartar emetic injections were conducted in the 1960s through 1980s. **Evidence suggests that inadequately sterilized needles used in these campaigns contributed to the transmission of HCV in the region.**

Schistosomiasis: effects on concurrent disease

- **CONVERSELY**, schistosomiasis might be beneficial during co-infection with other pathogens (*Trichuris muris*).
- Might help prevent the onset of Th1-mediated diabetes mellitus, and mitigating **allergy**.
- ‘Hygiene hypothesis’

Hygiene Hypothesis



Susceptibility Factors for Infection

- In endemic areas, individuals < puberty carry the most parasites.
- Drug treatment followed by re-infections leads to some level of protective immunity.
 - Correlation between **IgE** antibodies reactive to worm (not egg) antigens.
 - **Why so long to get anti-worm antibodies?**

Concomitant immunity...

Immunity to Schistosomes...

- **Is someone from a nonendemic area more likely to develop more severe disease?**

Schistosome vaccines, past

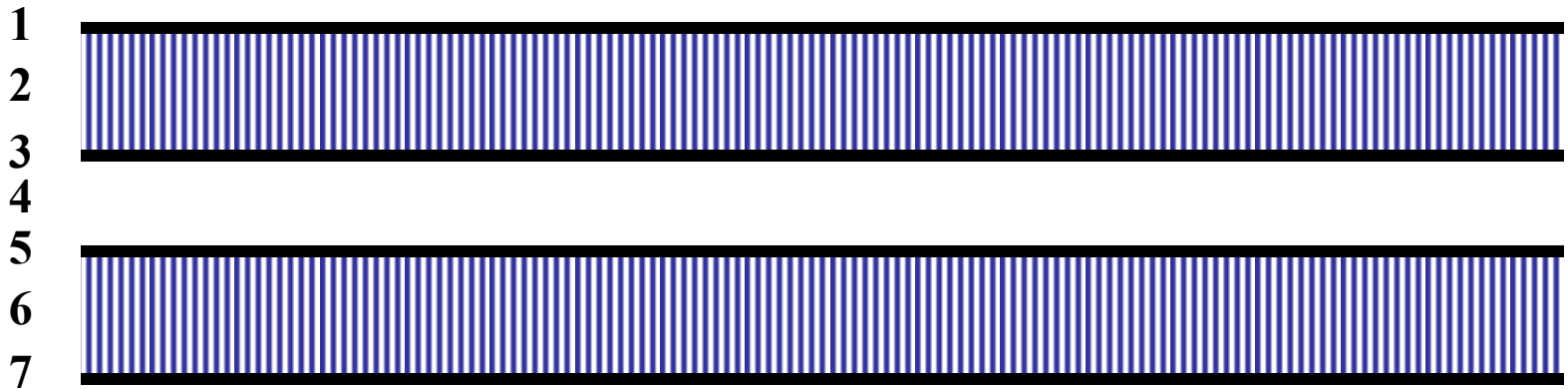
- **Vaccination with infective larva (cercariae) of *S. mansoni* that have been attenuated induced high levels of protection in animal models (Minard, 1978; Stek, 1981).**
 - **Not feasible approach for large-scale human vaccination.**

Schistosome vaccines—the tegument

- Heptalaminate membrane.
- Dynamic host-interactive layer involved in nutrition, immune evasion and modulation, excretion, osmoregulation, sensory reception and signal transduction, and importantly from a vaccine perspective, **it constitutes the host-parasite interface.**

Heptalaminate Membrane

Outer surface



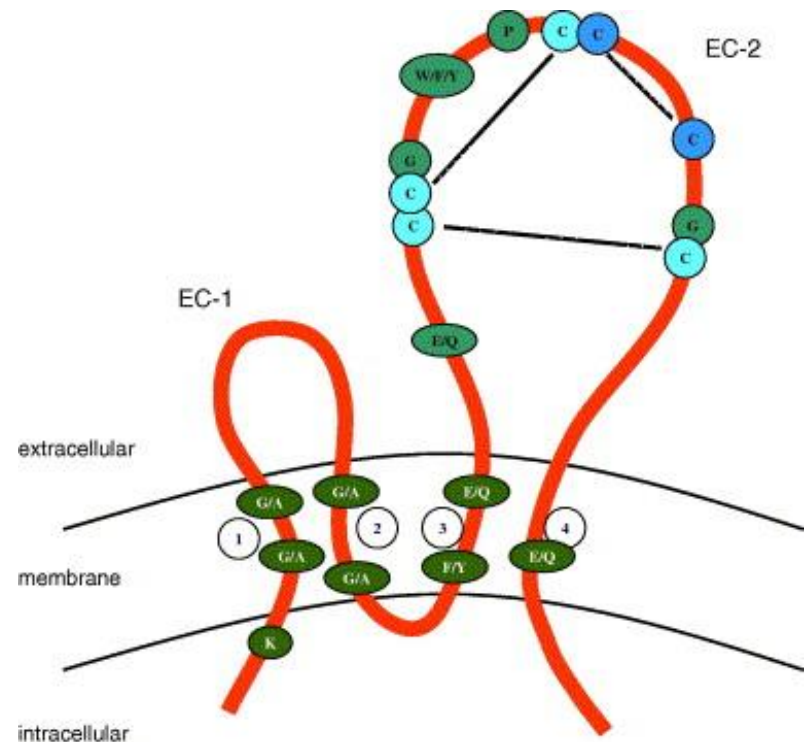
Parenchymal tissue

Schistosome vaccines—the tegument

- **Not all proteins inside the tegument are exposed to host tissues.**
- **Only a few proteins are truly ‘exposed’.**
- **A set of 43 proteins was identified which were expressed exclusively in the tegument and not in the underlying tissues.**

Schistosome vaccines—the tegument

- **Tetraspannins**
 - Short loop
 - Long loop
 - Mediate protein-protein interactions; ligands?
 - Sm23 expressed on Sm tegument.
 - **WHO vaccine candidate**
 - Effective if delivered as a DNA vaccine but not as a recombinant vaccine.

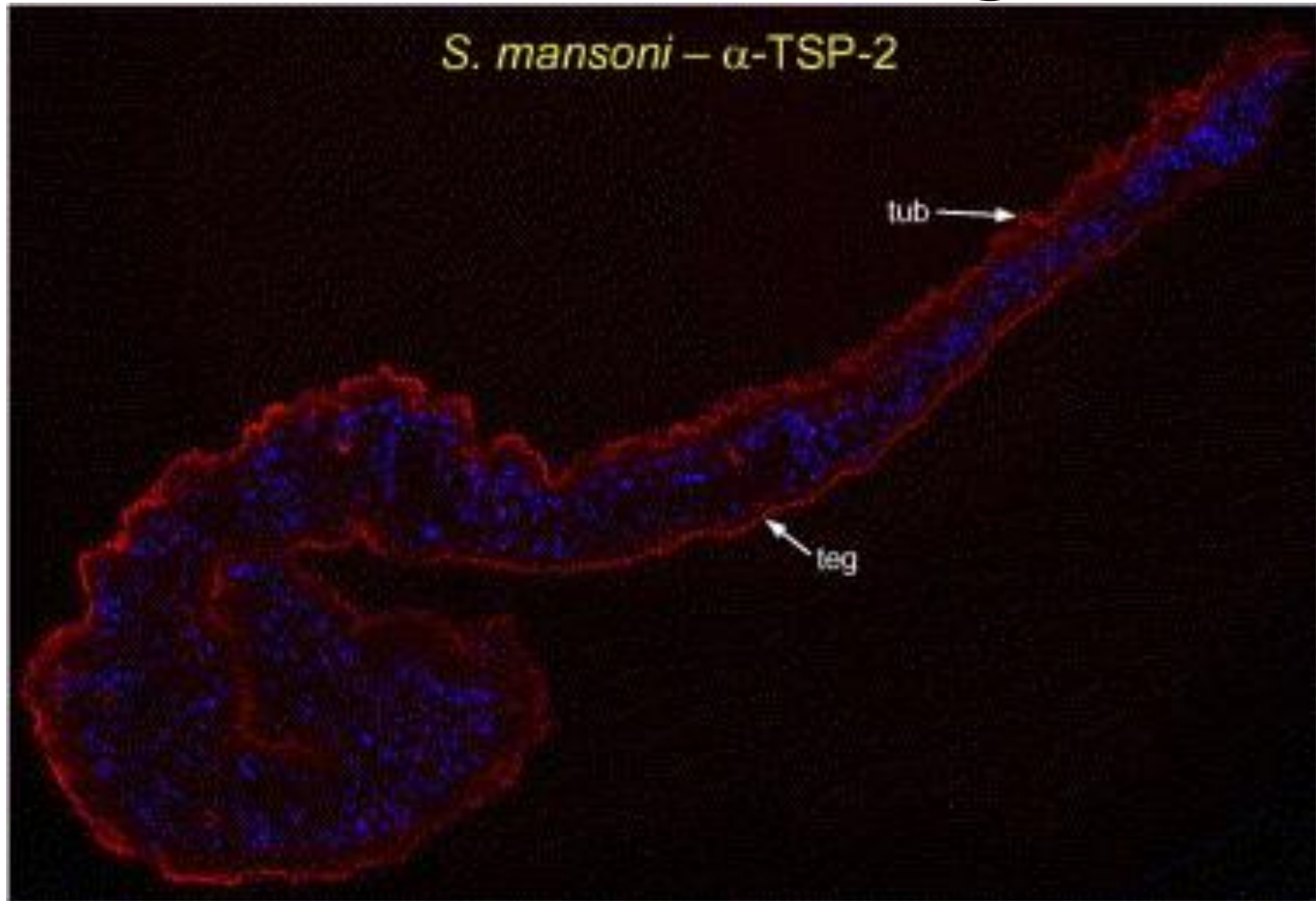


Schistosome vaccines—the tegument

- **Tetraspannins**

- Newly identified Sm-TSP1 and Sm-TSP2 (Smyth, 2003).
 - Effective as recombinant vaccinogens in mice studies.
- Examined levels of anti TSP1/2 antibodies in humans divided into **C**hronically **I**nfected or **P**utatively **R**esistant (Correa-Oliveira, 2006).
- **Found that PR individuals had had strong anti IgG1 and IgG3 TSP-2 responses.**
 - **CI** individuals and unexposed blood donors failed to mount any detectable antibody isotype response to TSP-2.

TSP-2 Staining

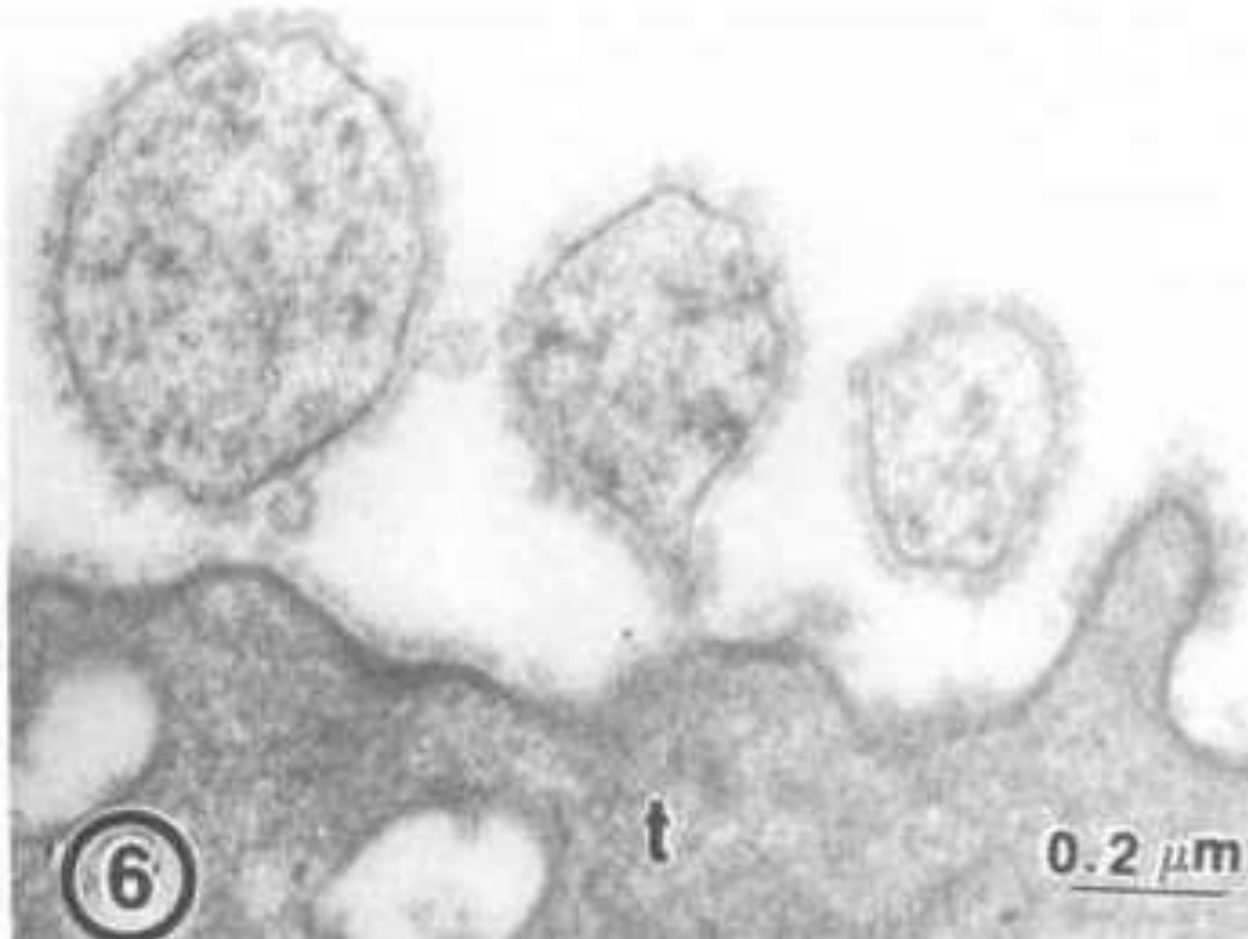


Immune Evasion

Avoidance of the immune response

- Molecular piracy [adult schistosomes]
Coating with host molecules (ABO, MHC, **Ab**)
- Protease cleavage of IgG
- Detoxification of free radicals (GST)
- Tegument blebbing...

Tegument Blebbing



Immune Modulation

Interference with or misdirection of the immune response

- **Concomitant immunity (larval vs. adult surfaces; stimulation of immunity toward new larvae).**
- **Direct suppression of T- and B-cells (anergy).**
- **Decoy antigens/immune exhaustion**
- **Polyclonal activation.**
- **Suppression of macrophage function.**
- **Host cytokines as growth factors.**

Diagnosis

- **Microscopic detection of schistosome eggs in feces or urine.**
- **Once diagnosis is made, morbidity needs to be assessed.**
 - **Ultrasound**
- **In endemic areas or for diagnosis during the prepatent stage:**
 - **ELISA or Western blot**
 - **Purified or crude egg antigens**
 - **Sm31/32 worm antigen**

Treatment

- **Prophylaxis**

- **Toweling off immediately after a brief wetting may prevent cercariae skin penetration.**
- **Hexachlorophene skin cleansers prevent cercariae penetration.**

- **Treatment**

- **Praziquantel*, metrifonate, oxamniquine and others.**

- ***Praziquantel interferes with Ca⁺ homeostasis, promoting sustained muscular contraction and tegument disruption, which leads to antigen exposure.**

Recorded Cure Rates

- 75 to 85% for *S. hematobium*
- 63 to 85% for *S. mansoni*
- 80 to 90% for *S. japonicum*
- 89% for *S. intercalatum*
- 60 to 80% for double infections with *S. mansoni* and *S. hematobium* .

Schistosoma Control Measures

Molluscicide

Disruption of local ecology

Eradication impossible

Targeted chemotherapy

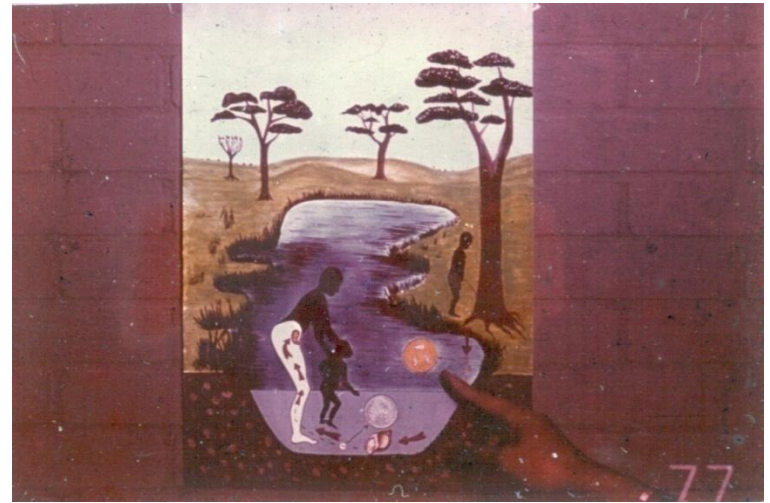
Detection of infection

Expense of drug and delivery

Prevention

Education, changing behavior

Vaccine development





CENTRO DE SALUD PISAC



**MEDICINA
PEDIATRIA
GINECOLOGIA y OBSTETRICIA
PLANIFICACION FAMILIAR
FARMACIA LABORATORIO
EMERGENCIA HOSPITALIZACION**

HORARIO DE ATENCION LUNES A DOMINGO 24 HORAS