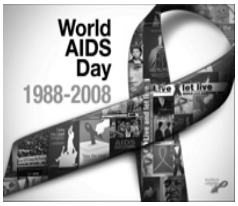
Pneumocystis jirovecii and *Toxoplasma gondii*:
A Tale of Two Parasites or

Opportunistic Infections In Immuno-deficient Hosts

Charles Knirsch, MD, MPH



Protozoan Parasites

1. *Toxoplasma gondii*

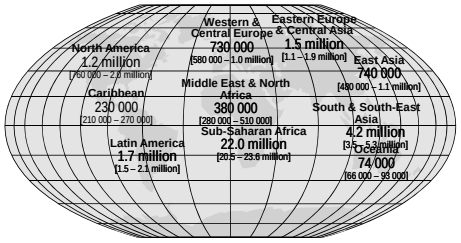
2. The Malarias
   - *Plasmodium falciparum*
   - *Plasmodium vivax*
   - *Plasmodium ovale*
   - *Plasmodium malariae*

3. Diarrheal disease-causing protozoa:
   - *Giardia lamblia*
   - *Entameba histolytica*
   - *Cryptosporidium parvum*
   - *Cyclospora cayetanensis*

World Health Organization

UNAIDS

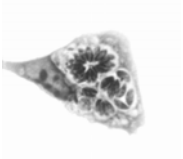
Adults and children estimated to be living with HIV, 2007



Total: 33 million (30 – 36 million)

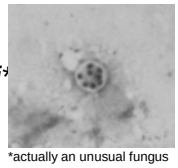
Protozoa:

Toxoplasma gondii



and

*Pneumocystis jirovecii**
formerly *P. carinii*

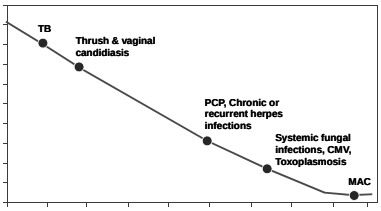


*actually an unusual fungus

And the Band Played On

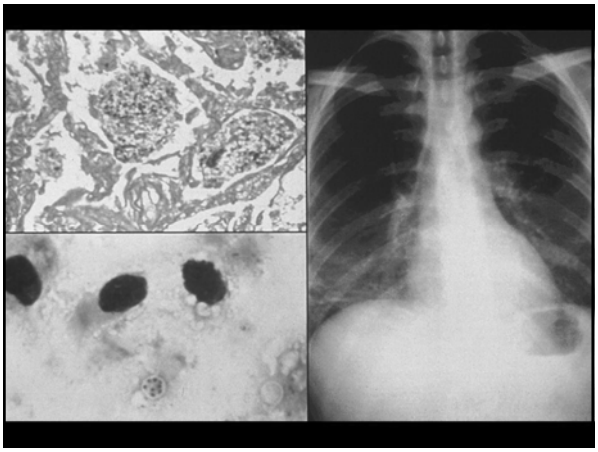
- Politics, people and the AIDS epidemic
- CDC April 1981: “This guy should go back to medical school if he can’t find some simple neoplasm”
- June 1981 MMWR: Pneumocystis pneumonia in young men
- GRID

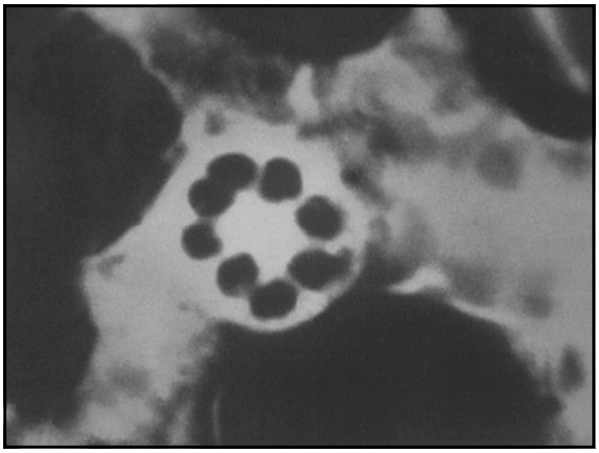
Opportunistic Infections Associated with Progressive Immunodeficiency



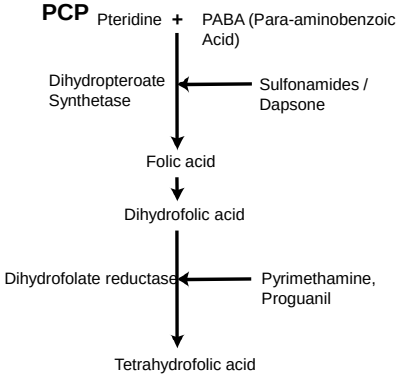
Pneumocystis jirovecii (PCP)

- Commensal organism and opportunistic pathogen
- Morphologically resembles protozoan
- Difficult to grow in vitro
- Life cycle???
  - Cyst stage : 5 um in diameter with 4-8 sporozoites
  - Trophozoite : 2-5 um in diameter – attach to cell surfaces





Folic Acid Inhibitors are Drugs of Choice for PCP



Is P. carinii a Fungus or Protozoon?

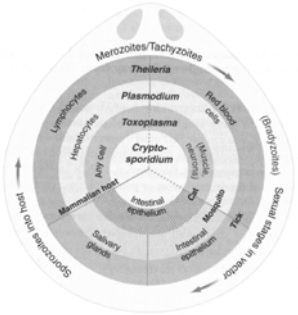
Protozoon

- Morphology
- Inability to culture in vitro
- Response to anti-protozoal drugs

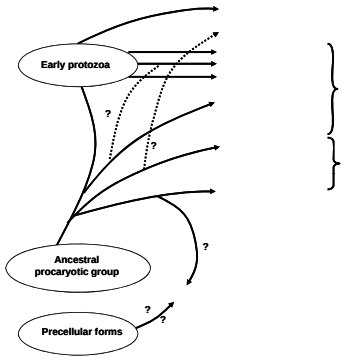
Fungus

- Ribosomal rRNA sequence homology
- ELF3

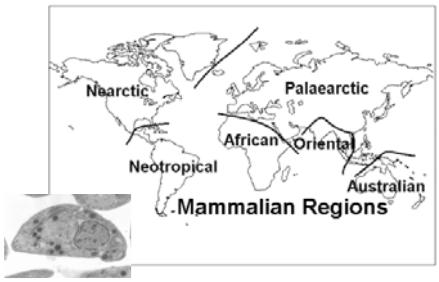
The Apicomplexa



Toxoplasma gondii
The Plasmodia (malaria)
Cryptosporidium hominis

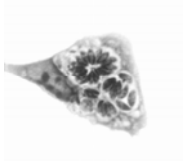


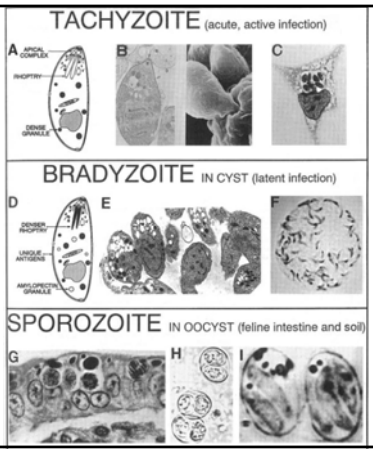
Toxoplasma gondii infects all mammals and all tissues in each of them.



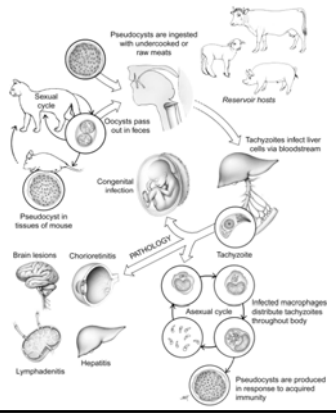
Protozoa:

Toxoplasma gondii



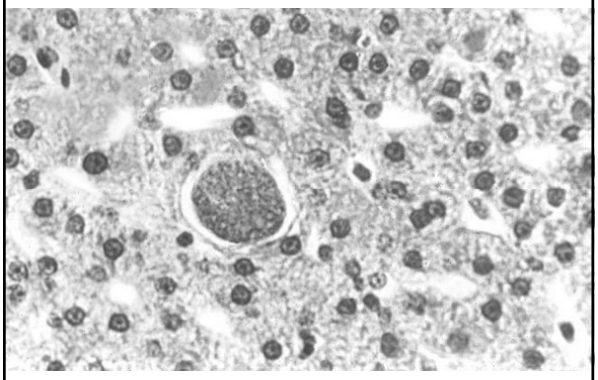


Toxoplasma gondii



Rack of lamb is usually served rare

Felines are the definitive hosts for *Toxoplasma gondii*

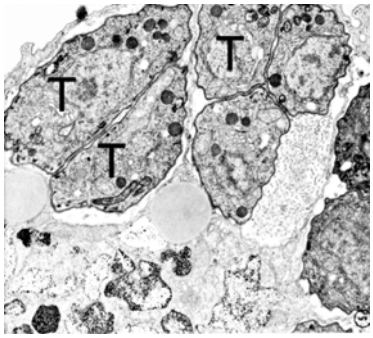


Oocysts of *Toxoplasma gondii*

Macrophage Infected With *Toxoplasma gondii**

* The hunter becomes the hunted

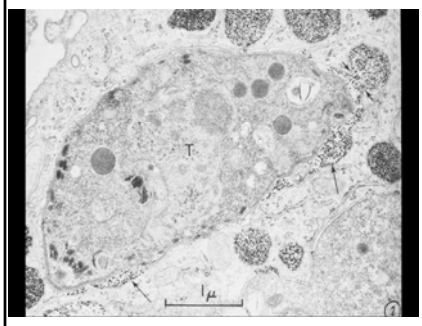
Toxoplasma gondii in culture



Trophozoites (T) prevent fusion of lysosomal menebranes to the parasitophorous vacuole, there escaping digestion

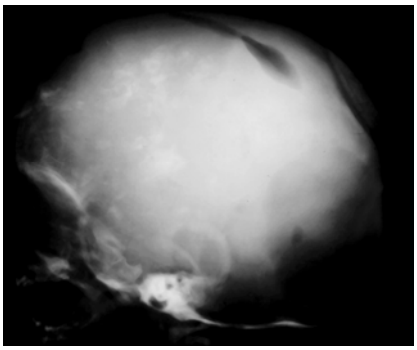
Congenital Toxoplasmosis

Toxoplasma gondii in culture



Heat-killed organisms cannot prevent fusion of lysosomal membranes with the parasitophorous vacuole

Calcified Lesions Due To Congenital Toxoplasmosis



Clinical Disease:

Congenital

Adult-acquired

AIDS-related

Congenital Toxoplasmosis

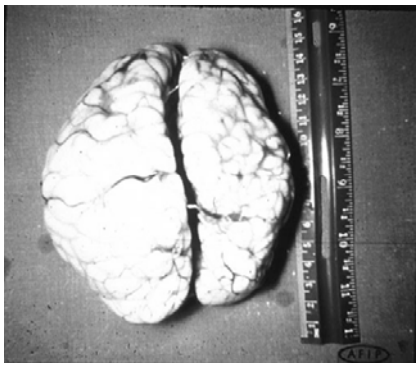


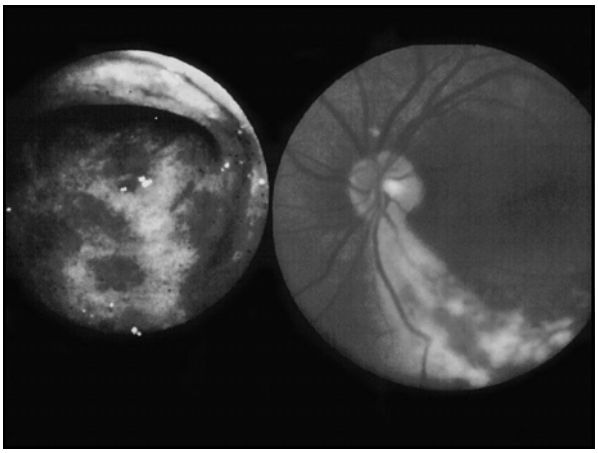
Photo courtsey: Gary Baumbach, M.D., Department of Pathology, University of Iowa College of Medicine

Congenital Toxoplasmosis:

Still Birth

Chorioretinitis

Mental Retardation



Congenital Toxoplasmosis Following Maternal Infection During First and Second Trimester*

Not Infected	73%
Subclinical Infection	13%
Mild Infection	7%
Severe Infection	6%

** From Desmonts and Couvier, NEJM 290: 1110, 1974*

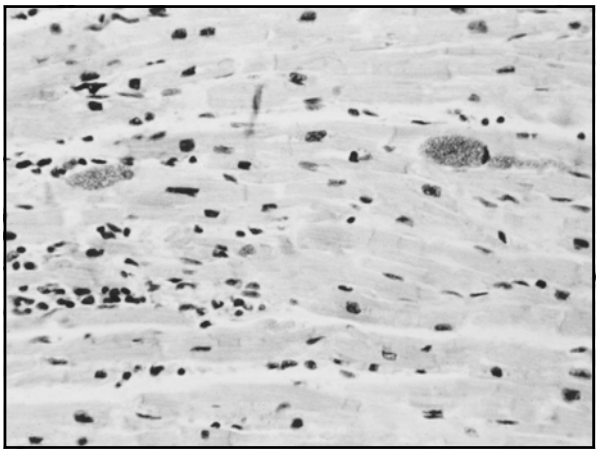
Adult-Acquired Toxoplasmosis

Toxoplasma Ocular Disease

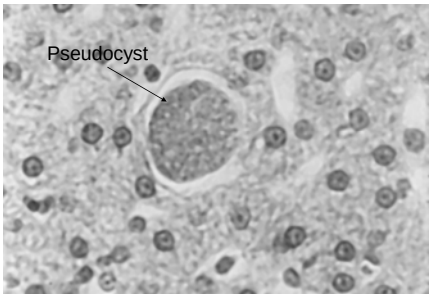
- Usually from congenital infection manifesting in adults
  - Episodic flares may destroy retinal tissue
  - Specific treatment necessary

Infection by Blood or Organ Transplant

- Parasitemia (WBC's) for up to 1 year post infection
- Heart, bone marrow, liver, kidney donors
  - Dangerous when recipient toxo (-)
- Myocarditis, diffuse lymphadenopathy



Pseudocyst of *Toxoplasma gondii* in Liver



Adult-Acquired Toxoplasmosis

Signs and symptoms:

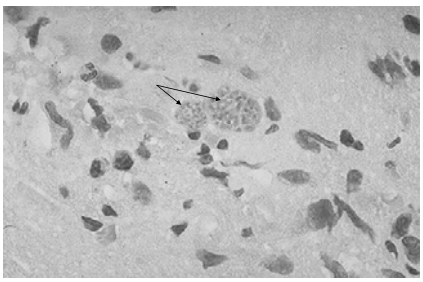
- Lymphadenopathy
- Fever
- Headache
- Chronic Malaise

AIDS-related Disease

Differential Diagnosis of Lymphadenopathy

	Toxoplasmosis	*Inf. Mono*	*Lymphoma*
Lymphadenopathy Without Other Symptoms	+++	+	+++
Pharyngitis	+	+++	+
Monocytosis, Eosinophilia	+++	+	+++
Atypical Lymphocytes	+	++++	+
Anemia	0	+	+++
Positive Heterophil	0	++++	0
Altered Liver Function	0	++++	++
Hilar Lymphadenopathy	+	+	+++
Lymph Node Pathology	Reticulum Cells	Germinal Cells	Bizarre Cells

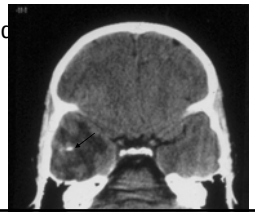
Pseudocysts of *Toxoplasma gondii* in a microglial nodule with a variety of inflammatory cell types in an HIV/AIDS patient



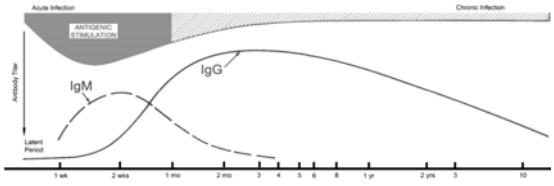
AIDS-related Disease:

1. CD4 < 200 and reactivation of latent infection

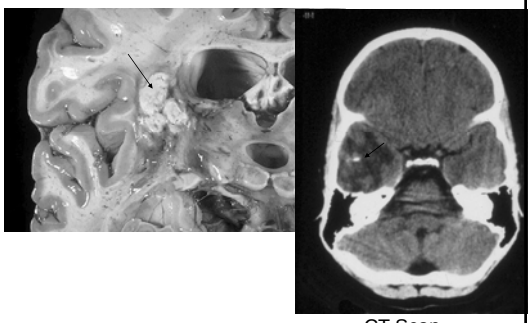
2. Encephalitis
    1. Diffuse inflammation and swelling
    2. Localized ring enhancing lesions on CT scan
    3. Herniation
    4. Death if untreated



Serological correlates in acute and chronic infection

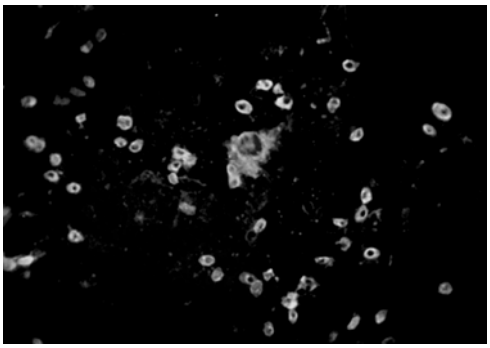


Toxoplasma abscess in the brain would appear as a ring-enhancing lesion with CT scan.



CT Scan

Indirect Fluorescent Antibody (IFA)Test



Diagnosis

Folic Acid Inhibitors are Drugs of Choice

Pteridine + PABA (Para-aminobenzoic Acid)

Dihydropteroate Synthetase ← Sulfonamides / Dapsone

Folic acid

Dihydrofolic acid

Dihydrofolate reductase ← Pyrimethamine, Proguanil

Tetrahydrofolic acid

Prevention:

1. Prevent pregnant women from handling cat litter
2. Avoid eating raw or under-cooked meats

Trained cat

Automated litter collection box

The Most Common Neglected Infections of Poor People

Disease	Number of Cases	Population at-risk
Ascariasis	807 million	4.2 billion
Trichuriasis	604 milion	3.2 billion
Hookworm	576 million	3.2 billion
Amebiasis	500 million	ND
Schistosomiasis	200 million	0.6 billion
Lymphatic Filariasis	**120 million**	**1.0 billion**
Trachoma	84 million	0.5 billion
Onchocerciasis	**18 million**	**0.1 billion**
Chagas Disease	**16 million**	**0.1 billion**
Leishmaniasis	**12 million**	**0.4 billion**
Leprosy	0.4 million	ND
Dracunculiasis	**0.01 million**	**ND**

Host status

- *Pneumocystis carinii*
  - No Life cycle!
  - Lung disease in AIDS
  - Malnourished children
  - Organ Transplants
- *Toxoplasma gondii*
  - Cat definitive host
  - Disease: Host status
  - CNS Disease in AIDS
  - Congenital Infections
  - Organ Transplants

Global Network for Neglected Tropical Diseases
http://www.GNNTDC.org

- Schistosomiasis Control Initiative
- International Trachoma Initiative
- Helen Keller International
- Liverpool School - GAELF
- Human Hookworm Vaccine Initiative
- Earth Institute at Columbia Univ.
- Task Force for Child Survival
  - Mectizan Donation Program
  - Albendazole Donation Program
  - Mebendazole Donation Program

GNNTDC
GLOBAL NETWORK FOR NEGLECTED TROPICAL DISEASE CONTROL

Some Good News Regarding Extinction:

Smallpox - eliminated (probably)

Polio - nearly gone

Yaws - almost eliminated

Onchocerciasis - on its way out

More Bad News:
Most vector-borne diseases are on the rise