Human African Trypanosomiasis

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MBChB Level IV

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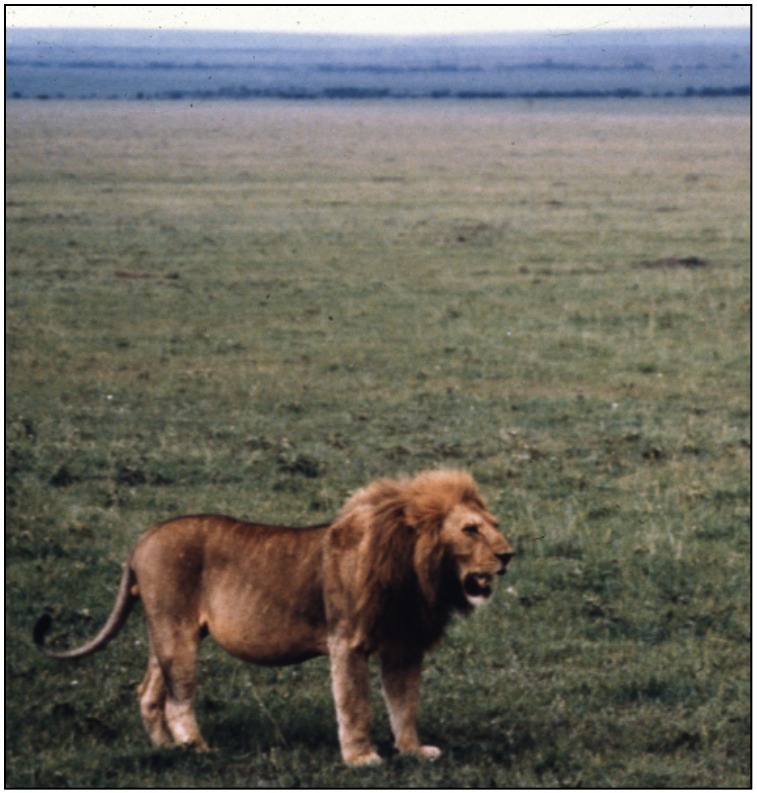
Outline

- Case Presentation
- History
- Lifecycle of trypanosomes
- Epidemiology
- East African HAT
- West African HAT
- Diagnosis
- Treatment
- Prevention

Fever from Tanzania

Case Presentation



- 67 year old American male travelled to Tanzania on a lion hunting safari
- About 5 days into the trip he recalls being bitten by flies and mosquitoes on exposed surfaces of the legs. Did not recall any tick bites
- 2 days later he noted a tender, purple black area on the posterior aspect of his left calf. No other symptoms at the time.

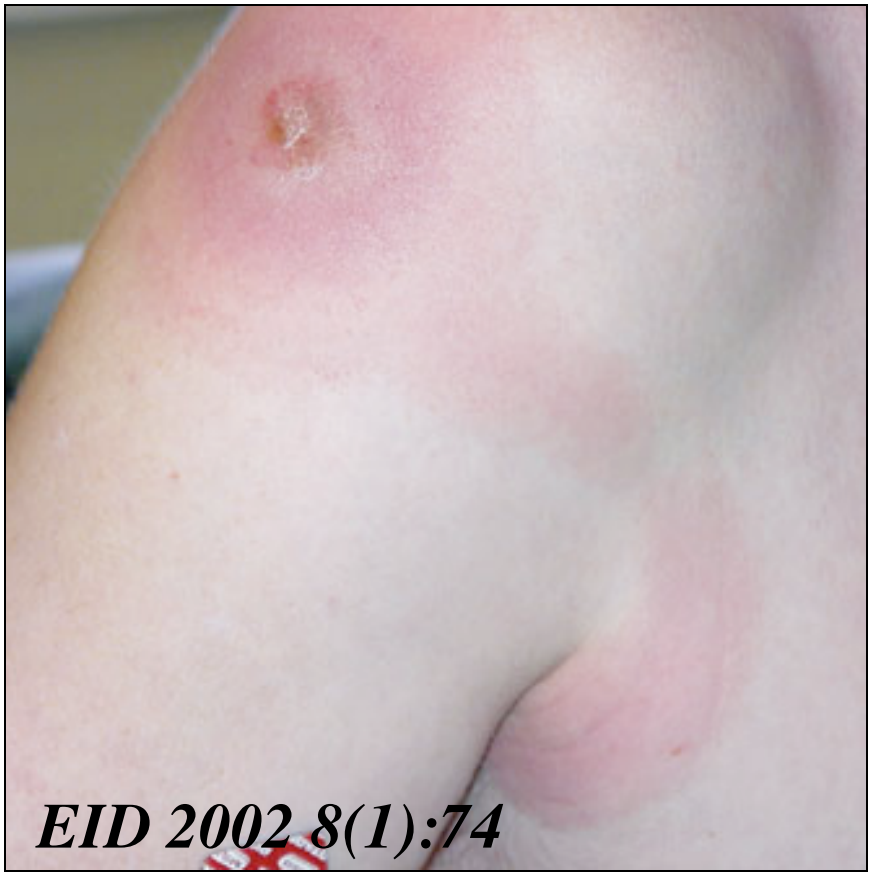
Case Continues…

- While on his flight out of Africa 2 weeks after the calf lesion appeared; he experienced onset of fever, chills, fatigue, and severe myalgias
- Evaluated by a physician in the Amsterdam airport en route and advised he had “the flu”
- Returned to the USA and continued to have nightly fever, chills, and myalgias involving thighs and calves.

Physical Examination

- T = 97.3F, P = 62, RR = 14, BP = 138 / 62
- 1 cm non-tender left SC node
- No hepatosplenomegaly
- Skin
  - Annular erythematous macules on trunk with some central clearing
  - Circular are of erythema, induration w/o warmth at insect bite site

Trypanosomal chancre: East African Trypanosomiasis

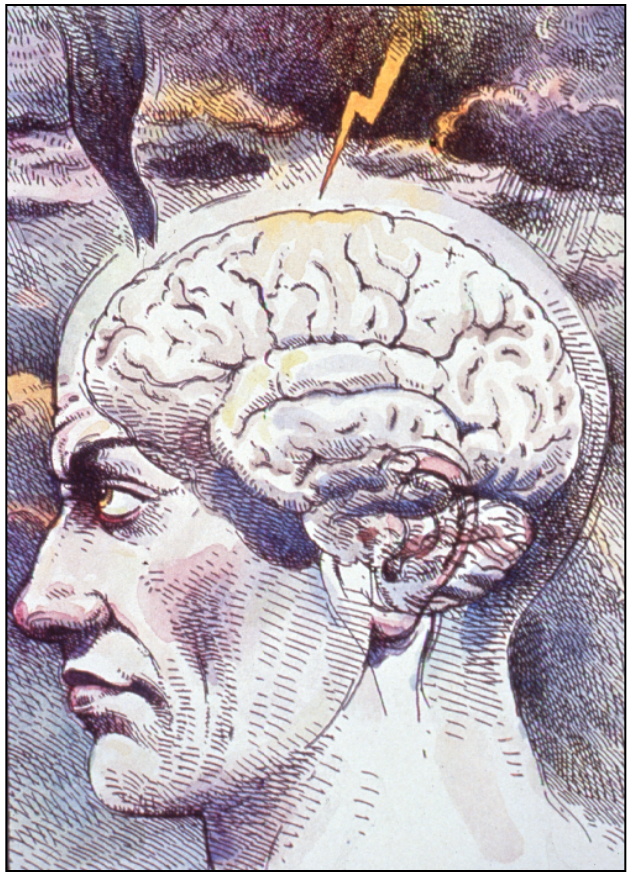


- Painless
- Enlarging over days
- Non-pruritic
- Regional adenopathy
- More common in East African HAT
- Non-immunes >> Africans

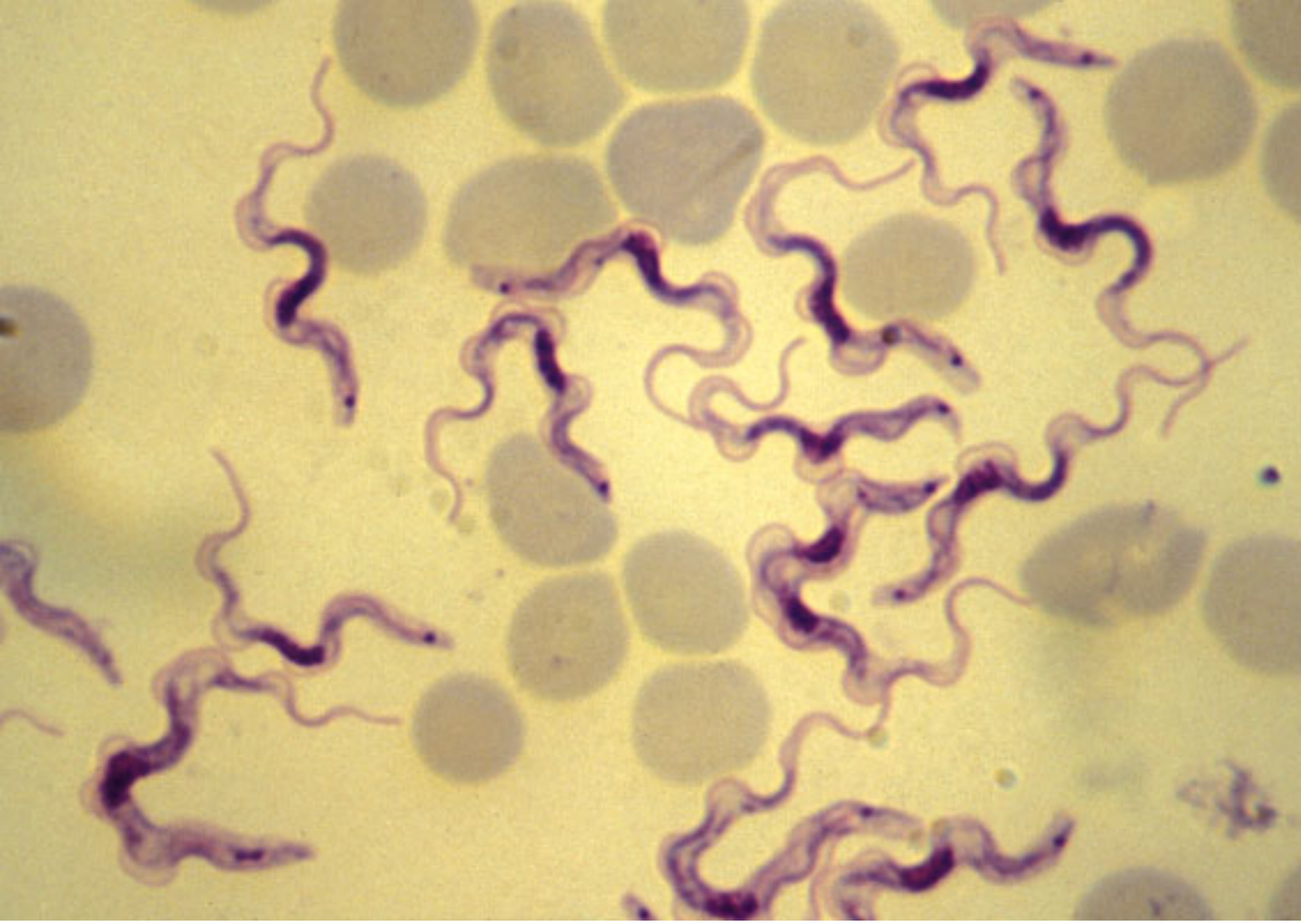
Laboratory

- CBC
  - WBC - 8.3 (51 segs, 28 bands, 2 lymphs, 5 monos, 14 atypical lymphs)
  - HCT - 40%
  - PLTs - 233K
- BUN/Cr = 24 / 1.3
- Alk phos - 125 / GGT - 148 / LDH - 576

Initial Differential Diagnosis?



- Falciparum malaria
- Tick typhus
- East African trypanosomiais
- West African trypansomiasis
- Relapsing fever (Borrelia sps.)



Additional lab and Imaging

- Peripheral blood quantitative Ig
  - IgM - 996 mg / dl (63-277)
  - IGG - 1070 mg / dl (723-1685)
- CSF
  - 2 WBCs (100% monos), 5 RBCs
  - Protein 89 mg / dl (ULN is 45 mg / dl)
  - Glucose 86 gm / dl
  - IgM 4.7 mg / dl (0 - 0.6 mg / dl)
  - Cytospin of CSF
    - No trypanosomes, no Mott cells, many lymphocytes and plasma cells
- MRI of head unremarkable, CXR WNL

Confirmation of CNS involvement

- 2 rats injected with fresh whole blood
- 2 rats injected with fresh CSF

- All successfully infected, confirming presence of CNS trypanosomes / infection

Management

1. Stage 1 disease - Intravenous suramin

2. Stage 2 disease (CNS Disease) - Intravenous suramin + Melarsoprol

Hospital Course

- Initially treated with IV Suramin
  - 100 mg test dose
  - 900 mg follow
- Following day began 1st dose of MEL B (melarsoprol/ dimercaprol) per WHO recs
- Afebrile within 48 hours of receiving suramin, rash resolved over several days
- Peripheral parasitemia resolved over 48 hours as well
- Tolerated drugs well, no further complications

History of HAT

- John Atkin (1685-1757) described '**a sleepy distempe**r' reminiscent of second stage trypanosomiasis off the coast of Guinea in 1721.
- Thomas Masterman Winterbottom (1766-1859) published an account of lethargy in Sierra Leone that was sometimes associated with "small glandular tumors in the neck" in West African slaves.
- David Livingstone (1813-1873) described (1858) *nagana*, a disease of horses ("which follows the bite of the tsetse").

History of HAT

- Captain David Bruce (1855-1931) identified trypanosomes in large mammals in Ubombo, Zululand (in 1895).
- The first human infection was described by Robert Forde (1861-1948) together with Everett Dutton (1877-1905). They identified trypanosomes in a sailor returning from The Gambia to Liverpool and classified them as a new species, *Trypanosoma gambiense* in 1902.

Taxonomy of Kinetoplastid Protozoa

- Phylum: Protozoa
- Order: Kinetoplastida
  - Possess a kinetoplast, a DNA containing granule located within the single mitochondrion associated with flagellar base

- Family: Trypanosomatidae
  - Flagellated parasites
  - Polymorphic life cycles
  - Saprozoic (nutrients absorbed through body)

- Genus: *Trypanosoma cruzi*
  Trypanosoma brucei gambiense
  Trypanosoma brucei rhodesiense
  Leishmania spp.

Human African Trypanosomiasis (HAT)

- “Sleeping Sickness”
- Trypanosoma brucei gambiense (West Africa)
- Trypanosoma brucei rhodesiense (East Africa)
- Transmitted by bite of the tsetse fly (Glossina sps.)
- Epidemiology:
  - 50 million at risk in 30 countries of Sub-Saharan Africa
  - 20,000 (?) new cases/year
- West African - human reservoir, ? animal reservoir
- East African - animal reservoir, man is accidental host

Gambian vs Rhodesian HAT

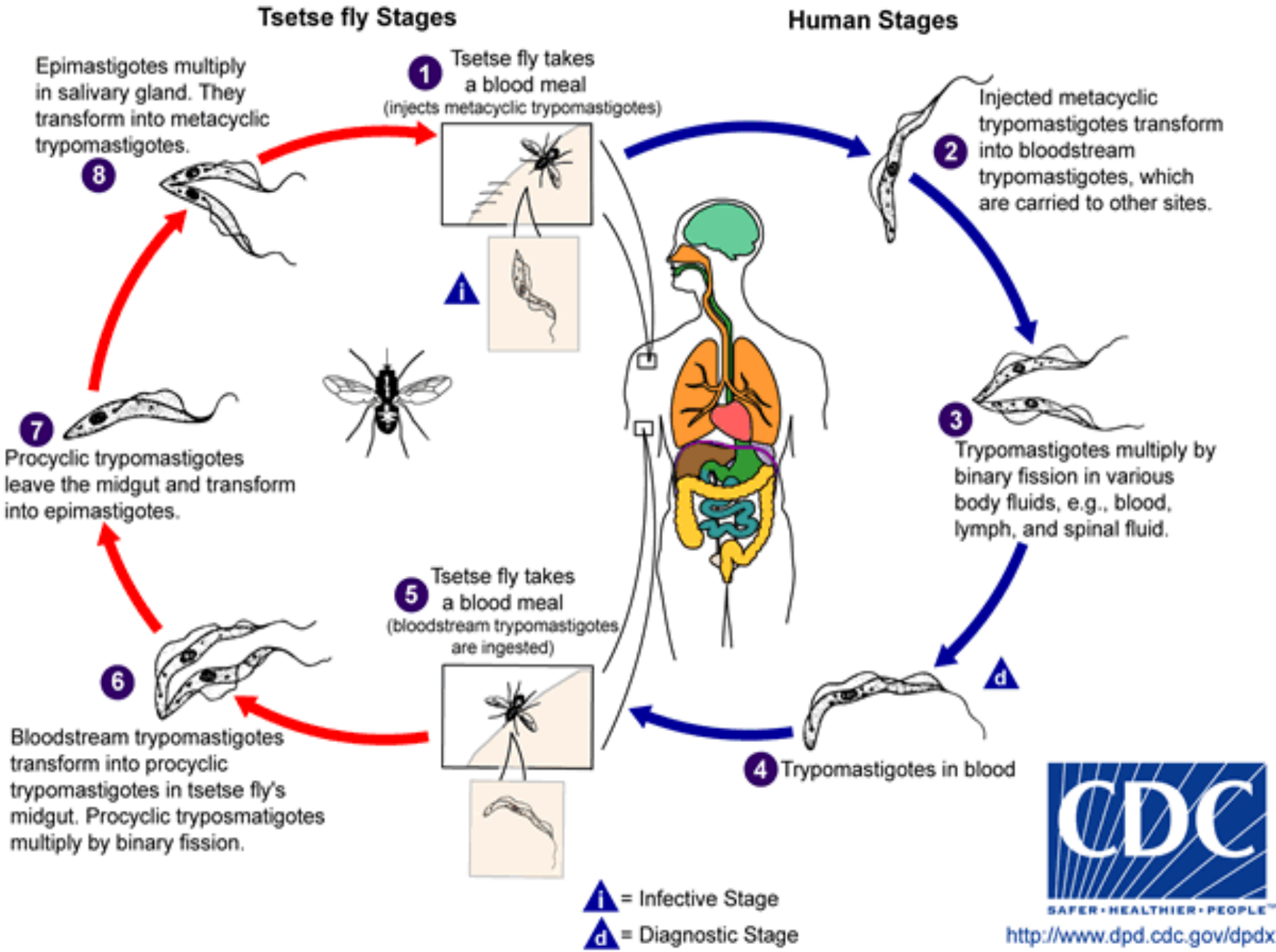
Agent	*T.b. gambiense*	*T.b. rhodesiense*
Main vectors	*G. Palpalis*	*G. Morsitans* group
Distribution	West and Central Africa	East Africa
Biotype	Riverine tsetse	Savanna tsetse
Type	Anthroponosis	Anthropozoonosis
Disease	Chronic-late CNS	Acute-early CNS
Duration	Months to years	Weeks to months
Rodent model	Poor	Good
Parasitemia	Low and cyclical	High and persistent
Diagnosis	Node aspirate, CSF	Blood, CSF
Endemic Risk	Rural endemic	Rural endemic
Non-endemic	Refugees, immigrants	Game park tourists

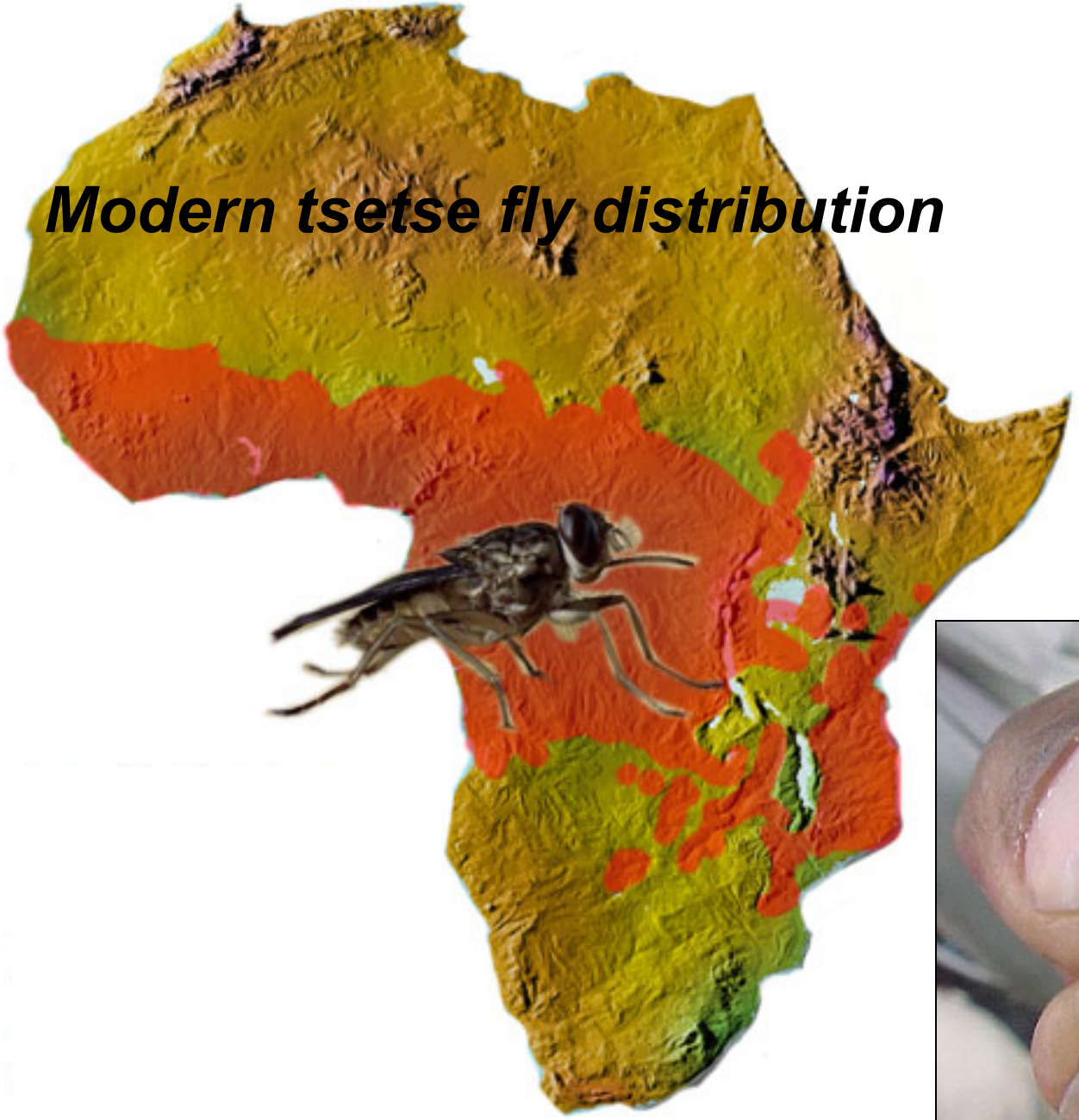
EAST AFRICAN SLEEPING SICKNESS

- Acute febrile course – symptoms begin within days of tsetse bite
- Chancre in > 50%
- Stage 1 (Hemolymphatic)
  - Fever, headache, severe generalized myalgias, Nausea,Vomiting, diarrhoea, abd pain, sweats and rigors
- Stage 2 (Central Nervous System)
  - Little demarcation between stage 1 and 2
  - Drowsiness and tremor
- Serology not useful
- > 80% deaths within 6 months

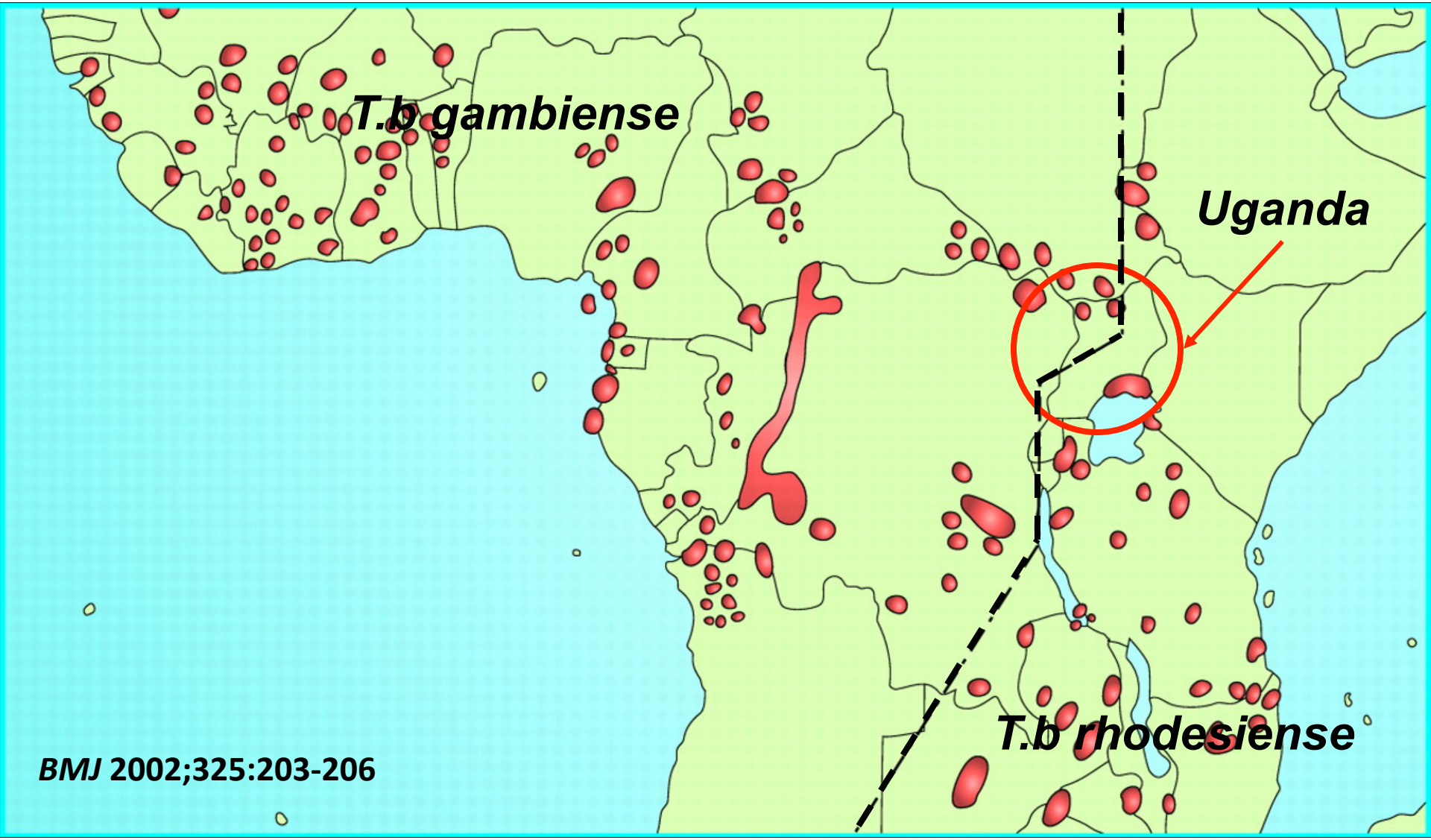
Tsetse fly habitat, East African Trypanosomiasis

Tsetse fly habitat, West African Trypanosomiasis


Tsetse fly Stages
Human Stages
Epimastigotes multiply in salivary gland. They transform into metacyclic trypomastigotes.
8
1 Tsetse fly takes a blood meal
(injects metacyclic trypomastigotes)
i
2 Injected metacyclic trypomastigotes transform into bloodstream trypomastigotes, which are carried to other sites.
3 Trypomastigotes multiply by binary fission in various body fluids, e.g., blood, lymph, and spinal fluid.
d
4 Trypomastigotes in blood
5 Tsetse fly takes a blood meal
(bloodstream trypomastigotes are ingested)
6 Bloodstream trypomastigotes transform into procyclic trypomastigotes in tsetse fly's midgut. Procyclic tryposmatigotes multiply by binary fission.
7 Procyclic trypomastigotes leave the midgut and transform into epimastigotes.
i = Infective Stage
d = Diagnostic Stage
CDC
SAFER·HEALTHIER·PEOPLE™
http://www.dpd.cdc.gov/dpdx

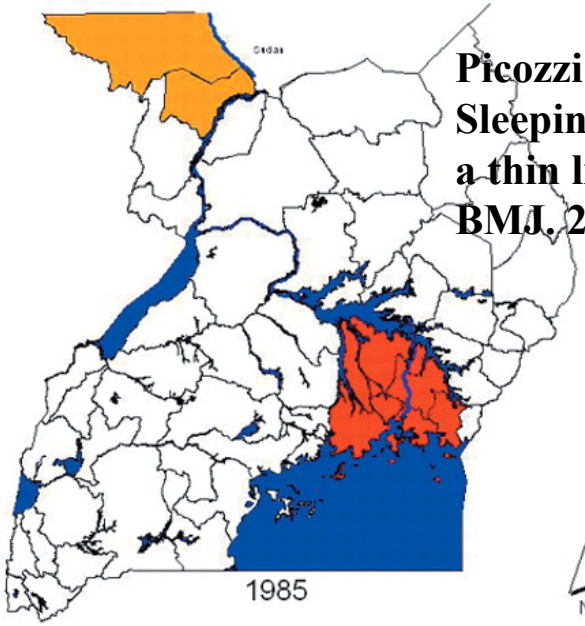


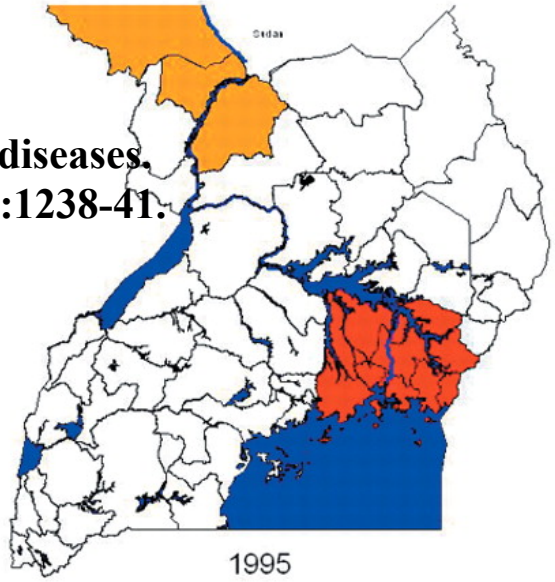
Tsetse flies live in moist savanna and woodlands, regions with > 500 mm of rain a year

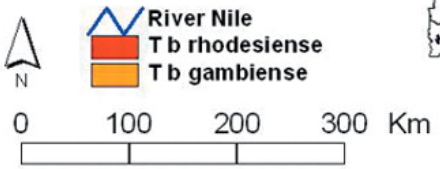


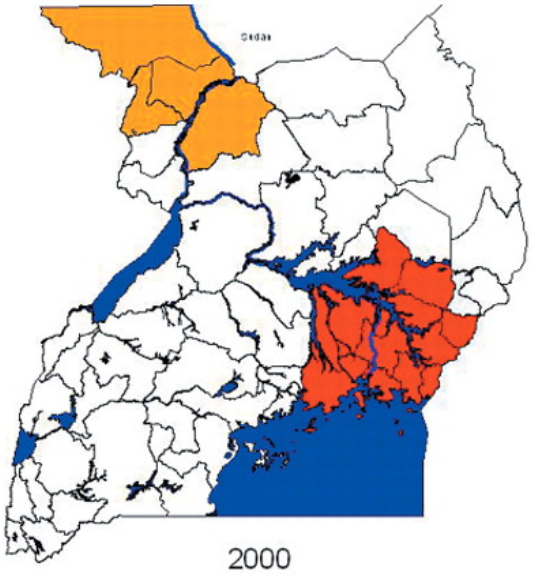
Distribution of human African trypanosomiasis in sub-Saharan Africa

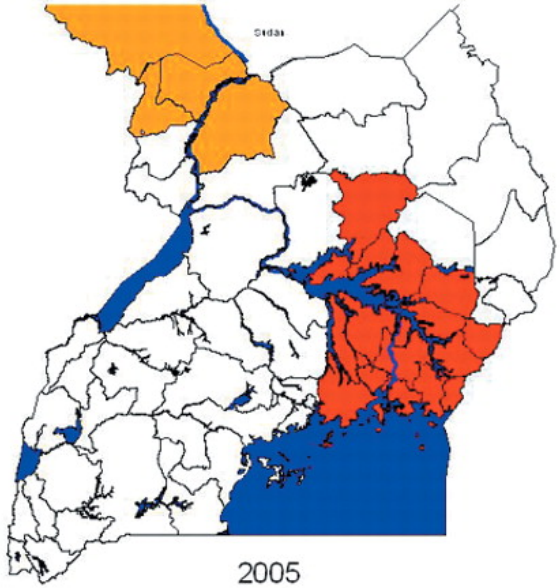
Picozzi K et al.
Sleeping sickness in Uganda:
a thin line between two fatal diseases.
BMJ. 2005 Nov 26;331(7527):1238-41.











Simarro et al. International Journal of Health Geographics 2010, 9:57
http://www.ij-healthgeographics.com/content/9/1/57

INTERNATIONAL JOURNAL OF HEALTH GEOGRAPHICS

RESEARCH Open Access

The Atlas of human African trypanosomiasis: a contribution to global mapping of neglected tropical diseases

Pere P Simarro[1*†], Giuliano Cecchi[2†], Massimo Paone[2], José R Franco[1], Abdoulaye Diarra[3], José A Ruiz[4], Eric M Fèvre[5], Fabrice Courtin[6], Raffaele C Mattioli[2], Jean G Jannin[1]

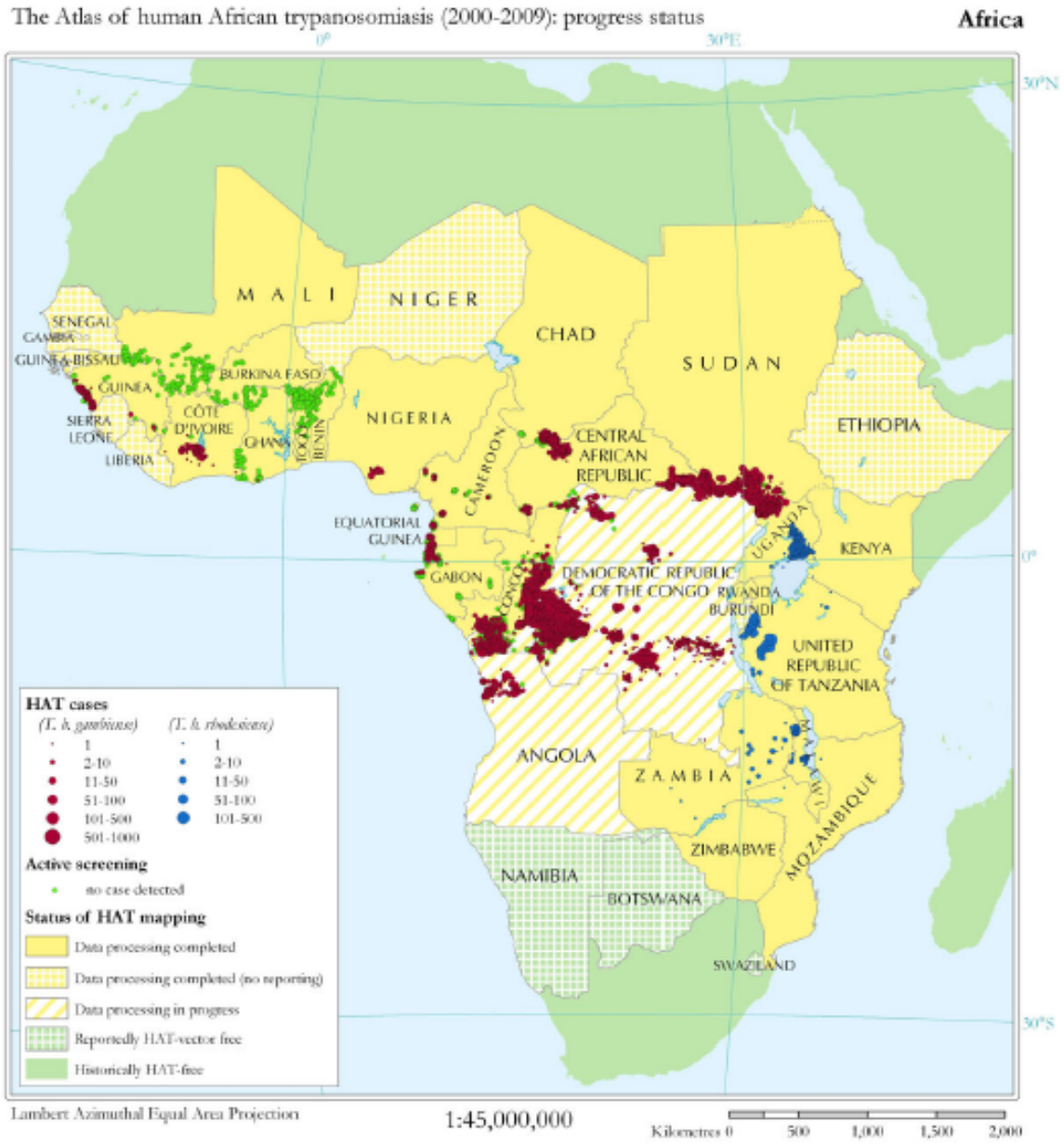


Figure 1 The Atlas of human African trypanosomiasis: progress status. For each country, data processing is considered complete when all available data sources for the study period (2000-2009) have been analysed and included in the HAT database.

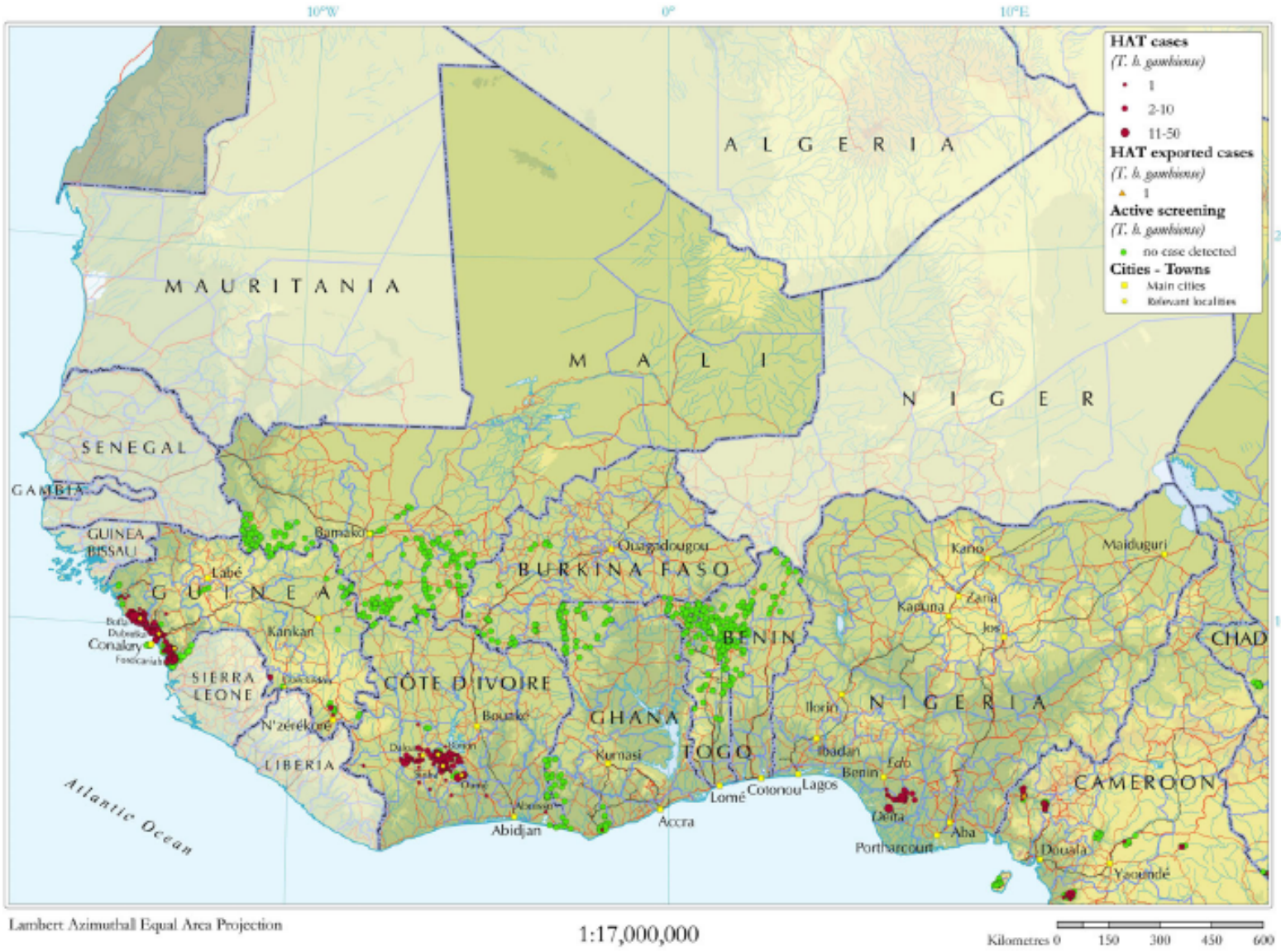
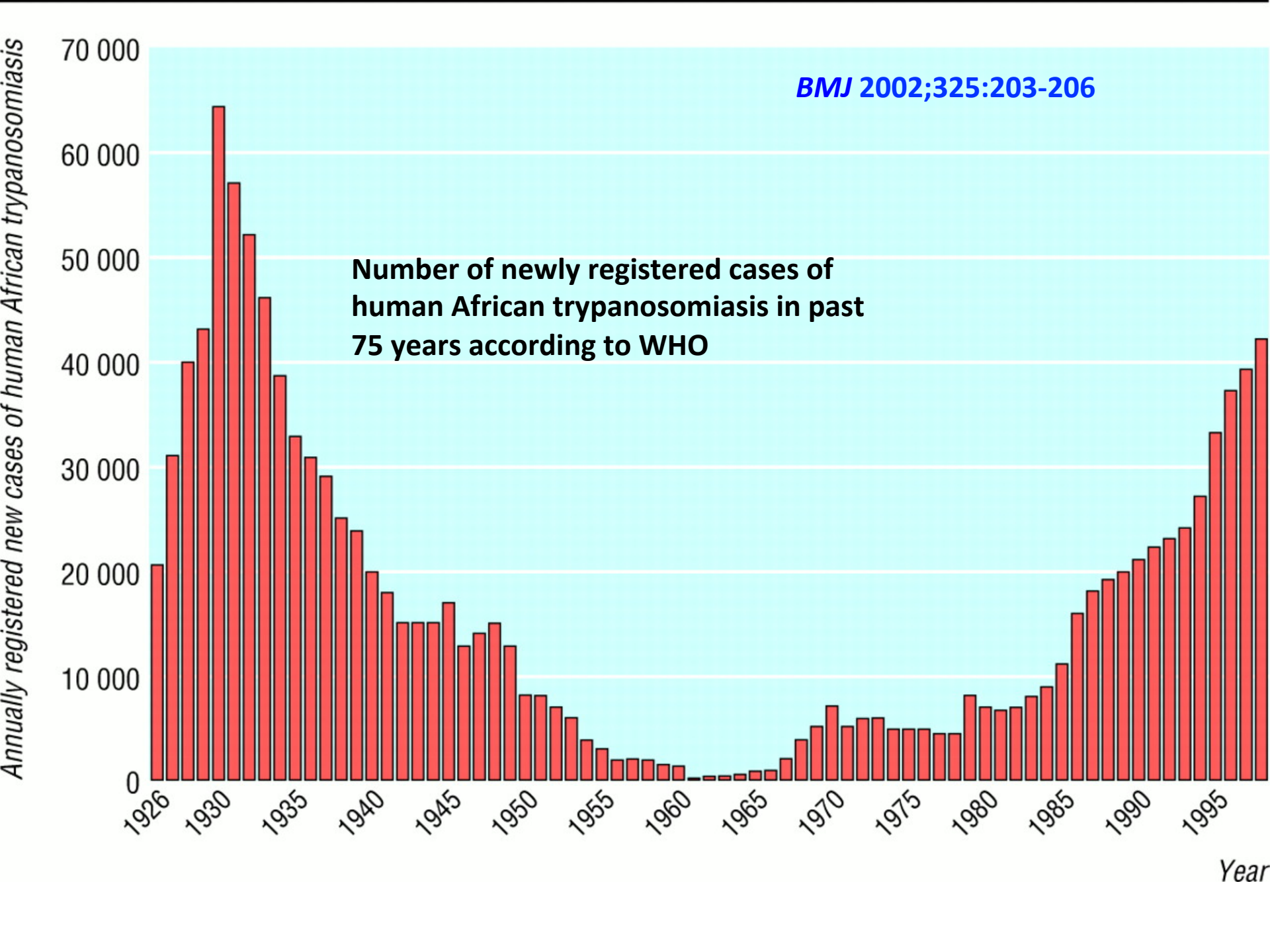


Figure 2 Cases of human African trypanosomiasis reported from Western Africa (period 2000-2009). Countries masked in white are (i) non-endemic for HAT, or (ii) those that did not report on the HAT epidemiological situation in the period 2000-2009. Areas masked in grey correspond to disputed territories and non-self-governing territories [39].


BMJ 2002;325:203-206
Number of newly registered cases of human African trypanosomiasis in past 75 years according to WHO
Annually registered new cases of human African trypanosomiasis
70 000
60 000
50 000
40 000
30 000
20 000
10 000
0
1926
1930
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
Year

WEST AFRICAN SLEEPING SICKNESS

- Indurated chancre 1-2 weeks post bite
- Stage 1 (Hemolymphatic)
  - Intermittent fever, headache, fatigue, pruritus, arthralgias
  - lymphadenopathy, Winterbottom's sign, transient edema, irregular circinate rash, splenomegaly
- Stage 2 (Central nervous system)
  - Insidious onset of neurological symptoms – irritability, personality change, day time somnolence and coma
- Serology useful
- Chronic illness lasting for years

Trypanosomal Chancre

- A small raised papule develops after about 5 days.
- It increases rapidly in size, surrounded by an intense erythematous tissue reaction with local edema and regional lymphadenopathy.
- Although some chancres have a very angry appearance, they are usually not very painful unless they become ulcerated and superinfected.
- They heal without treatment after several weeks, leaving a permanent, hyperpigmented spot.

Trypanosomal Chancre

- Trypanosomal chancres occur in more than half the cases of *T.b. rhodesiense*.
- In *T.b. gambiense*, they are much less common and often go undetected in endemic populations.
- Inexperienced clinicians might misdiagnose chancres as cutaneous manifestations of bacterial diseases such as superinfected insect bites, eschar or cutaneous anthrax.

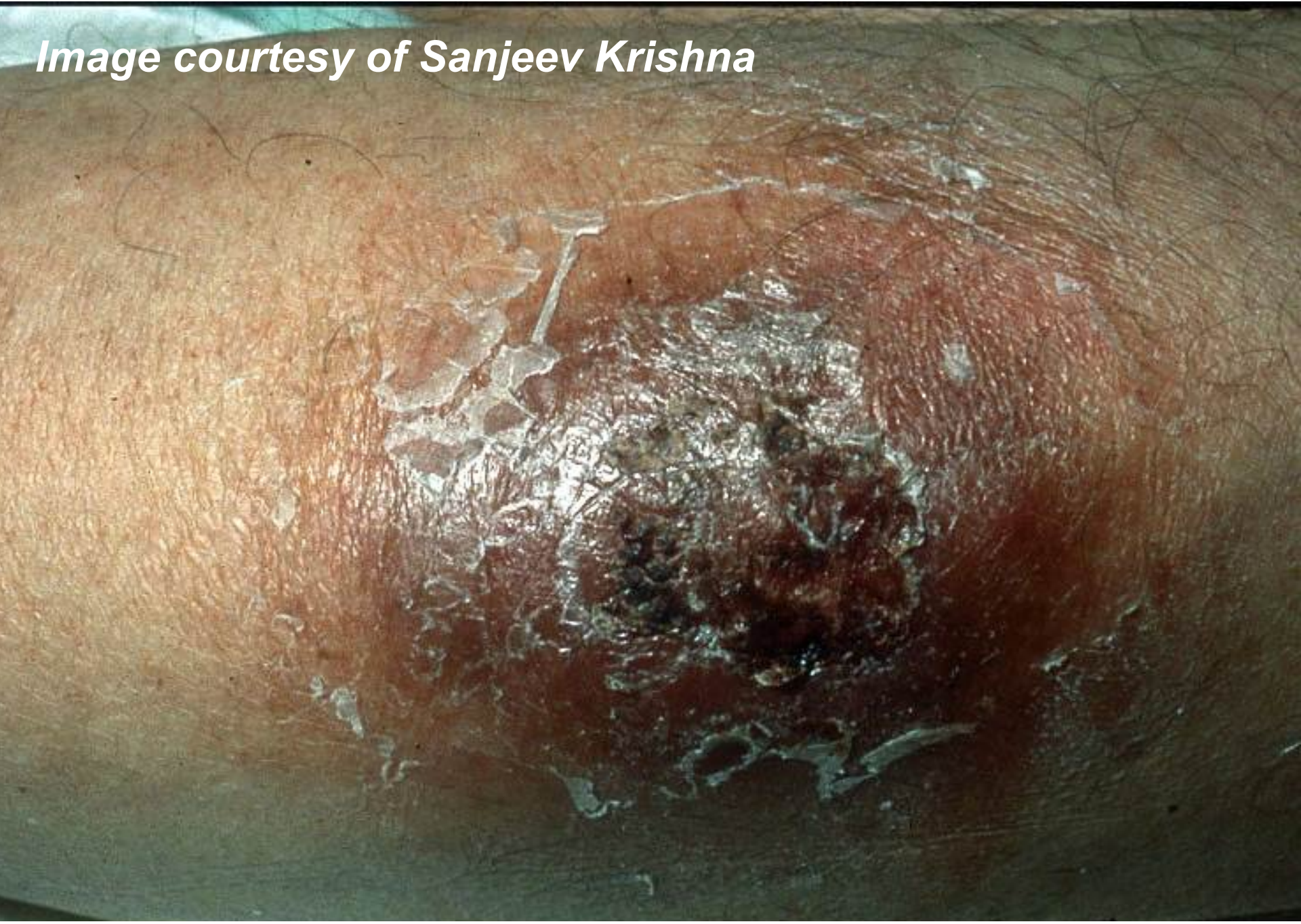
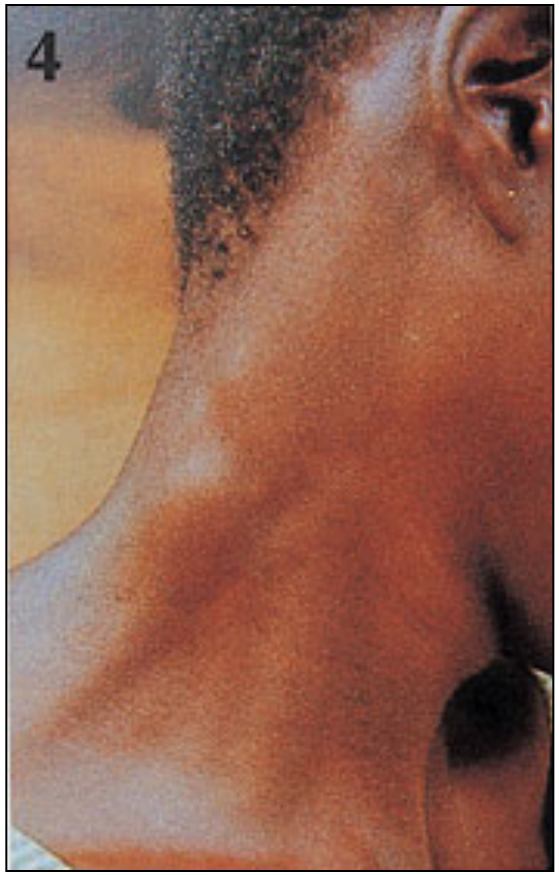


Image courtesy of Sanjeev Krishna

Winterbottom's sign.



- Enlargement of lymphatic lymphatic glands in the posterior triangle of the neck
- Important clinical feature of *T. b. gambiense* infection
- Slave traders avoided buying slaves with this sign


Image courtesy of Sanjeev Krishna

Early Hemolymphatic Disease

- Fever, headache, malaise, fatigue, myalgias, parasthesias.
- Weight loss, lymphadenopathy, hepatosplenomegaly, skin eruptions, facial edema

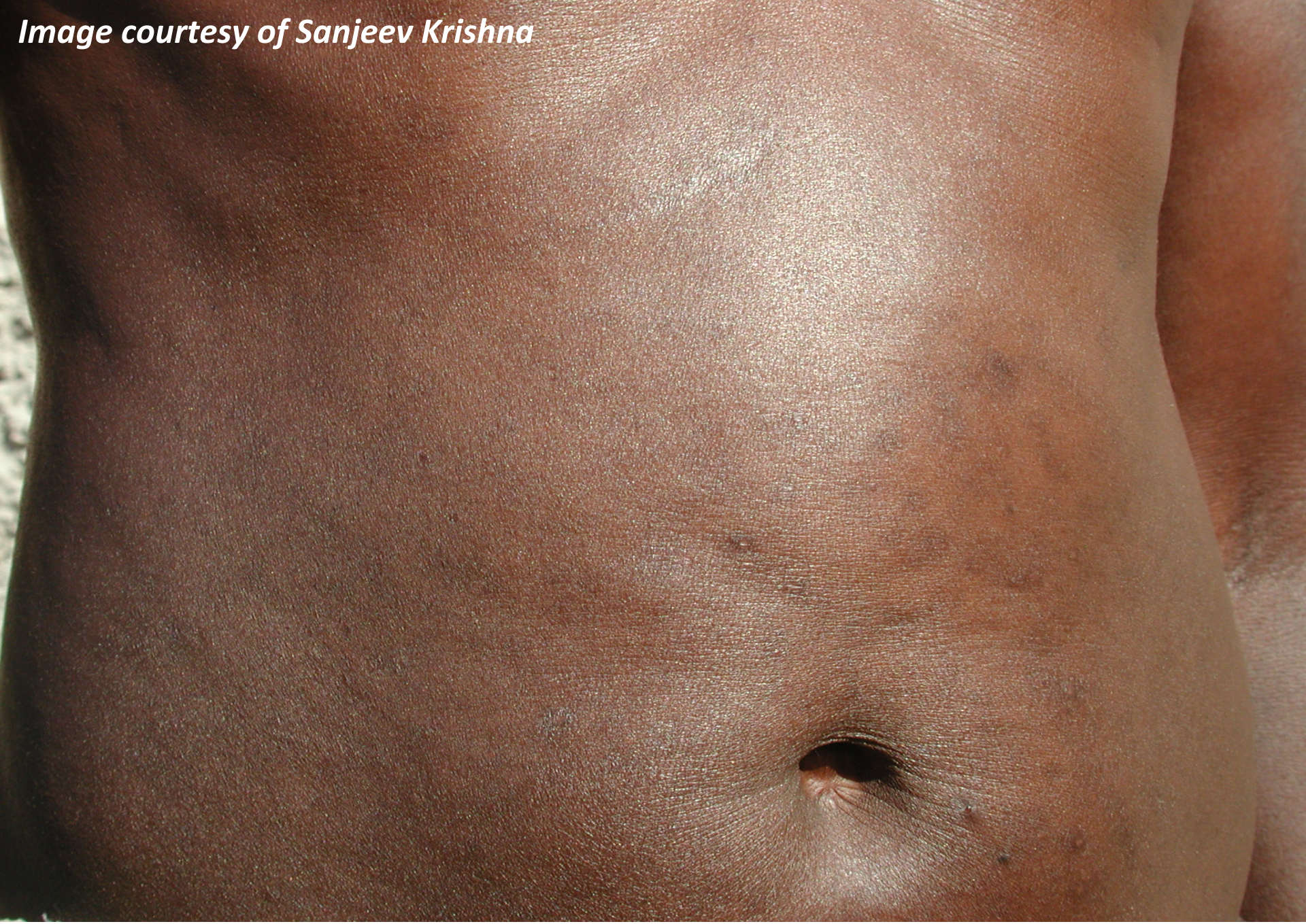
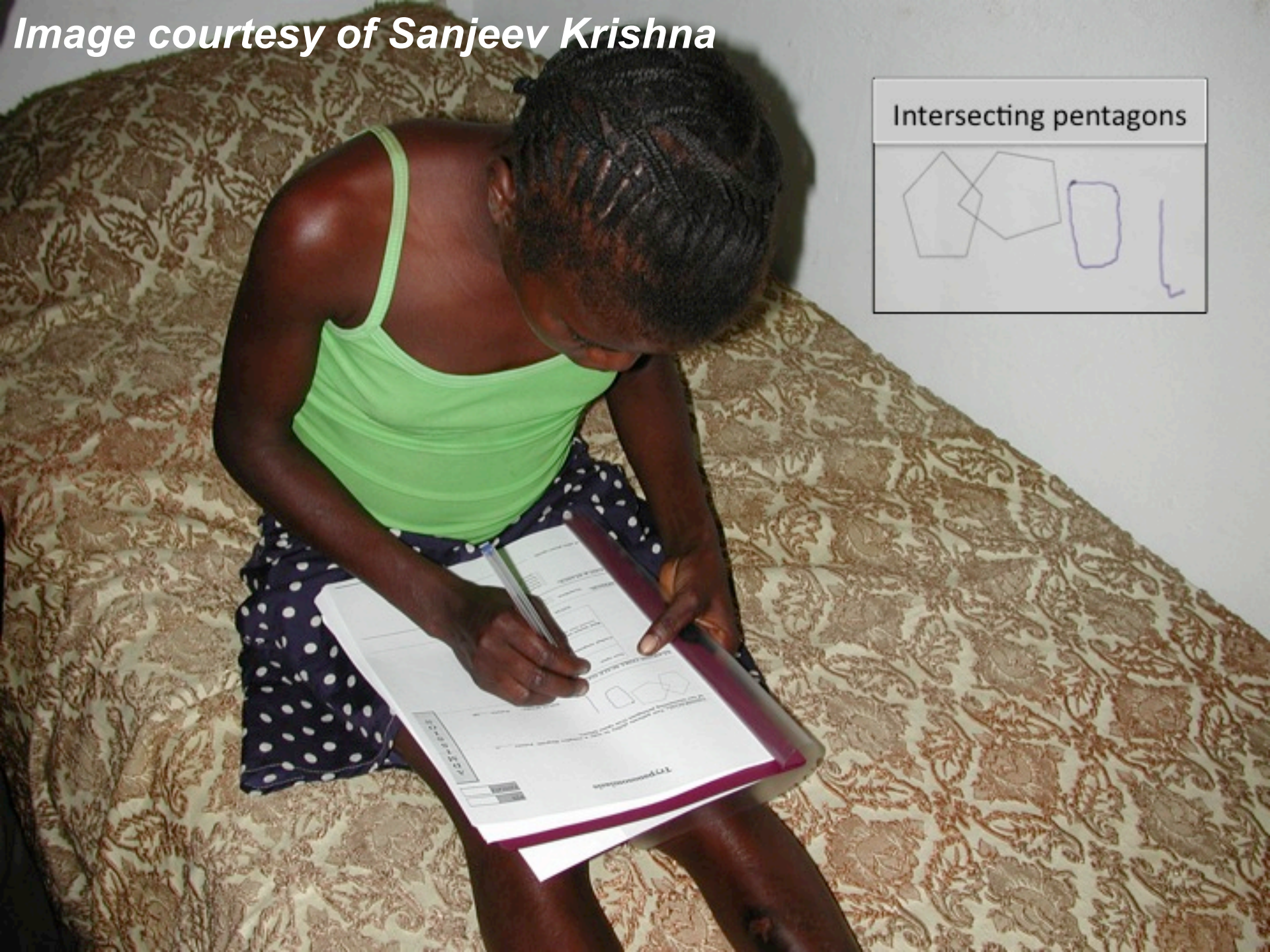


Image courtesy of Sanjeev Krishna

Late Meningoencephalitic Disease

- Insidious onset.
- Disorders of consciousness, extrapyramidal movement disorders, and psychiatric symptoms.
- Final stage is demyelinating encephalitis with dementia, decreased consciousness, cachexia, and death.

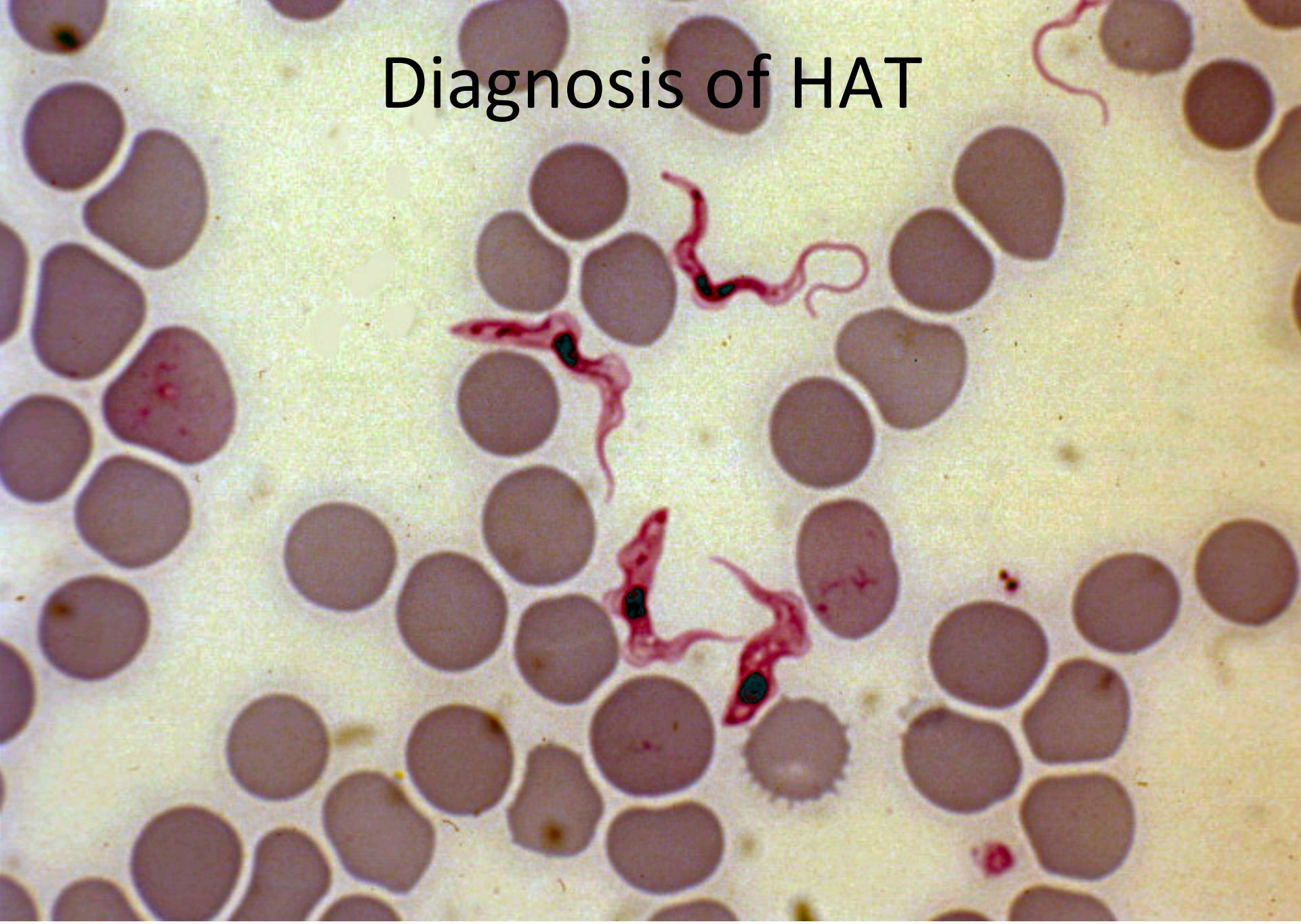
Image courtesy of Sanjeev Krishna



HAT or “sleeping sickness”

- HAT causes characteristic alterations of sleep architecture
- Reversal of normal sleep-wake cycles
  - Day time sleepiness
  - Nocturnal insomnia

Diagnosis of HAT



Non Parasitologic Laboratory Testing

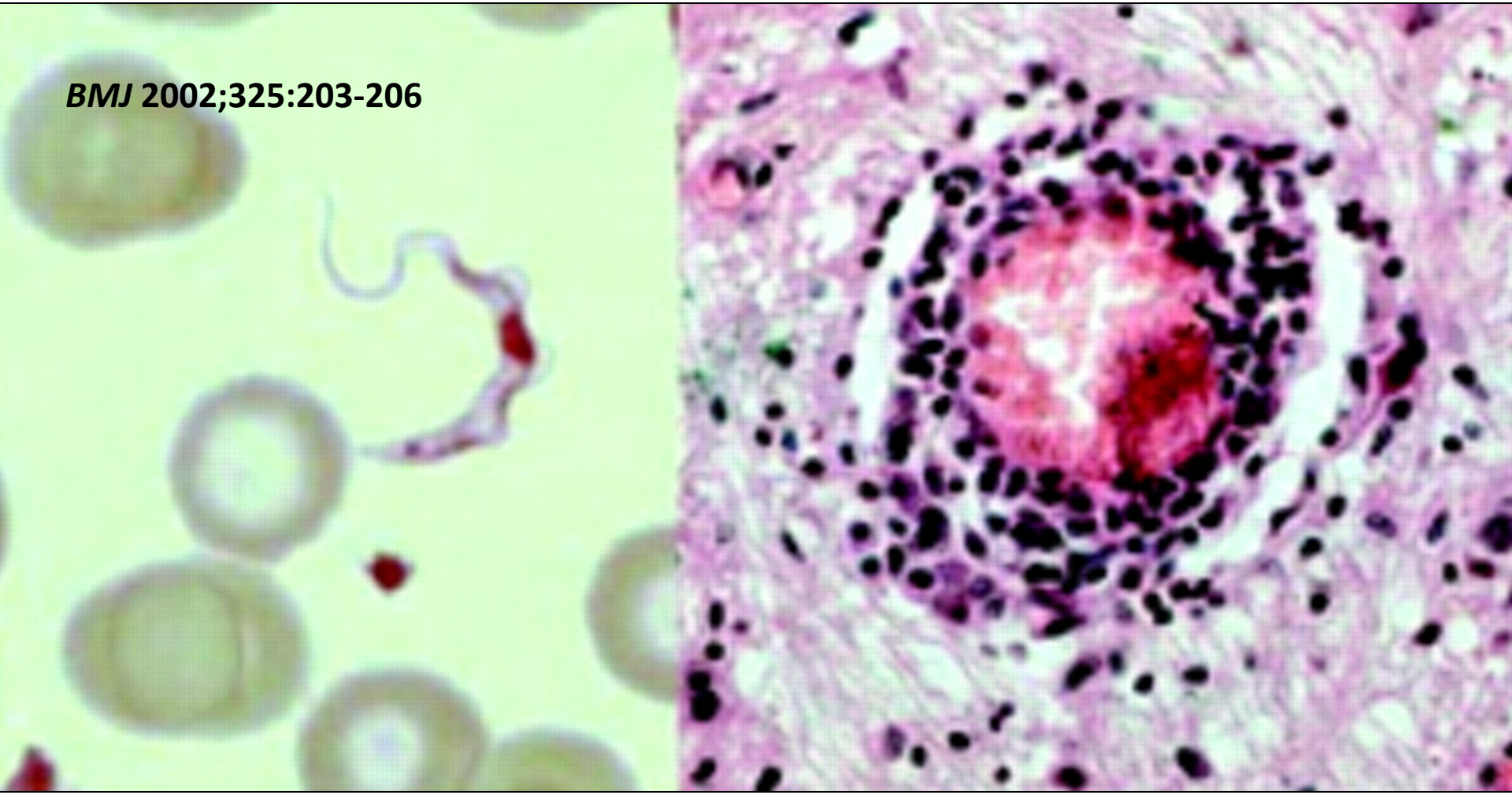
- Increased CRP / ESR
- Lymphopenia
- Thrombocytopenia
- Anemia
- Increased IgM

Parasitological Diagnosis of HAT

	West African HAT (gambiense)	East African HAT (rhodesiense)
Peripheral blood	**low**	**high**
Lymph node aspirate	**high**	**low**
CSF	**variable**	**variable**
Rat inoculation with CSF	**Not useful**	**Very useful**
Serology (CATT)	**Very useful, primary screen**	**Not useful**

DIAGNOSIS OF AFRICAN TRYPANOSOMIASIS

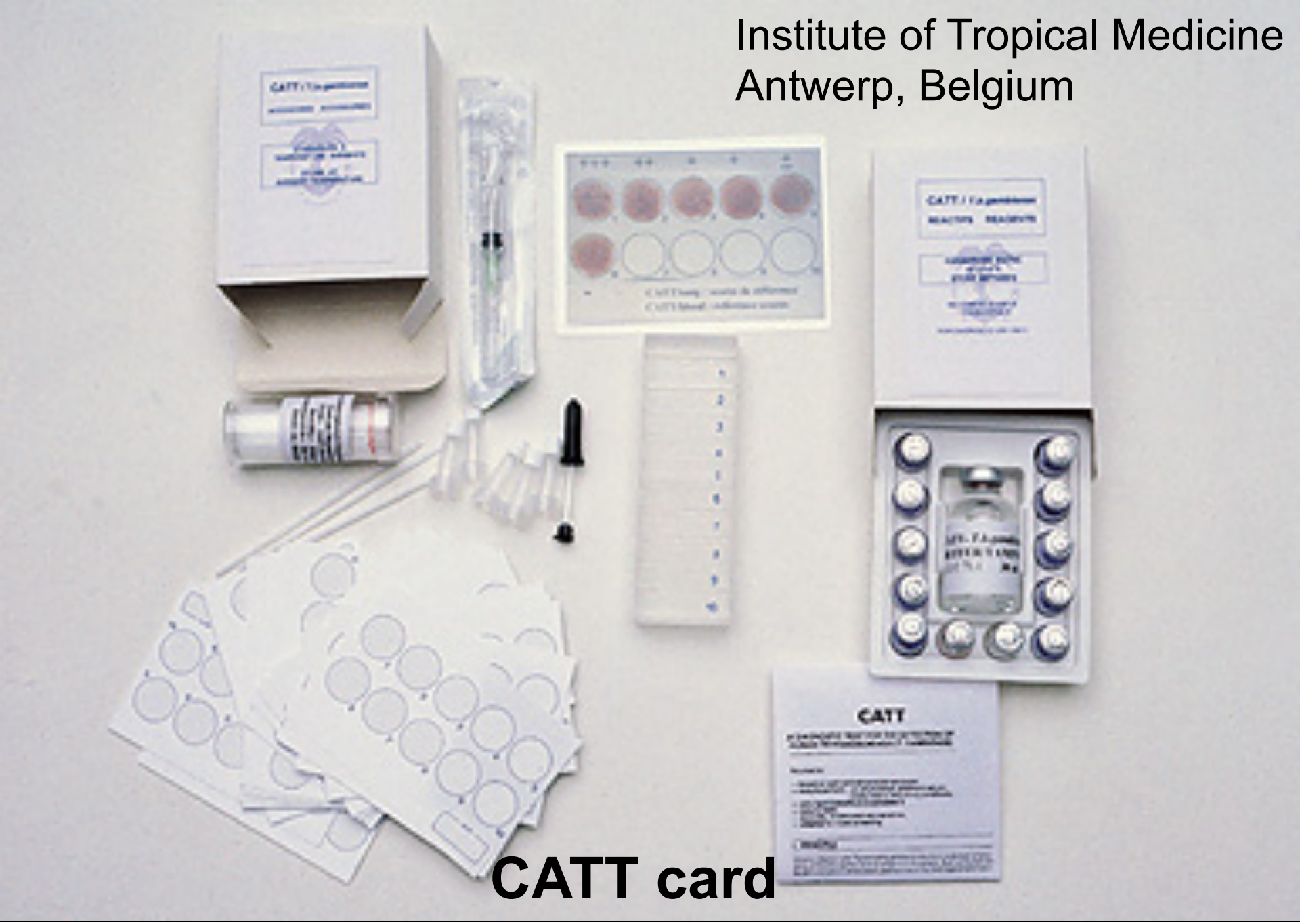
- Parasitologic Based Tests
- Identification trypomastigotes in blood, lymph node aspirate or CSF
  - Wet mount
  - Giemsa stained thick smear
  - Concentration technique – e.g. Miniature anion-exchange centrifugation
- PCR - based assays

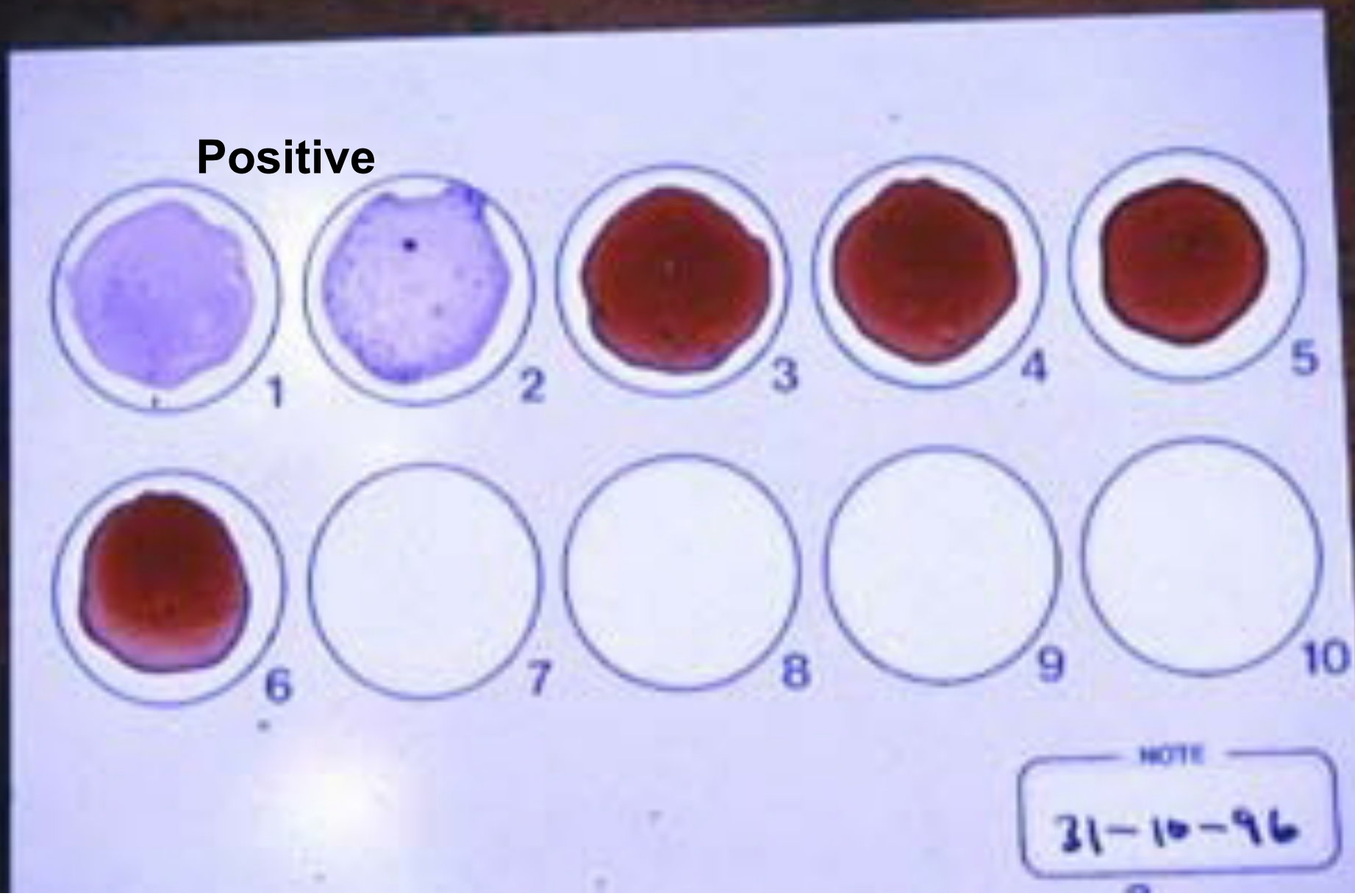


Left, *Trypanosoma brucei* in blood (Giemsa × 1000).
Right, typical pathohistological changes (perivascular cuffing)
in a brain section of patient with sleeping sickness (haematoxylin and eosin × 400)

DIAGNOSIS OF AFRICAN TRYPANOSOMIASIS

- Immunologic based tests (antibodies)
  - CATT - (Card Agglutination Test for Trypanosomes)
    - West African trypanosomiasis only
  - Detects Abs by agglutination assay
  - Ag = lyophilized bloodstream T.b. gambiense variable Ag type LiTat 1.3


Institute of Tropical Medicine
Antwerp, Belgium
CATT
CATT card


Positive
1
2
3
4
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6
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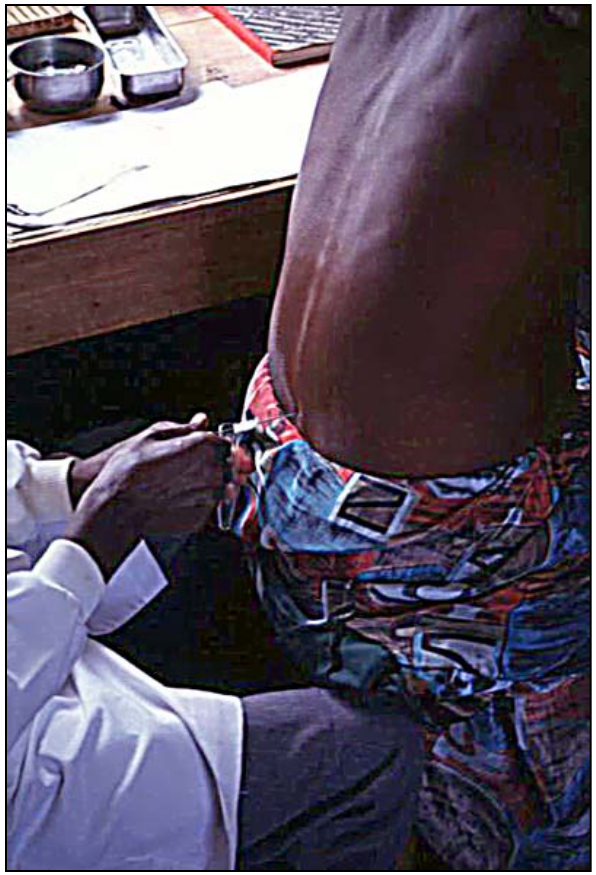
8
9
10
NOTE
31-10-96

CNS Involvement



- Examine fresh (within 20 minutes) CSF on day 5 after stage 1 drug Rx
- Parasites lyse spontaneously
- *Abnormal CSF if…*
  - Increased IgM
  - Pleocytosis (> 5 WBCs)
  - Trypomastigotes visualized

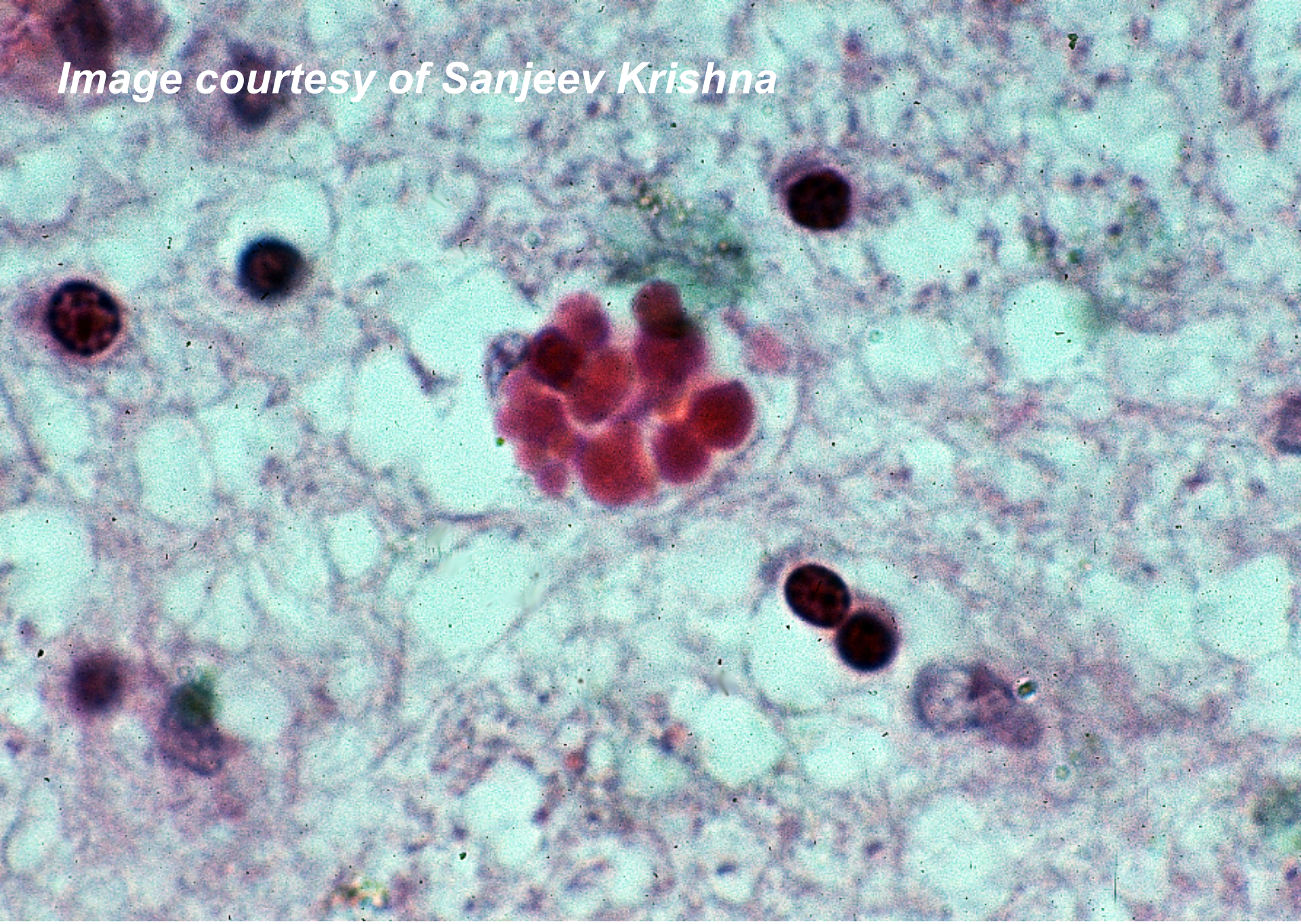


Image courtesy of Sanjeev Krishna

Diagnosis and Staging of HAT

- DX: HAT (clinical, epi, blood smear)
- Successful infection of rat with blood and CSF
  - Confirms CNS involvement
  - Confirms East African HAT caused by *T. b. rhodesiense*

Index of Suspicion for HAT

West African "sleeping sickness"	**East African Trypanosomiasis**
• Immigrant / refugee • Chronic illness • Mental status changes • Psychiatric illness • Post-traumatic stress disorder	• Acute East African fever • Tourist visiting game parks • Chancre • Hx of tsetse bite

RX of HAT: Hemolymphatic Stage

- *T. b. gambiense*
  - Pentamidine isethionate
    - 7 - 10 doses IM of 4 mg / kg QD or QOD
  - Eflornithine
- *T. b. rhodesiense*
  - Suramin
    - 5 mg / kg D1, 10 mg / kg D3, 20 mg / kg D5, 11, 23, 30 slow IV injection

Rx of HAT: Late stage with CNS Involvement

- Melarsoprol (arsenical drug)
  - *T. b. gambiense and T.b. rhodesiense*
  - Standard 26 day regimen
  - New short course 10 day regimen
  - Toxic fatal encephalopathy in 5 - 10% with 50% CFR
- Eflornithine
  - *T. b. gambiense* only, supplies limited
  - 4 daily IV infusions X 14 day regimen = 56 doses
  - Efficacious and better tolerated
  - Costly

Post-Treatment Reactive Encephalitis (PTRE)

- IV melarsoprol is a toxic drug
- 10% develop PTRE
- 50% with PTRE die
- 5% who get IV melarsoprol die
- Accurate diagnosis of late stage HAT is critical

PTRE (Arsenic Encephalopathy)

- Usually occurs 7-14 days following start of treatment
- Convulsive status with acute cerebral edema
- Rapidly progressive coma w/o seizures
- Acute non-lethal mental changes w/o neurological signs
- Acute peripheral neuropathy (Guillain-Barré mimic)

PTRE (Arsenic Encephalopathy)

- Severe headache, convulsions, rapid neurological deterioration, or deepening of coma are the indicators of PTRE
- PTRE is immune-mediated by release of parasite antigens in the first days of treatment

Treatment / Management of PTRE

- Stop Melarsoprol
- Supportive care
- Steroids may help in demyelinating neuropathy
- No specific treatment for encephalitis
- Simultaneous administration of glucocorticosteroids (prednisolone 1 mg/kg body weight; maximum 40 mg daily) might reduce mortality, especially in cases with high cerebrospinal fluid pleocytosis
  - *Pepin J, Milord F, Guern C, Mpia B, Ethier L, Mansinsa D. Trial of prednisolone for prevention of melarsoprol-induced encephalopathy in gambiense sleeping sickness. Lancet 1989; i, 1246–50*.

Prevention and Control of HAT

- West African HAT (*T. b. gambiense*)
  - Surveillance, case finding, treatment of infected individuals
- East African HAT (*T. b. rhodesiense*)
  - Vector Control: sterile flies, impregnated fly traps
  - Reservoir control: Transmission efficiency from cattle not related to parasitemia
- Personal Protection (Travelers)
  - Avoid tsetse flies infested areas
  - DEET repellents
  - Wear light colored clothing
- No vaccine available