

Filariae

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Talk Outline

- Background on filarial infections
- Lymphatic Filariasis
- Onchocerciasis
- Loa loa

What are filariae?

Filariae

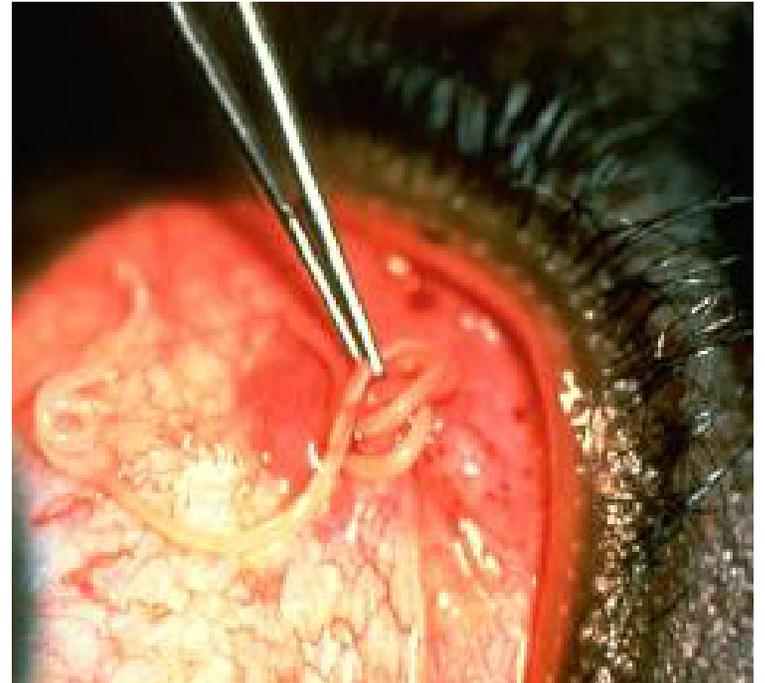
threadlike

(from Latin *filum* = thread)

tissue-invasive

roundworms

transmitted by insect vectors



What was the genius of Patrick Manson?



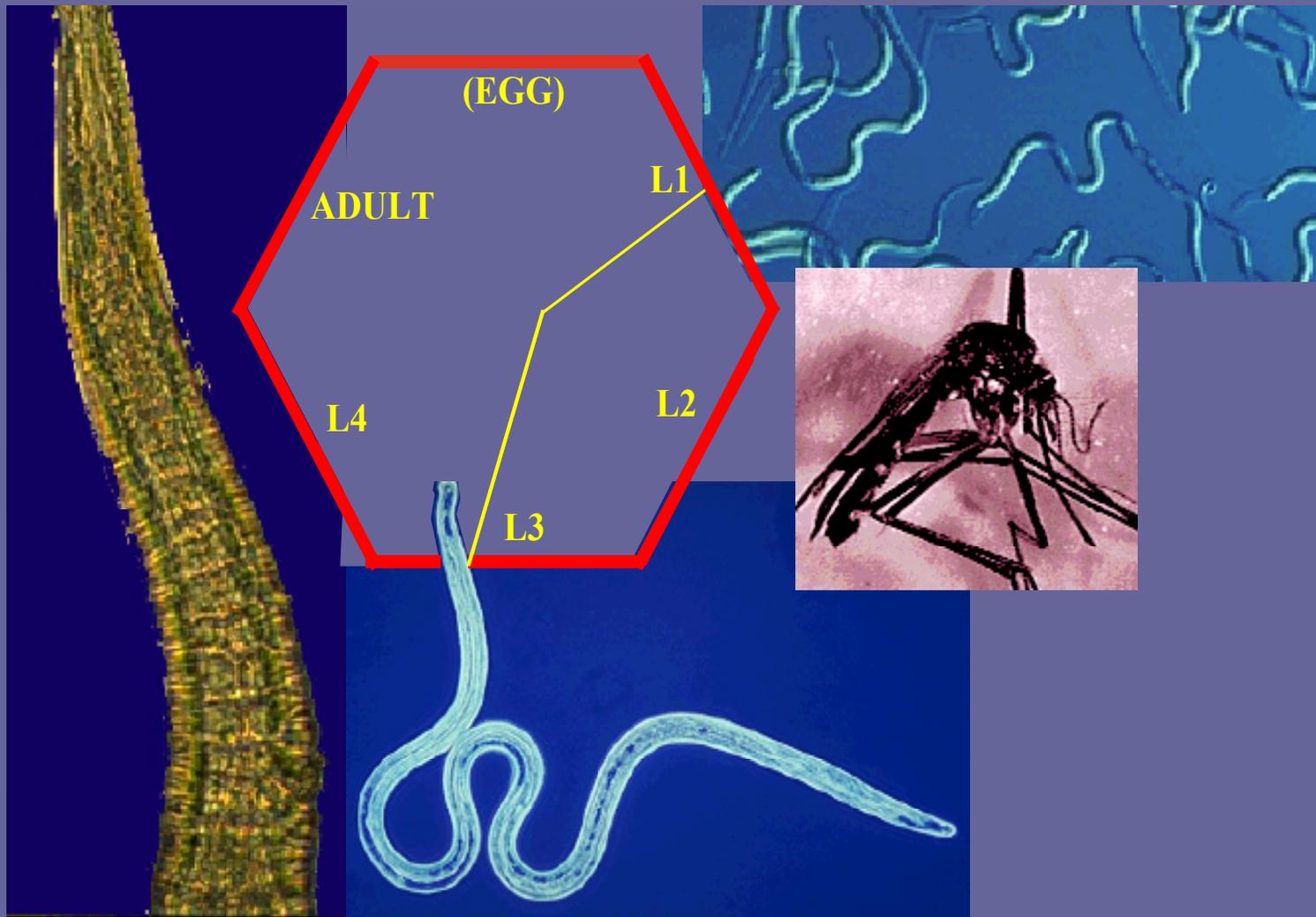
Scottish physician
Tropical medicine pioneer
1844-1921

What was the genius of Patrick Manson?

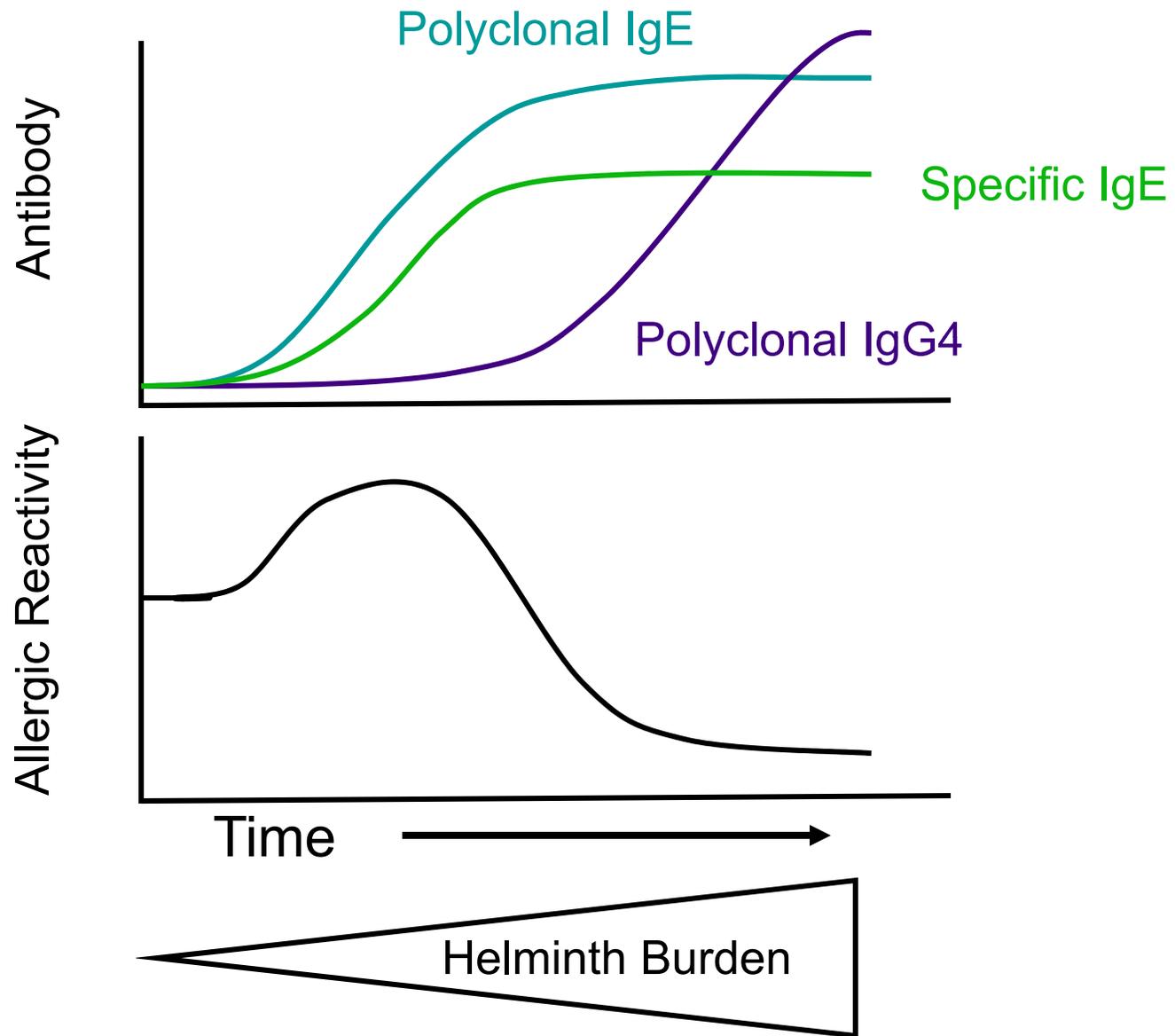
Hypothesized and then proved via experiment with Hin-Lo that filariae are transmitted via mosquitoes.

The first-ever demonstration that mosquitoes can harbor infectious disease.

General life cycle of filariae



Humoral parameters of helminth infections over time

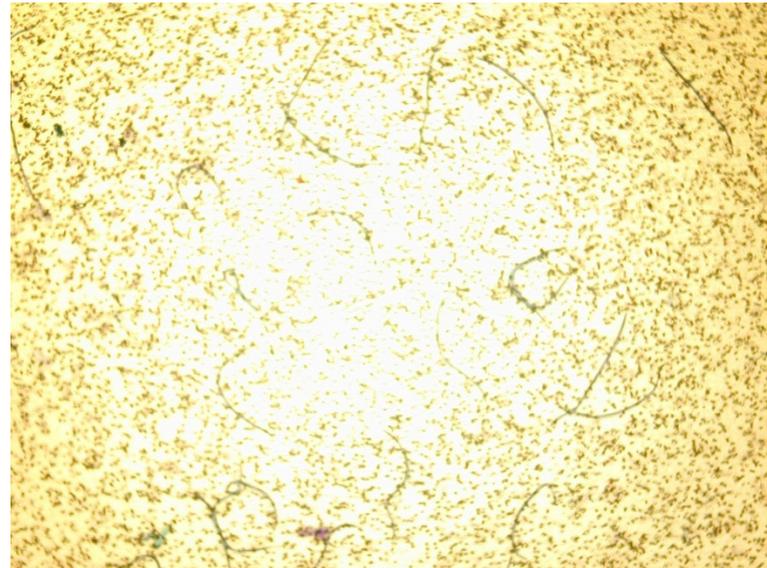


What is totally bizarre about the following case?

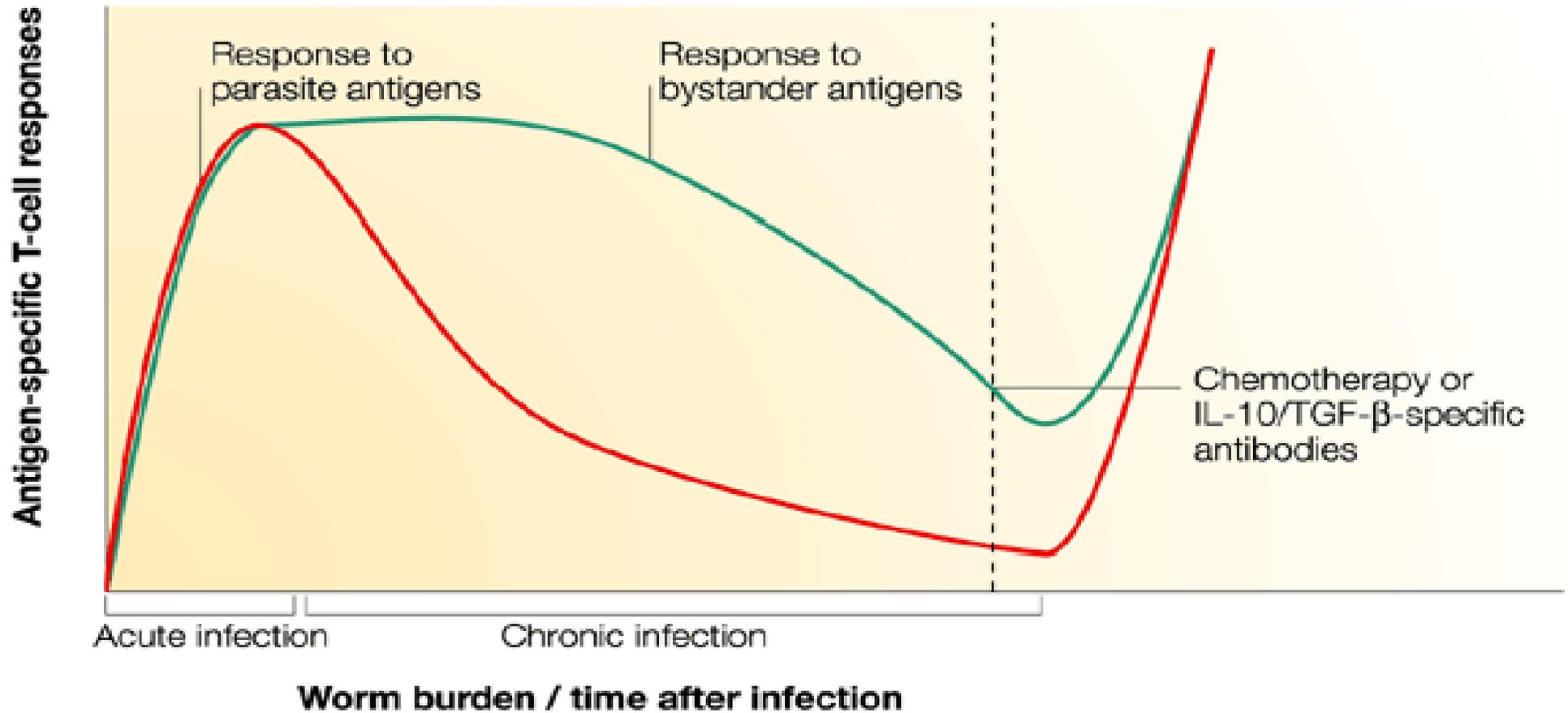
29yo M

- Anthropologist lived in Central African Republic for 6months/yr from 1993-2000.
- 1996 exhibited right hand swelling x 1 day, but nothing since.
- In 2001 a friend of his on the same expedition mentioned that he had recently been diagnosed with Loa loa.
- So, patient decided to get himself checked out for Loa loa, even though he felt perfectly well.

Daytime blood filtration →

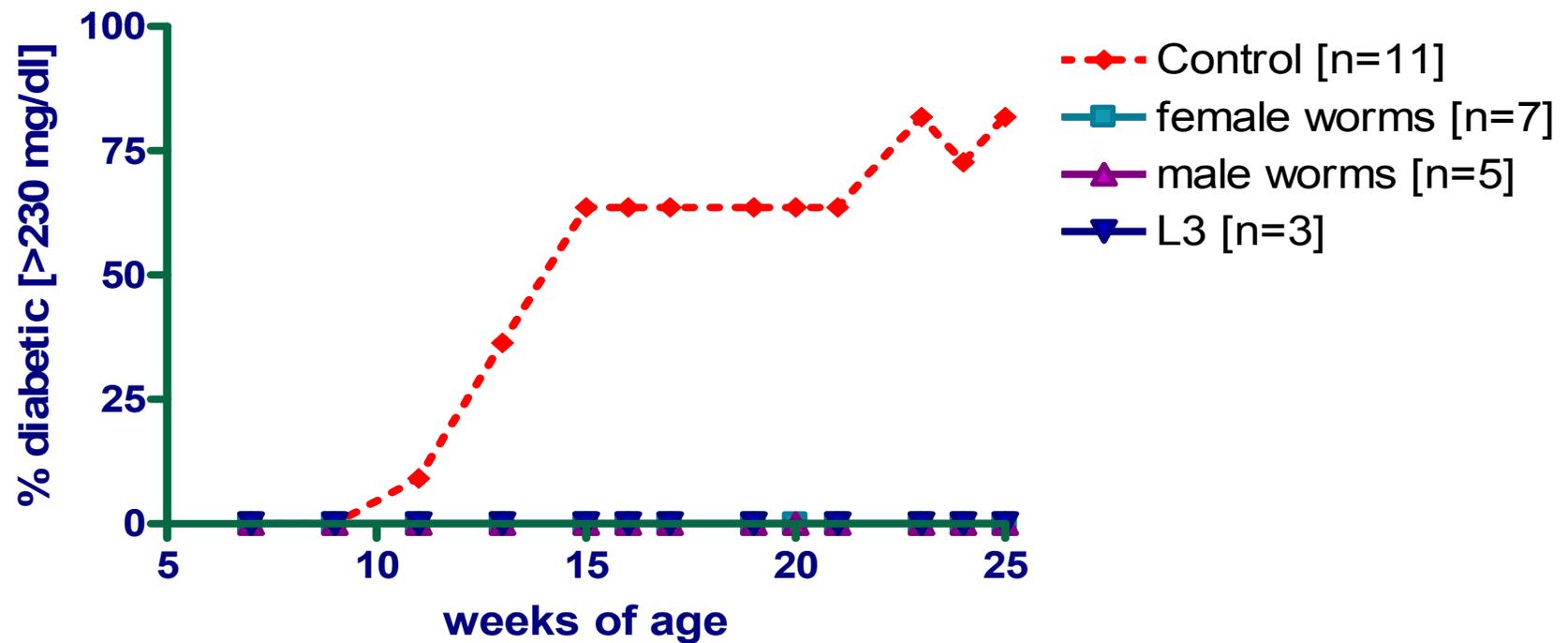


Helminth-specific T-cell responses over time



Maizels RM and Yazdanbakhsh M *Nat Rev Immunol.* 2003 3:733-44

Infection with filaria prevents autoimmune diabetes in NOD mice



Filarial Infections of Humans

<u>INFECTION</u>	<u>LOCATION</u>	<u># INFECTED</u>
<i>Wuchereria bancrofti</i>	Tropics worldwide	129 million
<i>Brugia spp.</i>	Asia	10 million
<i>Onchocerca volvulus</i>	Africa, Americas	18 million
<i>Loa loa</i>	Africa	13 million

Body location of filarial infections

Adults

Microfilariae

Lymphatic filariasis

lymphatics

blood (usually night)

Loa loa

SQ tissues (moving)

blood (day)

Onchocerciasis

SQ tissues (nodules)

skin

Treatment of Filariasis

	<u>Treatment</u>	<u>Avoid</u>
Lymphatic filariasis	DEC	-----
Loa Loa	DEC	DEC and Ivermectin if high mf level
Onchocerciasis	ivermectin	DEC

ADVERSE EFFECTS

Loa with high microfilaremia → encephalopathy and death
Onchocerciasis → severe skin inflammation and blindness

Talk Outline

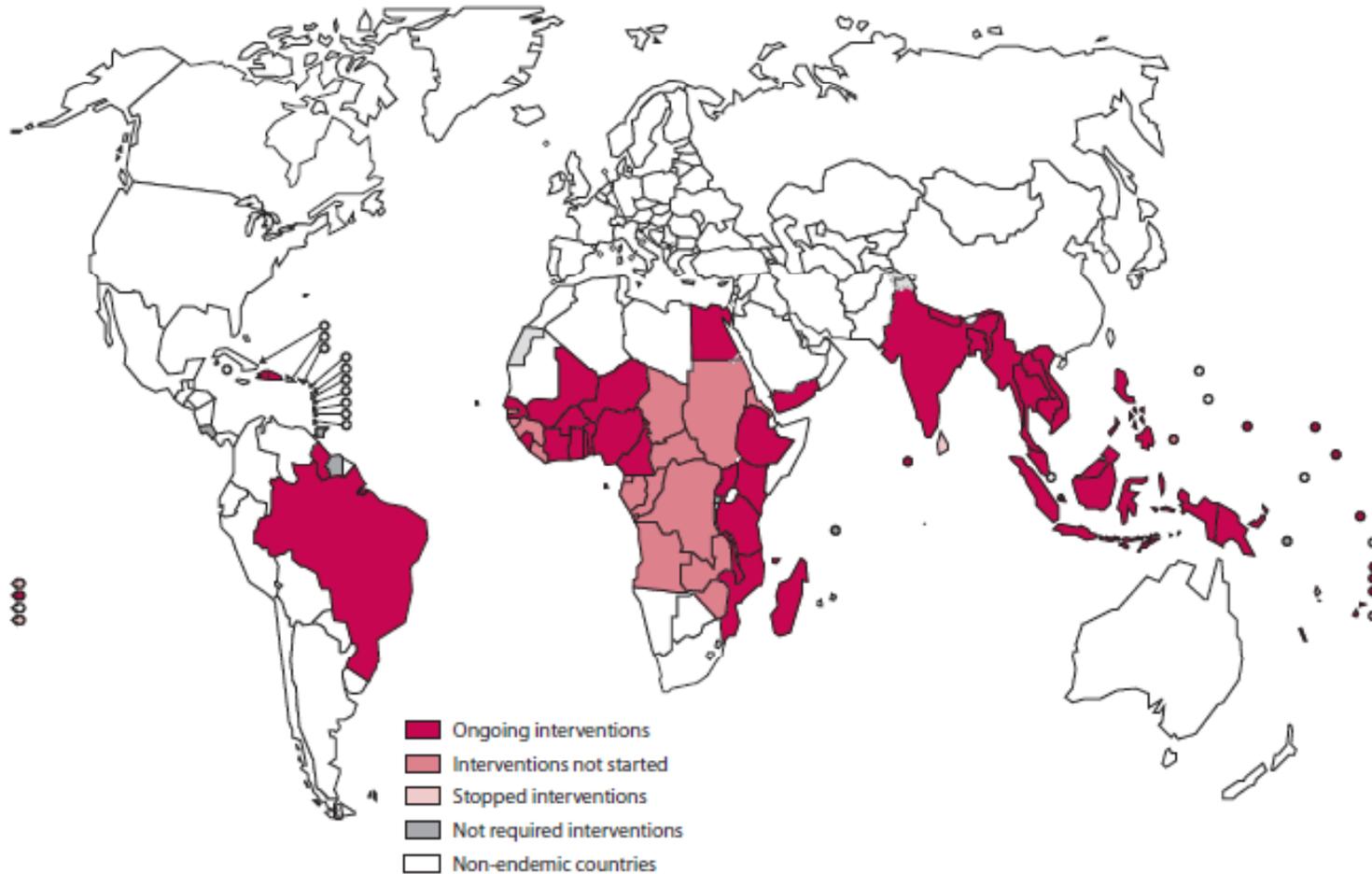
- Background on filarial infections
- **Lymphatic Filariasis**
- Onchocerciasis
- Loa loa

Lymphatic filariasis

- *W. bancrofti*, *Brugia malayi* and *Brugia timori*
- Vector: mosquitoes (Anopheles, Aedes, Culex, Mansonia)
- Host: human
- Microfilariae: blood-borne
- Adult worms: lymphatics
- Reservoir: Wb – none Bm – cats, macaques (rare)

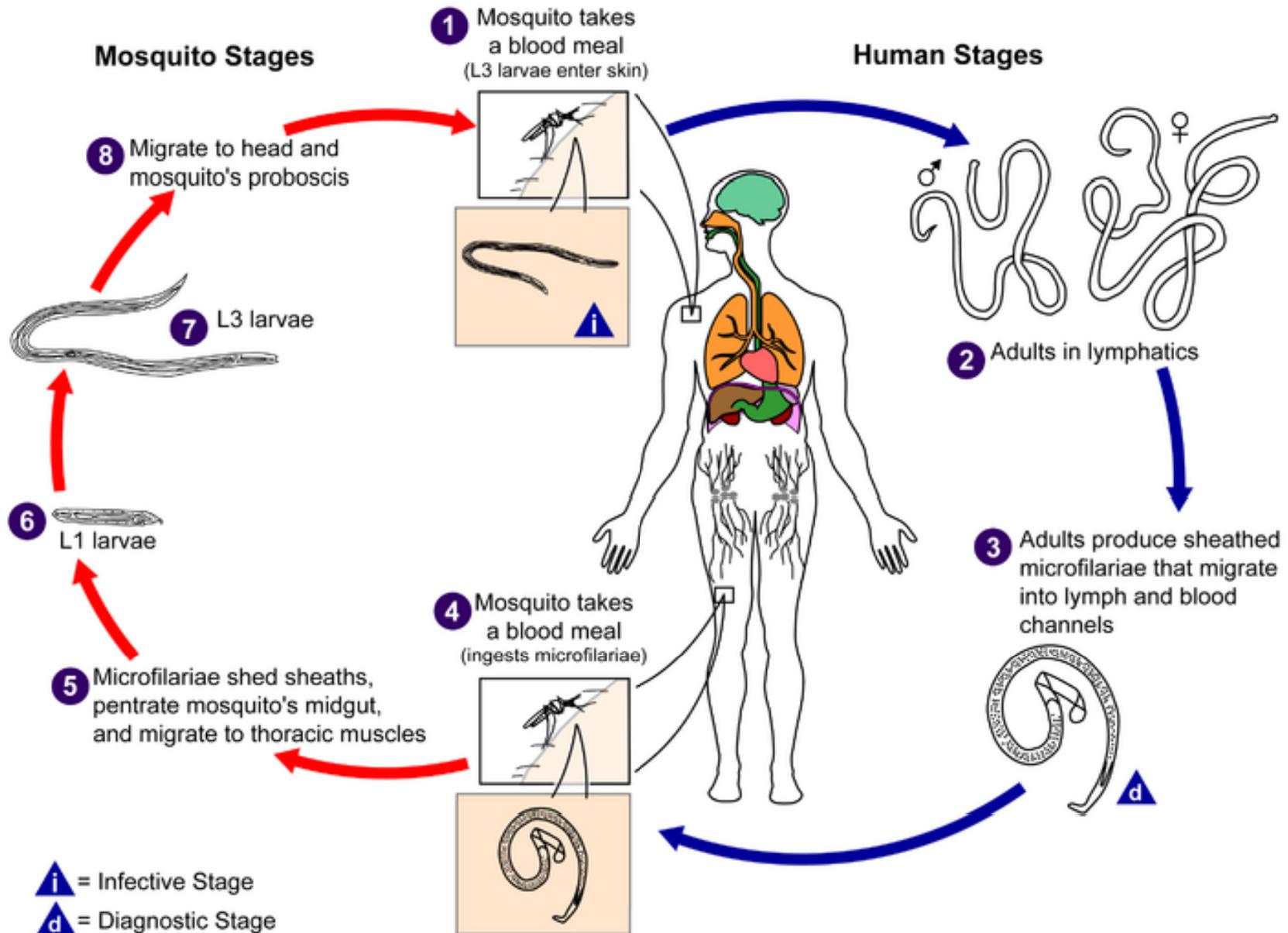
Lymphatic filariasis: epidemiology

Figure 2. Global distribution of lymphatic filariasis and status of mass drug administration (MDA), 2009



Filariasis

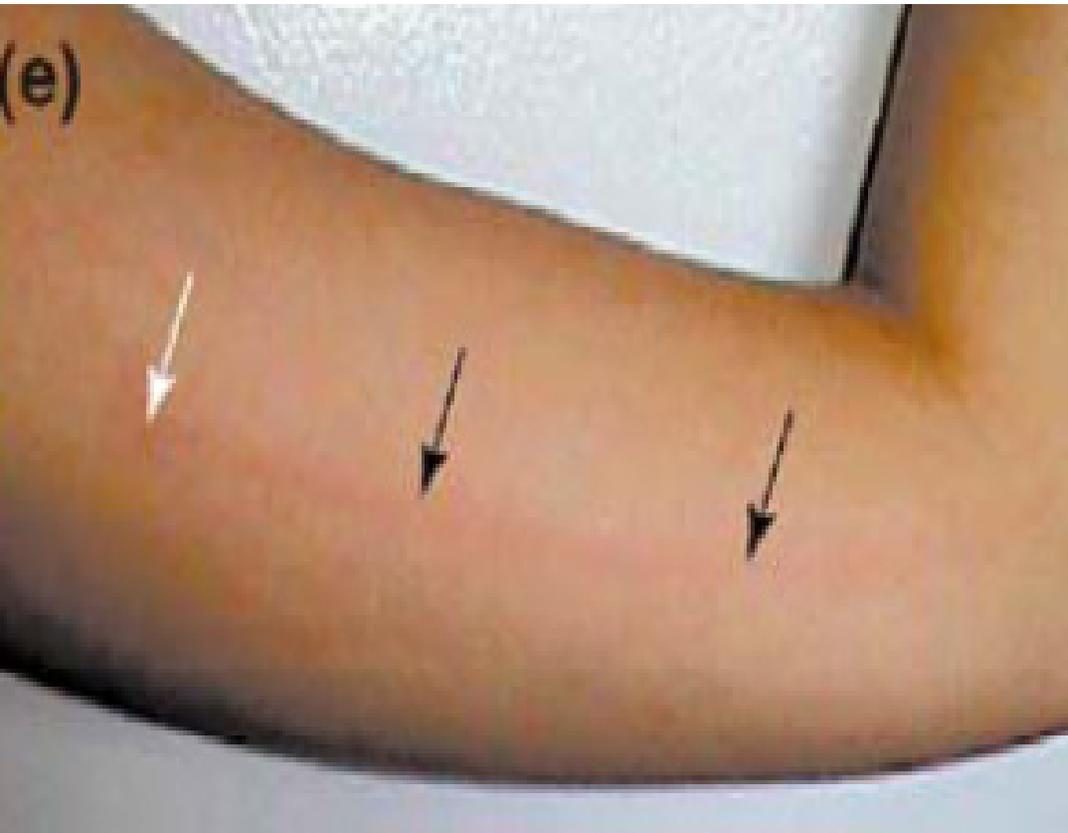
(*Wuchereria bancrofti*)



LF: clinical manifestations

- Asymptomatic microfilaremia
- Filarial fevers
- Lymphangitis
- Lymphatic obstruction
 - Lymphedema, elephantiasis, hydrocele, chyluria
- Tropical pulmonary eosinophilia

LF: clinical manifestations



lymphangitis

LF: clinical manifestations



hydrocele



lymphedema

LF: clinical manifestations



elephantiasis

LF: clinical manifestations



19yo Haitian man
May 2009

Courtesy Dr. Todd Gleeson, USS Comfort

LF: clinical manifestations



Courtesy Dr. Todd Gleeson, USS Comfort

LF: clinical manifestations



Courtesy Dr. Todd Gleeson, USS Comfort

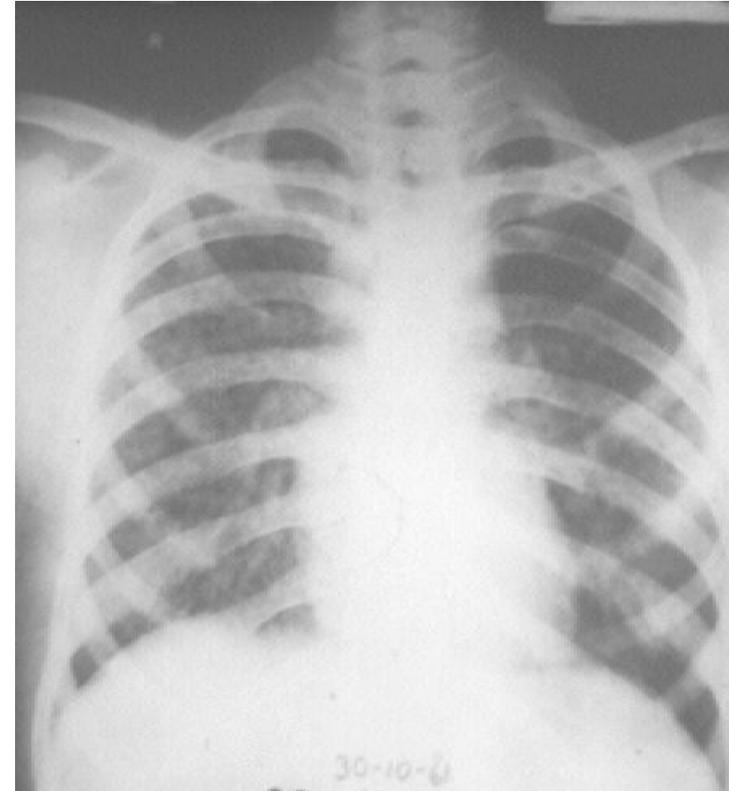
LF: a very morbid disease

Table 3. Infectious and parasitic diseases burden, worldwide and by region, 2001

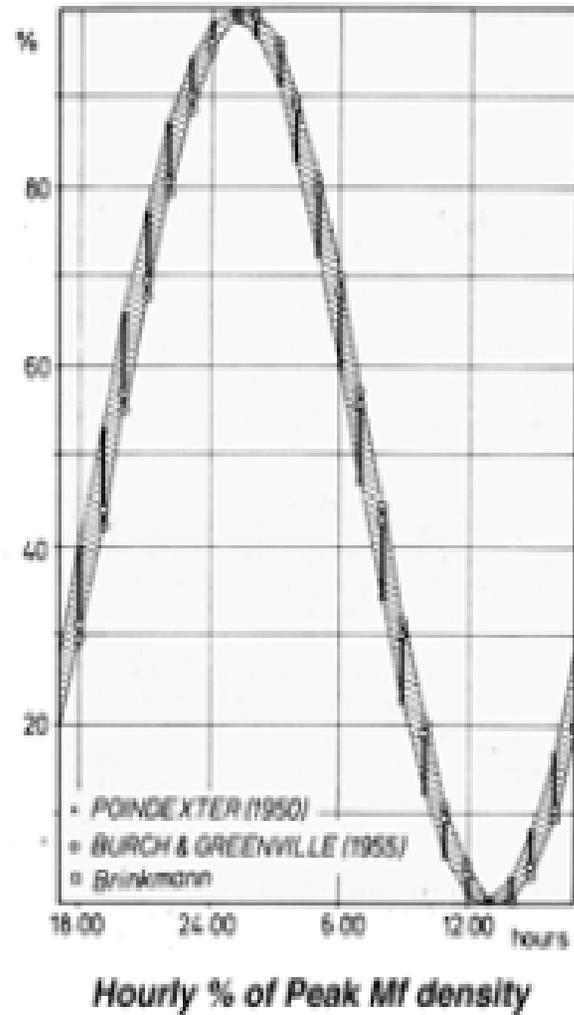
Disease	Disease burden worldwide, DALYs in thousands (%) ^a	Disease burden by region, % ^b					
		Africa	Southeast Asia	East Mediterranean	Western Pacific	The Americas	Europe
HIV/AIDS	88,429 (6.0)	65.0	15.4	1.9	2.2	3.1	1.0
Diarrheal disease	65,451 (4.3)	32.9	34.2	16.5	6.3	4.3	1.3
Malaria	42,280 (2.9)	85.2	8.7	4.8	1.0	0.3	0.1
Tuberculosis	36,040 (2.5)	24.8	44.3	8.3	15.3	2.6	4.7
Measles	26,495 (1.8)	57.1	26.1	11.5	4.4	0.0	0.9
Sexually transmitted disease ^c	12,101 (0.8)	41.1	31.8	10.7	5.1	5.1	2.9
Lymphatic filariasis	5,644 (0.4)	34.2	49.6	8.7	7.2	0.2	0.03
Trachoma	3,997 (0.3)	38.2	6.2	15.1	40.6	0.0	0.0
Leishmaniasis	2,357 (0.2)	17.0	67.3	11.8	1.1	2.5	0.3
Hookworm disease ^d	1,825 (0.1)	23.3	45.7	9.0	13.6	8.2	0.0
Schistosomiasis	1,760 (0.1)	80.6	0.2	11.5	2.9	10.1	0.0
Trichuriasis ^d	1,649 (0.1)	7.5	26.0	2.2	46.6	17.7	0.0
African trypanosomiasis	1,598 (0.1)	97.4	0.0	2.5	0.0	0.0	0.0
Ascariasis ^d	1,181 (0.1)	10.2	22.8	5.2	46.4	14.6	0.7
Onchocerciasis	987 (0.1)	95.0	0.0	4.7	0.0	0.3	0.0
Japanese encephalitis	767 (0.1)	0.0	45.2	10.6	44.3	0.0	0.0
Dengue	653 (0.0)	0.9	55.1	13.0	17.2	13.8	0.0
Chagas disease	649 (0.0)	0.0	0.0	0.0	0.0	99.8	0.0
Leprosy	177 (0.0)	9.0	67.2	9.0	4.0	10.2	0.0
All infectious and parasitic diseases	359,377 (24.5)	52.6	26.2	9.7	6.4	3.5	

Tropical pulmonary eosinophilia

- Paroxysmal nocturnal asthma
- Pulmonary infiltrates
- Peripheral blood eosinophilia ($>3,000/\text{mm}^3$)
- Marked elevation of serum IgE
- Very high filarial antibody titers
- Rapid response to anti-filarial chemotherapy



Lymphatic filariasis: diagnosis



Lymphatic filariasis: diagnosis

- Definitive diagnosis
 - Identification of microfilariae in nighttime blood (sheathed)
 - Detection of circulating antigen in blood (only Wb)
 - Identification of adult worm (by tissue biopsy or ultrasound “filaria dance sign”)
 - PCR
- Presumptive diagnosis
 - Compatible clinical picture + positive antifilarial antibodies

Lymphatic filariasis: diagnosis

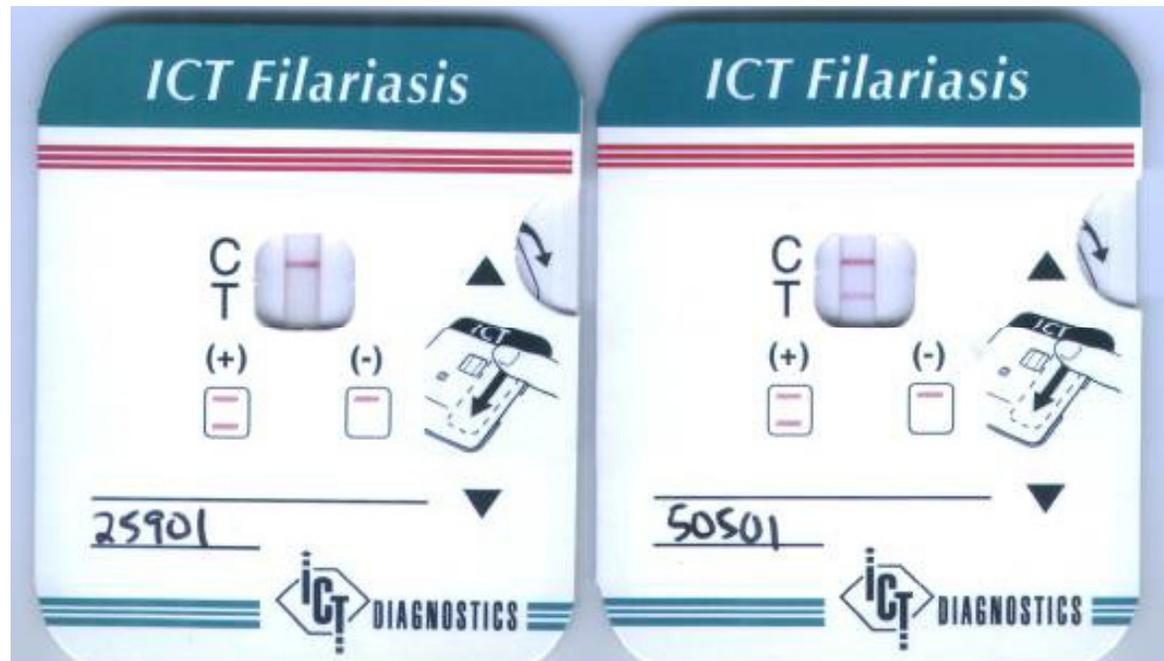
Filaria Ab testing:

Thomas Nutman, M.D.

NIH

301-496-5398

Lymphatic filariasis: diagnosis



Circulating antigen detection

- Identifies patients actively infected with *W. bancrofti*
- 100% sensitive for patients with microfilaremia
- 100% specific

Lymphatic filariasis: treatment

- **DEC (6 mg/kg/day for 12 days)**
 - the regimen recommended by the CDC
 - has both microfilaricidal and macrofilaricidal activity
 - can reverse early lymphatic changes

Alternative regimens, including yearly single dose ivermectin+albendazole or DEC+albendazole are effective at decreasing microfilaremia, but not necessarily adults

Lymphatic filariasis: treatment

Importance of understanding etiology of filarial fevers



Acute filarial lymphangitis

Acute dermatolymphangioadenitis

Lymphatic filariasis: treatment

Importance of understanding etiology of filarial fevers



Acute filarial lymphangitis

inflammatory nodule w/descending lymphangitis
probably response to adult worms

Uncommon, only occurring in 3% of infected pts
*THOUGH basically 100% of pts with LF have
lymphangiectasia on bx.*

Acute dermatolymphangioadenitis

→ ascending **bacterial**
cellulitis or lymphangitis

Lymphatic filariasis: treatment

-- aggressively treating and preventing bacterial skin and soft tissue infections is paramount (Gerusa Dreyer)

→ *elevation, hygiene, foot care, treating cutaneous fungal infxns, vigilance for bacterial infections*



Global Program to Eliminate LF (GPELF)

Biological considerations

- organism doesn't replicate in host
- infection requires prolonged exposure

Technical considerations

- treatment is very effective
- monitoring tools excellent
- cost is inexpensive
- examples of successful eradication exist

GSK → donating albendazole

Merk → donating ivermectin

WHO, World Bank, CDC, UK, Japan, Arab Fund for Economic and Social Development, and many more countries and organizations

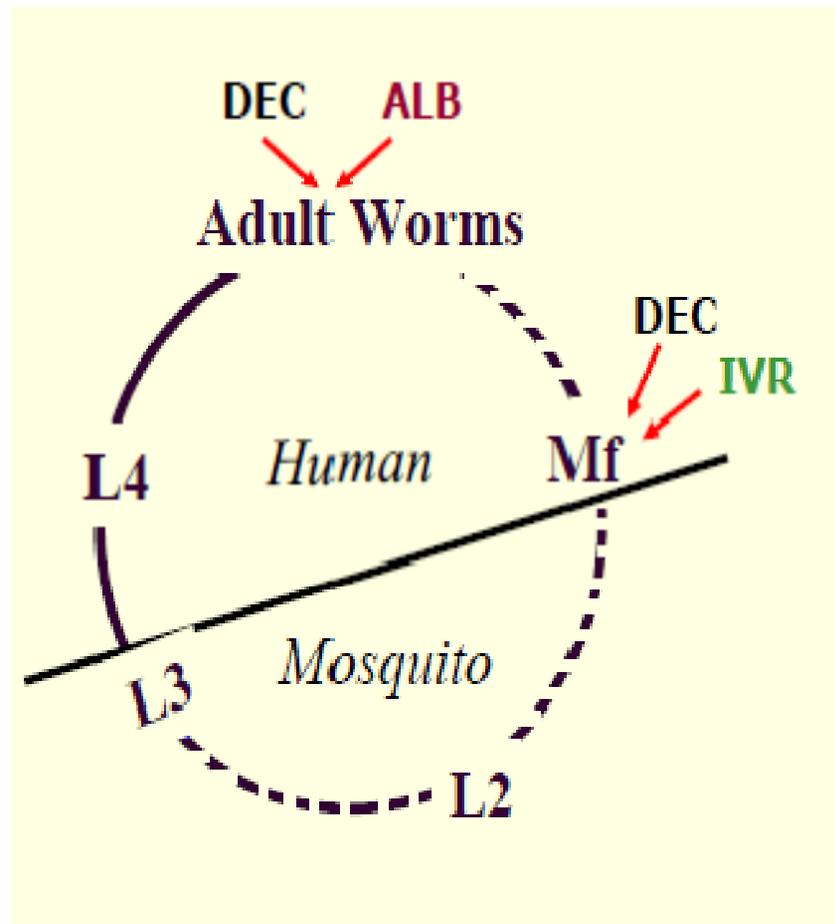
www.filariasis.org

Effects of anti-LF drugs: interruption of transmission

Diethylcarbamazine (DEC)

Albendazole (ALB)

Ivermectin (IVR)

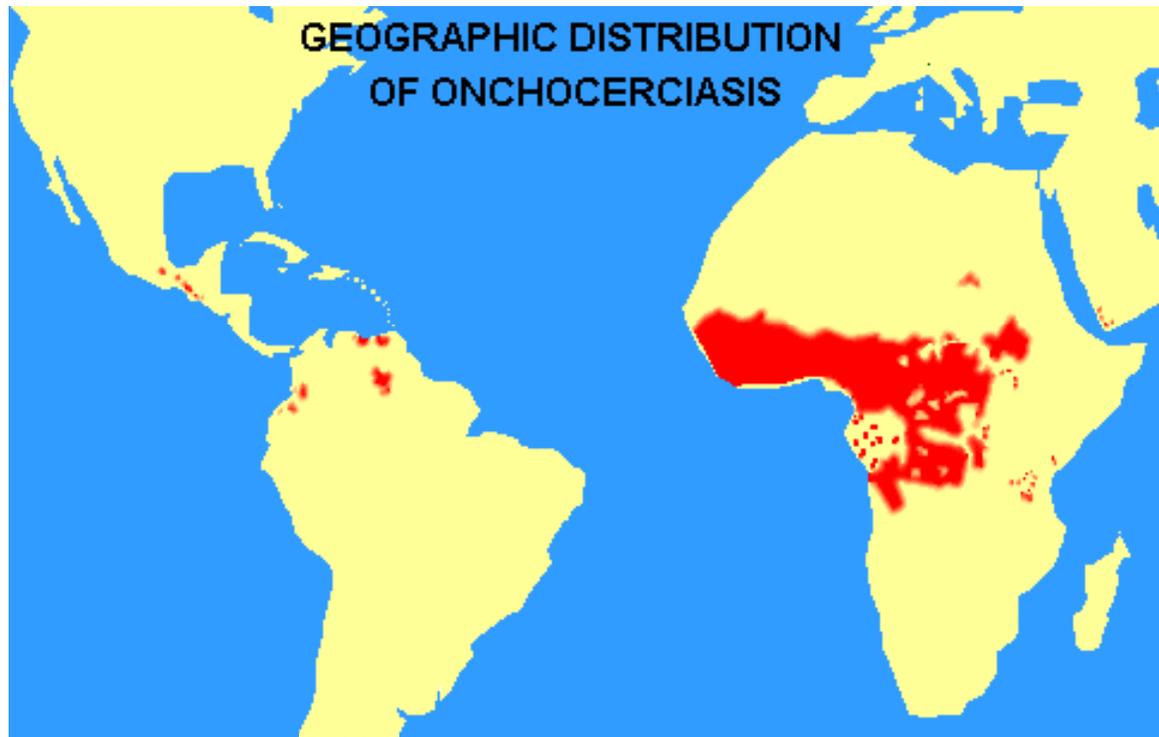


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- Lymphatic Filariasis
- **Onchocerciasis**
- Loa loa

Onchocerciasis

- caused by *Onchocerca volvulus*
- a chronic, progressive disease
- high morbidity: eye, skin, lymphatic disease

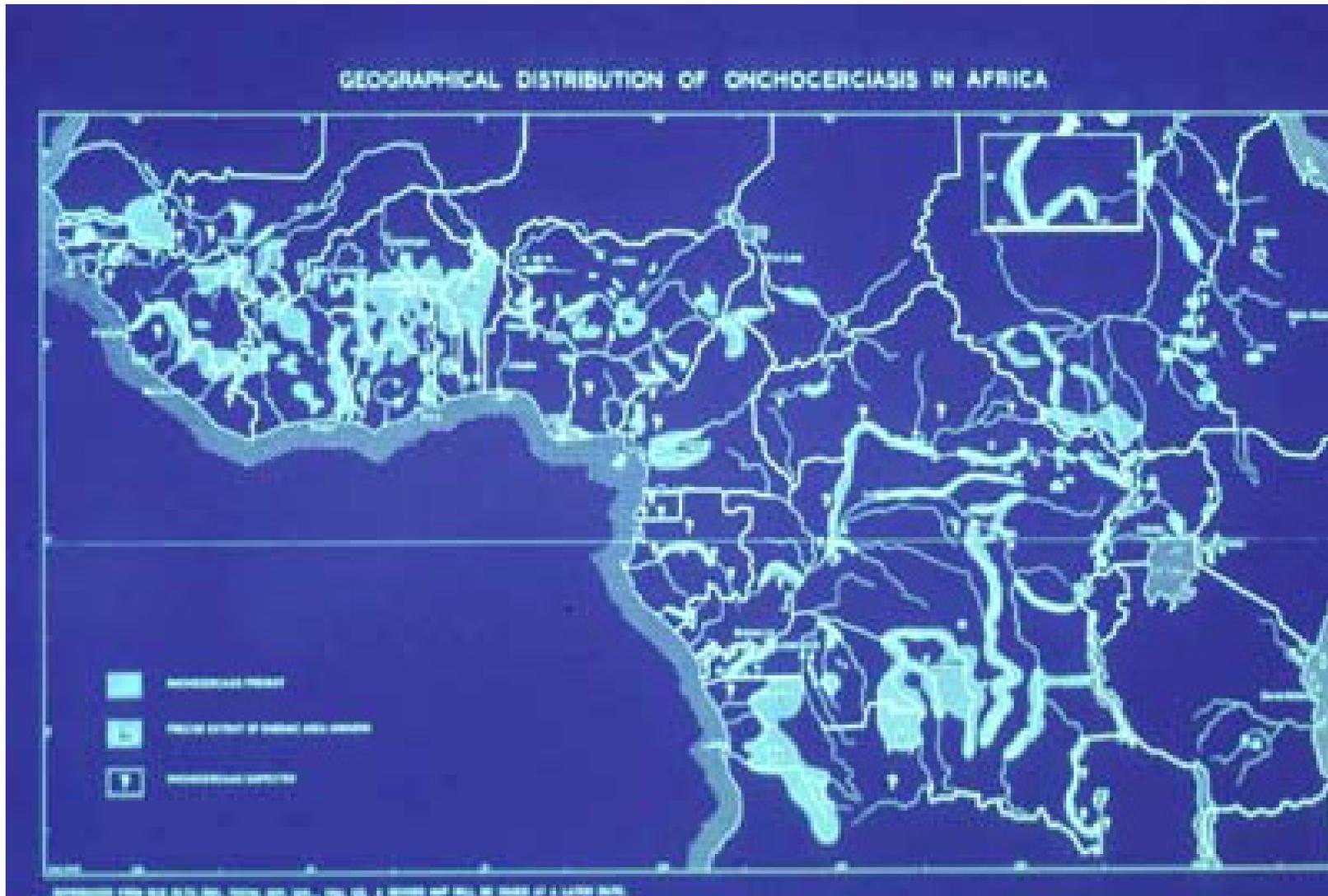


Atlas of Medical Parasitology www.cdfound.to.it/HTML/onco2.htm

- *120 million people at risk in 34 countries (99% in Africa)*
- *18 million people infected (17M in Africa and 1M in South and Central America)*
 - *4 million with skin manifestations*
 - *2 million with blindness or severe visual impairment*

Why is it called river blindness?

Why is it called river blindness?



Onchocerciasis



- Vector: *Simulium* spp. (blackflies)
- Adult worms: subcutaneous nodules
 - L3s undergo two molts over 6-12 months to become adults
 - males 2-5cm long, females 30-80cm long
 - males appear to migrate from nodule to nodule inseminating females
 - live 10-15 years
- Microfilariae: skin-dwelling
 - 300 microns long, live 6-24 months
- Animal reservoir: None

Clinical Manifestations in Chronic Infection

- Skin
 - nodules, pruritus, rash, depigmentation, lichenification, sowda
- Eye
 - keratitis, chorioretinitis
- Lymphatic obstruction
 - hanging groin, elephantiasis

Onchocercal nodule



Onchocercal dermatitis



Onchocercal dermatitis



Onchocercal dermatitis



Peau d'orange

Depigmentation

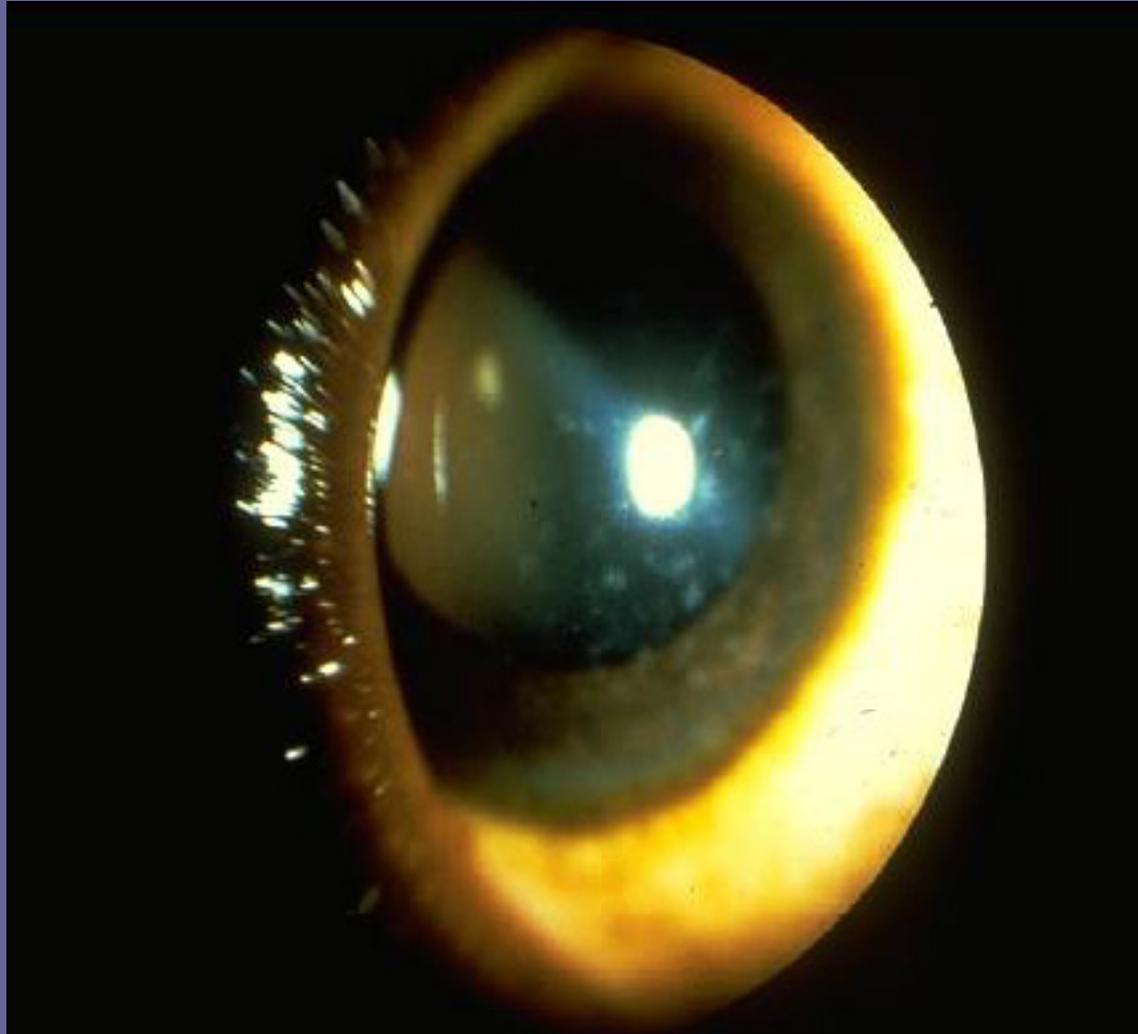
Onchocerciasis - Sowda



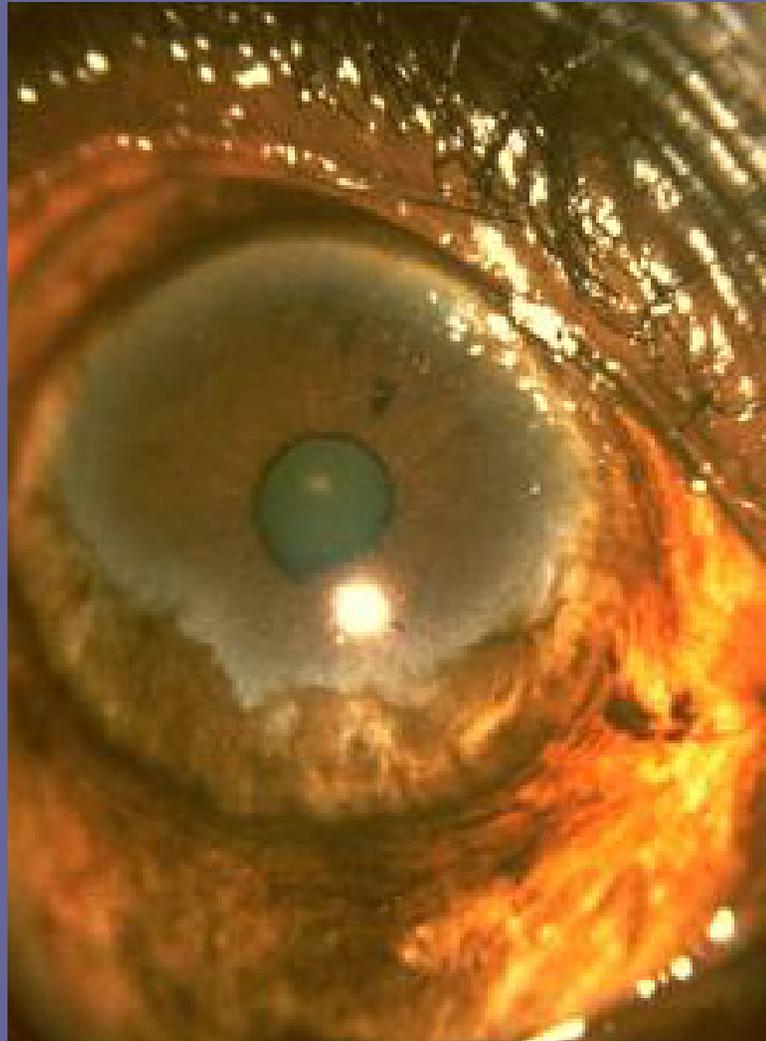
Onchocercal Eye Disease



Onchocerciasis – Punctate Keratitis



Onchocerciasis – Sclerosing Keratitis



Onchocerciasis – Hanging Groin



Onchocerciasis: worm burden

Females per nodule	2-50
Males per nodule (always changing)	1-10
Microfilariae per female per day	1600
Daily microfilariae turnover	10,000-3,000,000
Total microfilariae in body	up to 150 million

Udell D, Clinical Infectious Diseases 2007;44:53-60.

Onchocerciasis: diagnosis

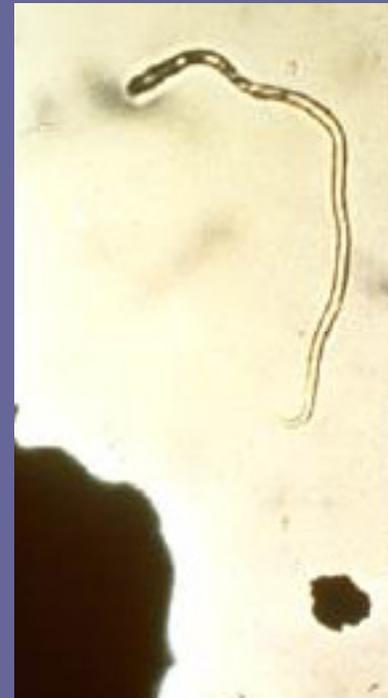
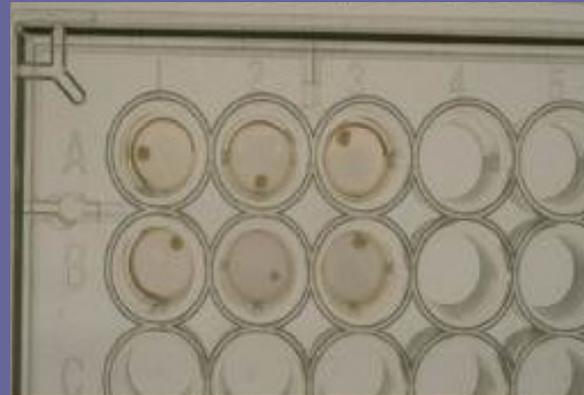
- Serology
 - anti-filarial
 - onchocerca-specific
- Parasitologic: skin snips, nodulectomy
- PCR of skin snips (increases sensitivity)
- Mazzotti test
- In development: urine antigen tests

(Ayong LS et al, Trop Med Int Health 2005;10:228-33)

Onchocerciasis: serology

- Antifilarial IgG and IgG4 (anti-BmAg)
 - 100% sensitive
 - does not distinguish between the different filariae
 - Some cross-reactivity with other nematodes (ex. Strongyloides)
- Onchocerca-specific (anti-Ov16)
 - 80% sensitive
 - >98% specific for onchocerciasis

Onchocerciasis: skin snips



Onchocerciasis: nodulectomy



Onchocerciasis: Treatment

- Ivermectin → microfilaricidal, but does not kill adult worms
- 150 μg per kg orally given every 3-12 months to prevent blindness and decrease skin symptoms
- treatment should be continued in the setting of persistent symptoms, eosinophilia, parasitologic evidence of infection or continued exposure
- No effective prophylaxis is available

Is there something inside Onchocercal worms we can target in treatment?

Wolbachia

-Obligate intracellular bacteria

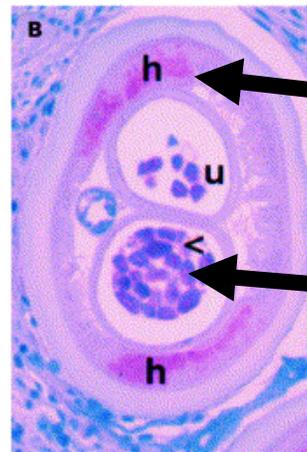
-Treatment with doxycycline for 6 weeks leads to disruptions of usual embryogenesis in adult worms for up to 18 months. Optimal duration/dose of doxycycline is under active study.

-NOTE: the corneal inflammation induced by Onchocerciasis mfs may due to an immune response against these bacteria

Saint AA et al Science 2002;295:1892-5.

Wolbachia

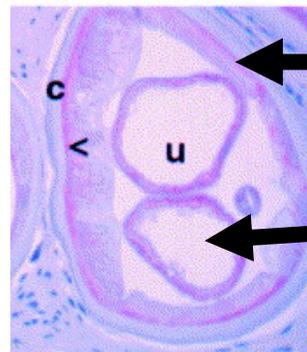
Ivermectin alone



Wolbachiae

Intrauterine microfilariae

Ivermectin
+ 6 weeks doxycycline



No Wolbachiae

No intrauterine microfilariae

Hoerauf et al Lancet 2001;357:1415-16.

Targeting of *Wolbachia* is effective at treating Onchocerciasis

Med Microbiol Immunol (2008) 197:295–311
DOI 10.1007/s00430-007-0062-1

 Open Access

ORIGINAL INVESTIGATION

***Wolbachia* endobacteria depletion by doxycycline as antifilarial therapy has macrofilaricidal activity in onchocerciasis: a randomized placebo-controlled study**

Achim Hoerauf · Sabine Specht · Marcelle Büttner · Kenneth Pfarr · Sabine Mand · Rolf Fimmers · Yeboah Marfo-Debrekyei · Peter Konadu · Alexander Yaw Debrah · Claudio Bandi · Norbert Brattig · Anna Albers · John Larbi · Linda Batsa · Mark J. Taylor · Ohene Adjei · Dietrich W. Büttner

Targeting of Wolbachia is also effective in treating lymphatic filariasis

www.thelancet.com Vol 365 June 18, 2005

Macrofilaricidal activity after doxycycline treatment of *Wuchereria bancrofti*: a double-blind, randomised placebo-controlled trial

Mark J Taylor, Williams H Makunde, Helen F McGarry, Joseph D Turner, Sabine Mand, Achim Hoerauf

8 weeks of doxycycline had significant effects on both microfilariae and adult worms

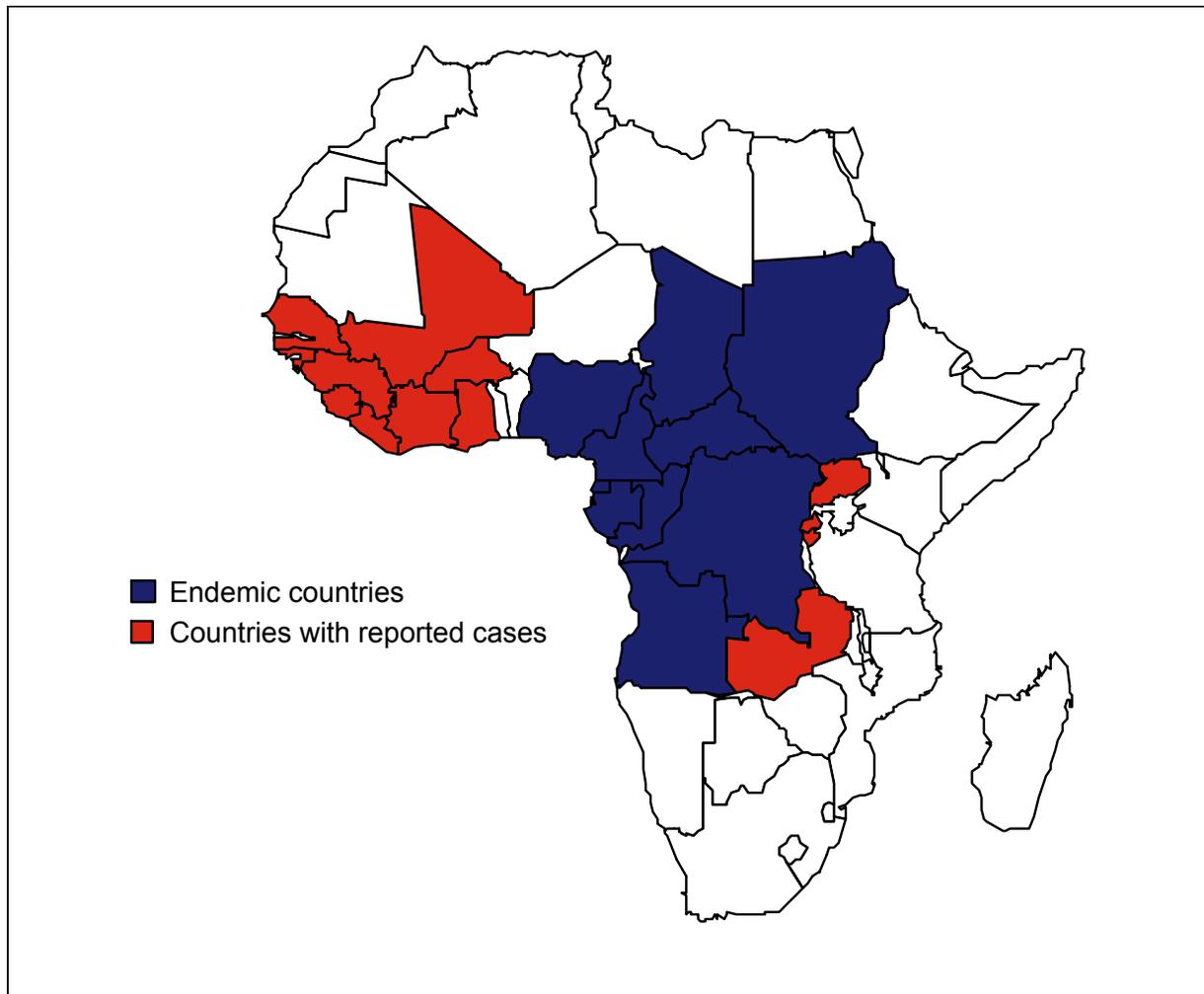
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Loiasis

- Vector: Chrysops spp. (deerfly)
- Host: human
- Microfilariae: blood-borne
- Adult worms: subcutaneous tissue
- Animal reservoir: None

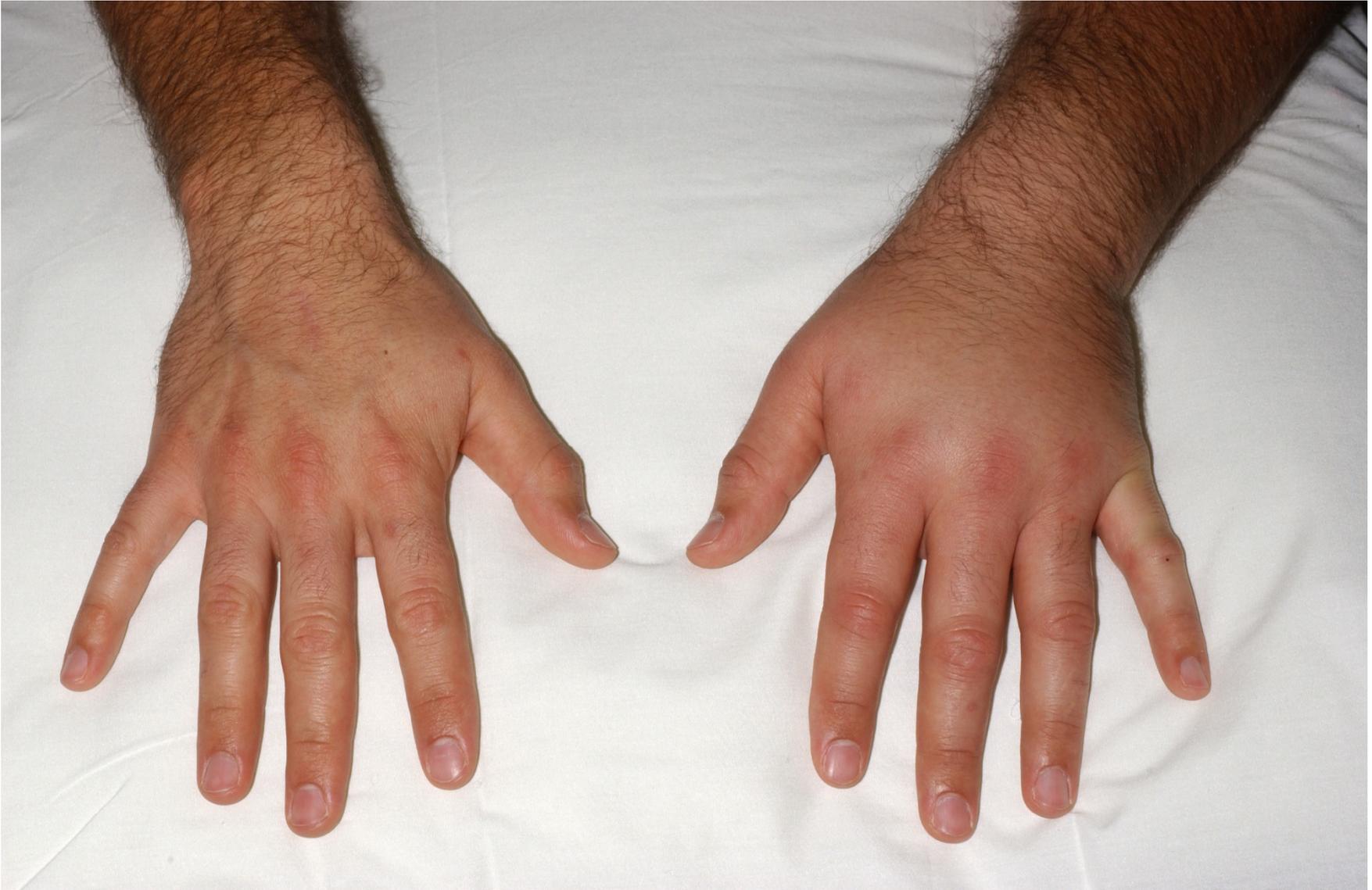
Loiasis: epidemiology



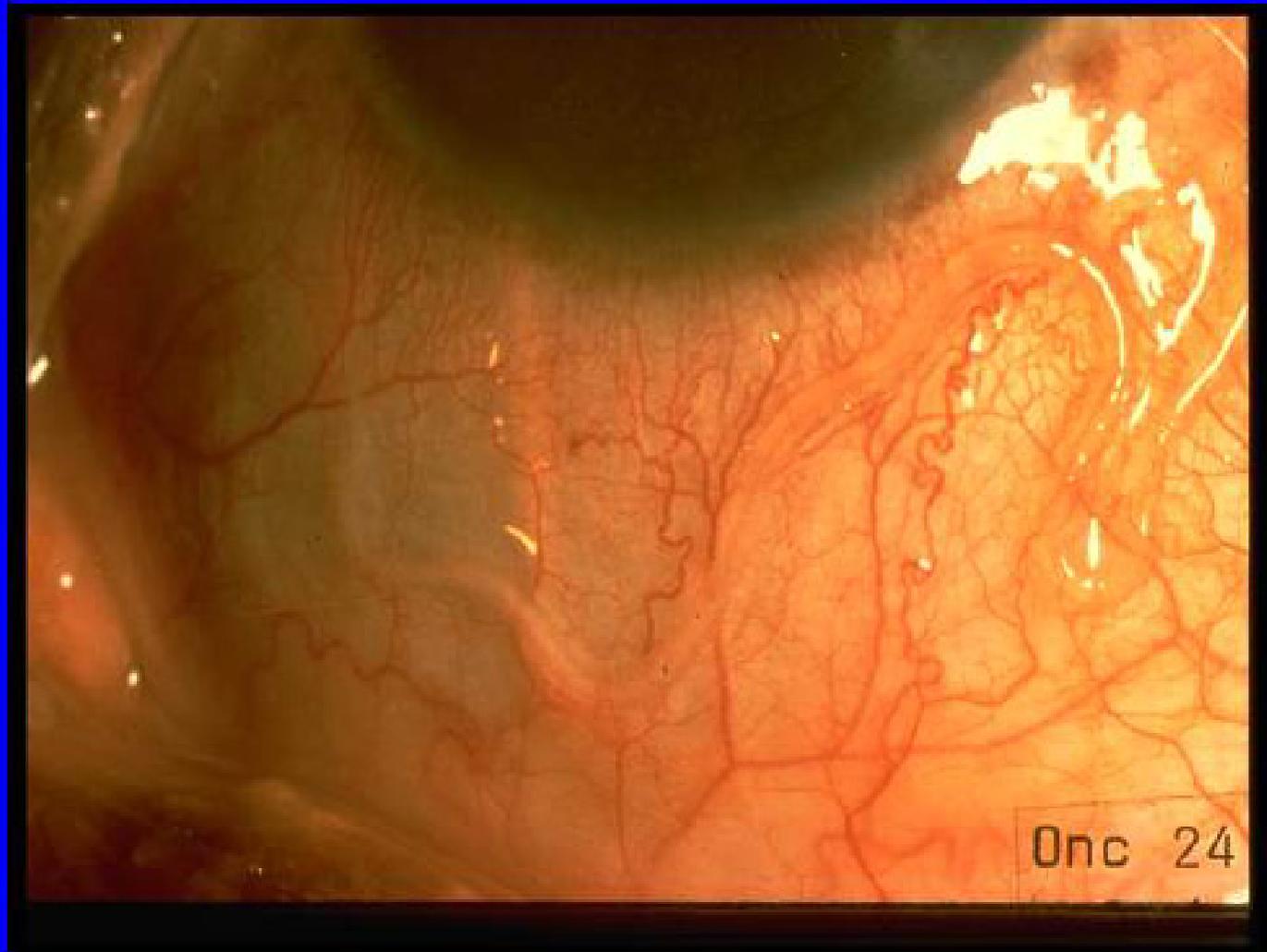
Loiasis: clinical manifestations

- Asymptomatic microfilaremia
- Non-specific symptoms
 - fatigue, urticaria, arthralgias, myalgias
- Calabar swellings
- Eyeworm
- End organ complications (rare)
 - endomyocardial fibrosis, encephalopathy, renal failure

Calabar swelling



Loiasis: eyeworm



Loiasis in travelers

Symptoms at onset

◆ Calabar swelling	40/41 (95%)
◆ Urticaria	22/41 (54%)
◆ Myalgia/Arthralgia	7/41 (17%)
◆ Eyeworm	4/41 (10%)
◆ Asymptomatic	8/41 (20%)

Loiasis in travelers

Laboratory findings at onset

◆ Microfilaremia	4/42 (10%)
◆ Eosinophilia	42/42 (100%)
◆ Elevated IgE	35/42 (80%)
◆ Increased antifilarial IgG	42/42 (100%)
◆ Hematuria	9/42 (21%)

Loiasis:Diagnosis

- Definitive diagnosis
 - Detection of microfilariae in daytime blood
(Thick smear (insensitive), Saponin lysis, Knott's concentration, Nuclepore filtration)
 - Identification of adult worm in the subconjunctiva or subcutaneous tissues
 - PCR blood
- Presumptive diagnosis
 - Compatible clinical picture + positive antifilarial antibodies

Loasis: Treatment

- DEC → course results in clinical cure in 50% of patients
- Can repeat if necessary
- Can try albendazole

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