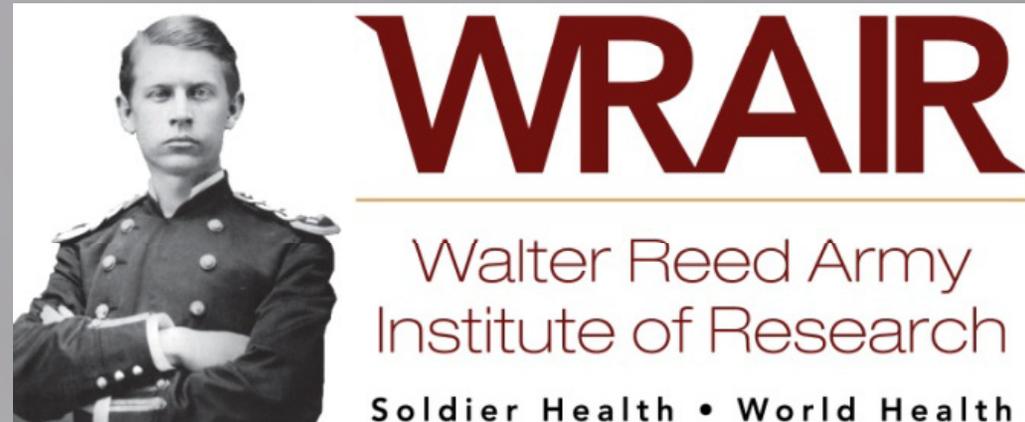




LEISHMANIASIS

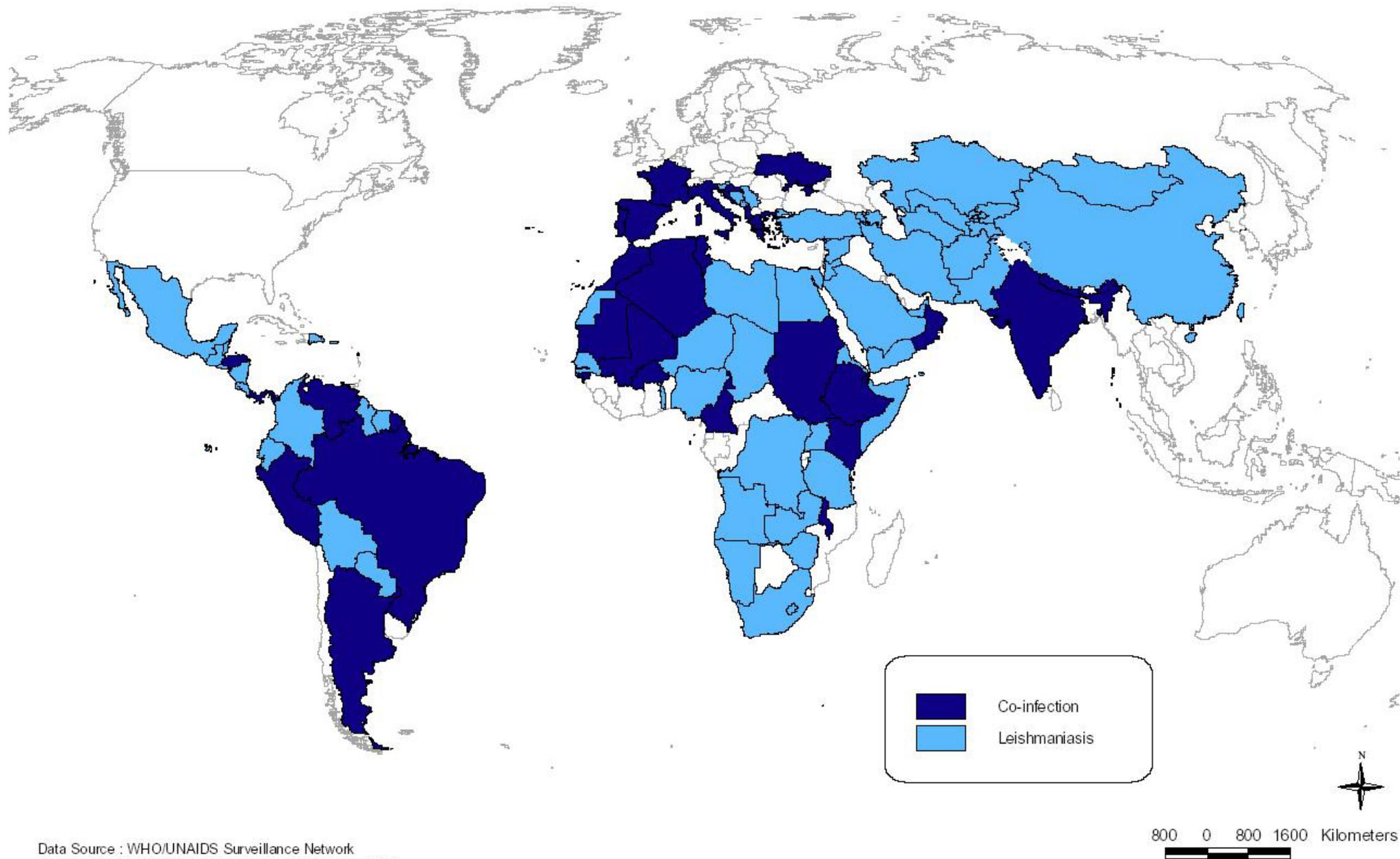
‘ANCIENT SCOURGE’

Peter J. Weina, PhD, MD, FACP, FIDSA
Colonel, Medical Corps, US Army
Walter Reed Army Institute of Research



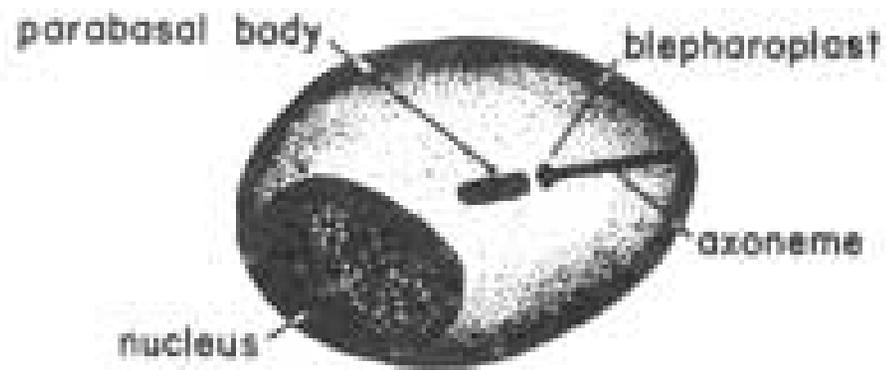
Leishmania

- One of the “truly most neglected diseases”
- Protozoan infection of macrophages
- Leishmania threatens 350 million individuals in 88 countries (72 are “developing countries”).
 - 90% Visceral leishmaniasis
 - Bangladesh, Brazil, India, and the Sudan.
 - 90% Mucocutaneous leishmaniasis
 - Bolivia, Brazil and Peru.
 - 90% Cutaneous leishmaniasis
 - Afghanistan, Brazil, Iran, Peru, Saudi Arabia and Syria.

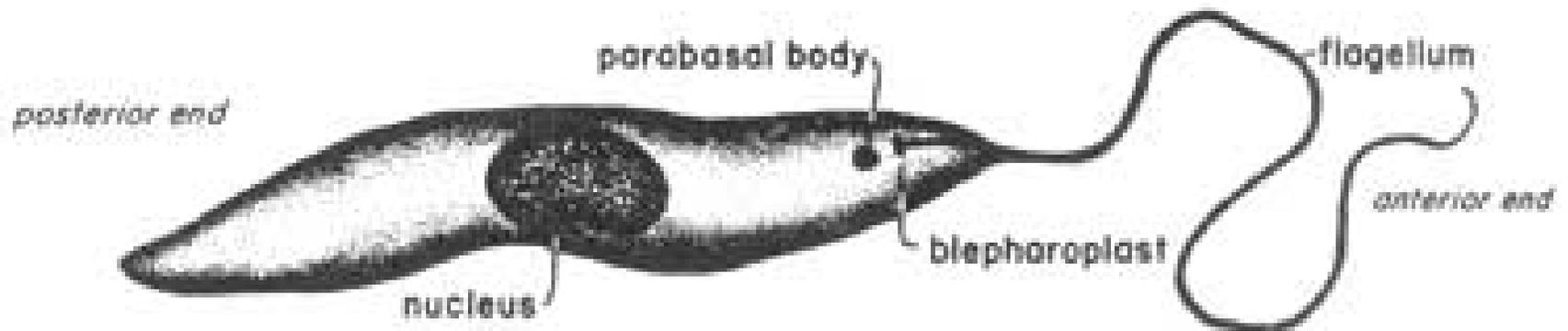


Data Source : WHO/UNAIDS Surveillance Network
Prepared by WHO/UNICEF HealthMap Programme, 2000

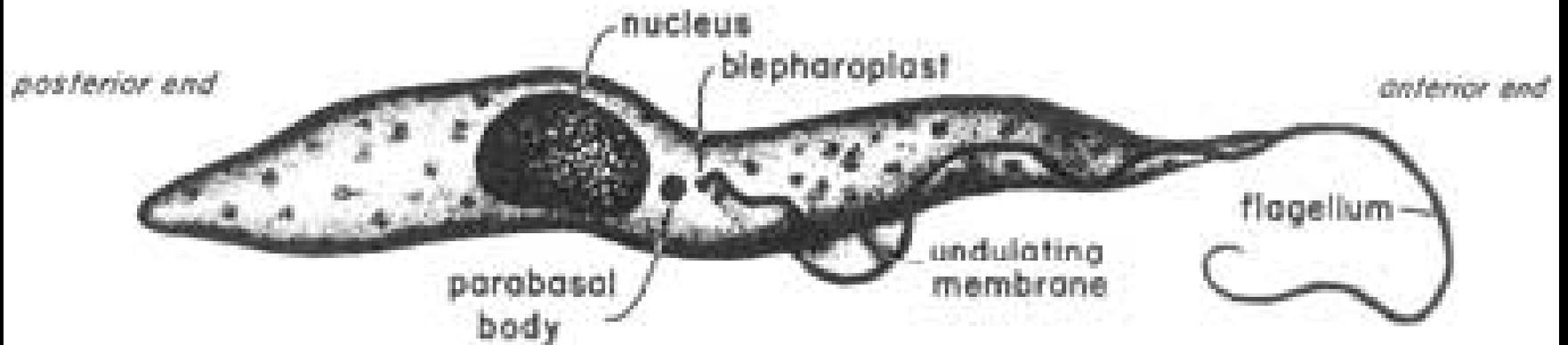
Areas with Leishmaniasis – all blue areas; Dark blue areas are co-infected with HIV



LEISHMANIAL FORM



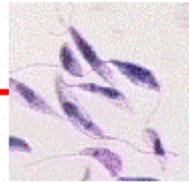
LEPTOMONAD FORM



CRITHIDIAL FORM

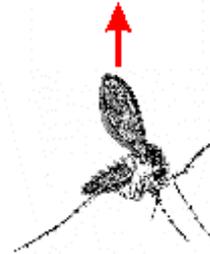
THE LIFE CYCLE OF *LEISHMANIA* SPP. (VARIOUS FORMS OF LEISHMANIASIS)

The vertebrate host is infected with promastigotes when bitten by the vector.

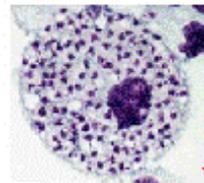


The amastigotes are released in the vector's gut, and the parasite reproduces as promastigotes.

The promastigotes enter circulating macrophages and reproduce as amastigotes.



The vector (a sand fly) ingests macrophages when it ingests blood.



The macrophage dies, the amastigotes are released, and they infect more circulating or fixed macrophages.

The "type" of leishmaniasis (i.e., cutaneous, visceral, etc.) is determined by the primary location of the macrophages that are infected.





Size Comparison
between a Sandfly and a
Mosquito

Leishmania

- Three clinical syndromes:
 - Cutaneous (skin)
 - Mucocutaneous (mouth, nose) – only in S.A.
 - Visceral (internal organs)
- All have common lifecycle...
 - Sandfly with promastigote
 - Innoculates human
 - Amastigote replicates in the macrophages

New World Species		Old World Species	
<i>L. chagasi</i>	V	<i>L. infantum</i>	V
<i>L. mexicana</i>	C	<i>L. donovani</i>	V
<i>L. amazonensis</i>	C	<i>L. tropica</i>	C/V
<i>L. braziliensis</i>	M	<i>L. aethiopica</i>	C
<i>L. guyanensis</i>	C/M	<i>L. major</i>	C
<i>L. panamenensis</i>	C/M		

V = Visceral Disease

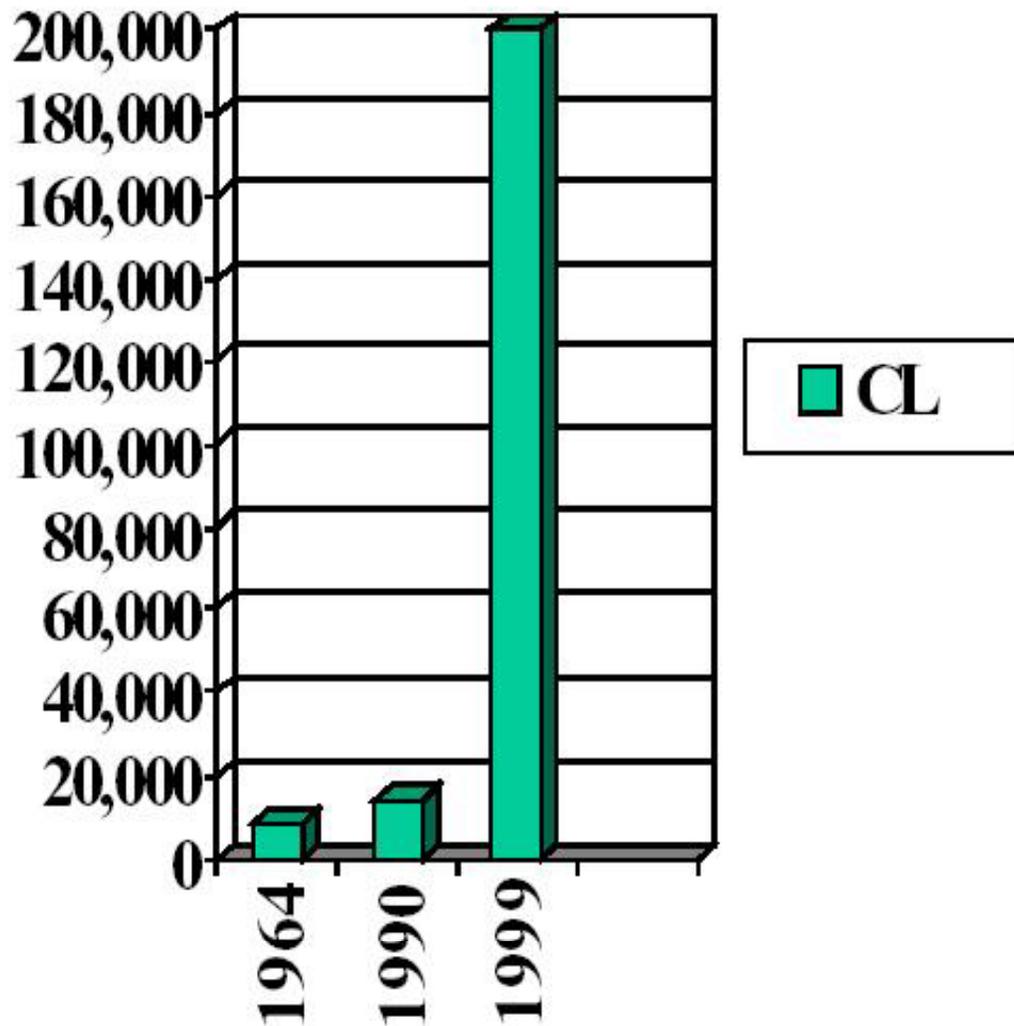
M = Mucocutaneous Disease

C = Cutaneous Disease

Cutaneous Leishmaniasis

- Most classic cutaneous leishmaniasis resolves spontaneously
 - Leaves depressed, atrophic scar
- Some notable dermatologic syndromes
 - Diffuse cutaneous leishmaniasis – looks like lepromatous leprosy (*aethiopica/amazonensis*)
 - *Leishmania recidivans* – pigmented papules like lupus vulgaris (*tropica*)
- Viscerotropic Disease – *L. tropica* (Gulf War)
- Several treatment approaches

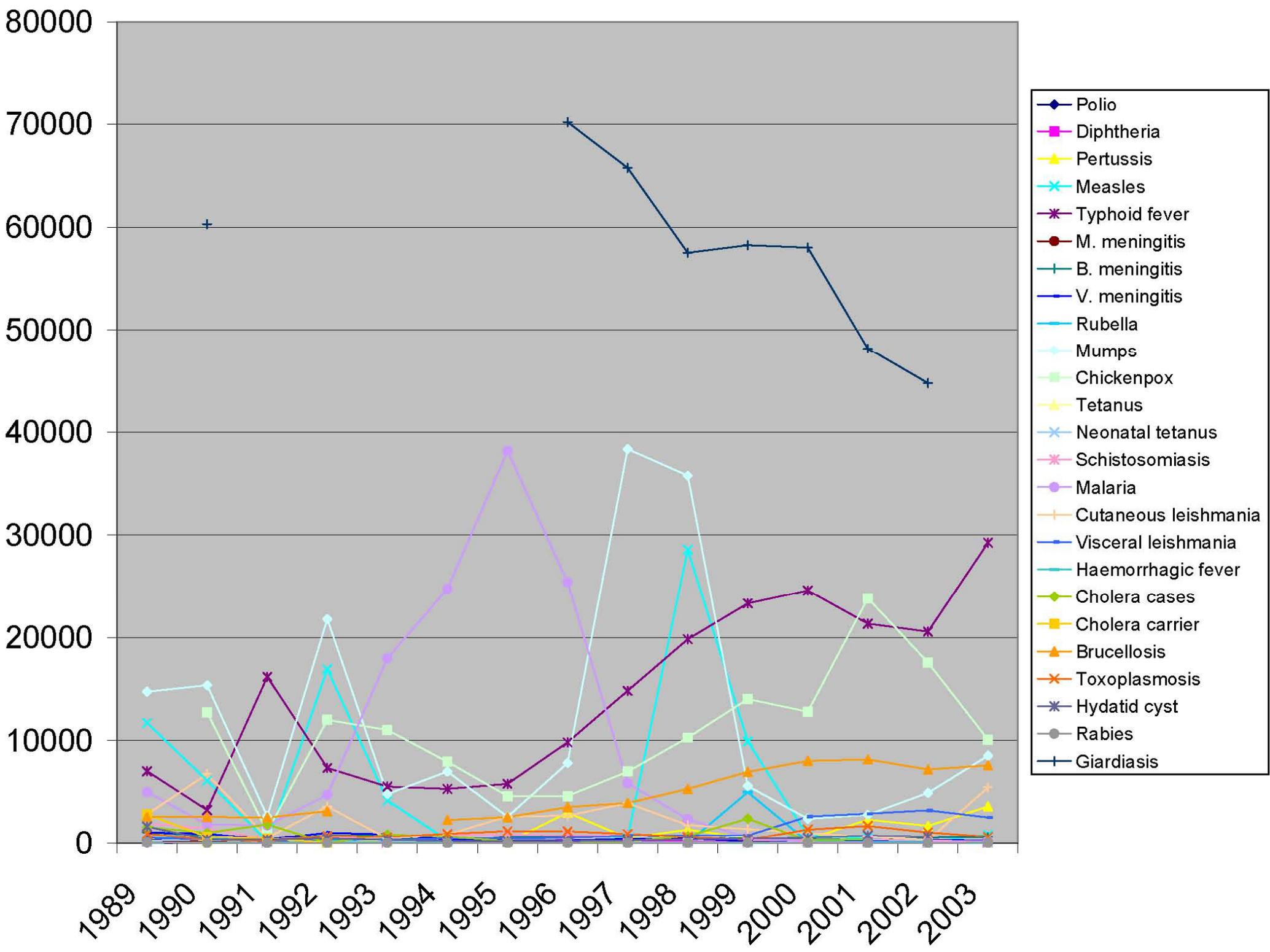
Cutaneous Leishmaniasis in Afghanistan



- 1964: 8,500 cases
- 1990: 14,200 cases
- 1999: 200,000 cases









Cutaneous Leishmania during GWOT

(>97% of cases from Iraq)

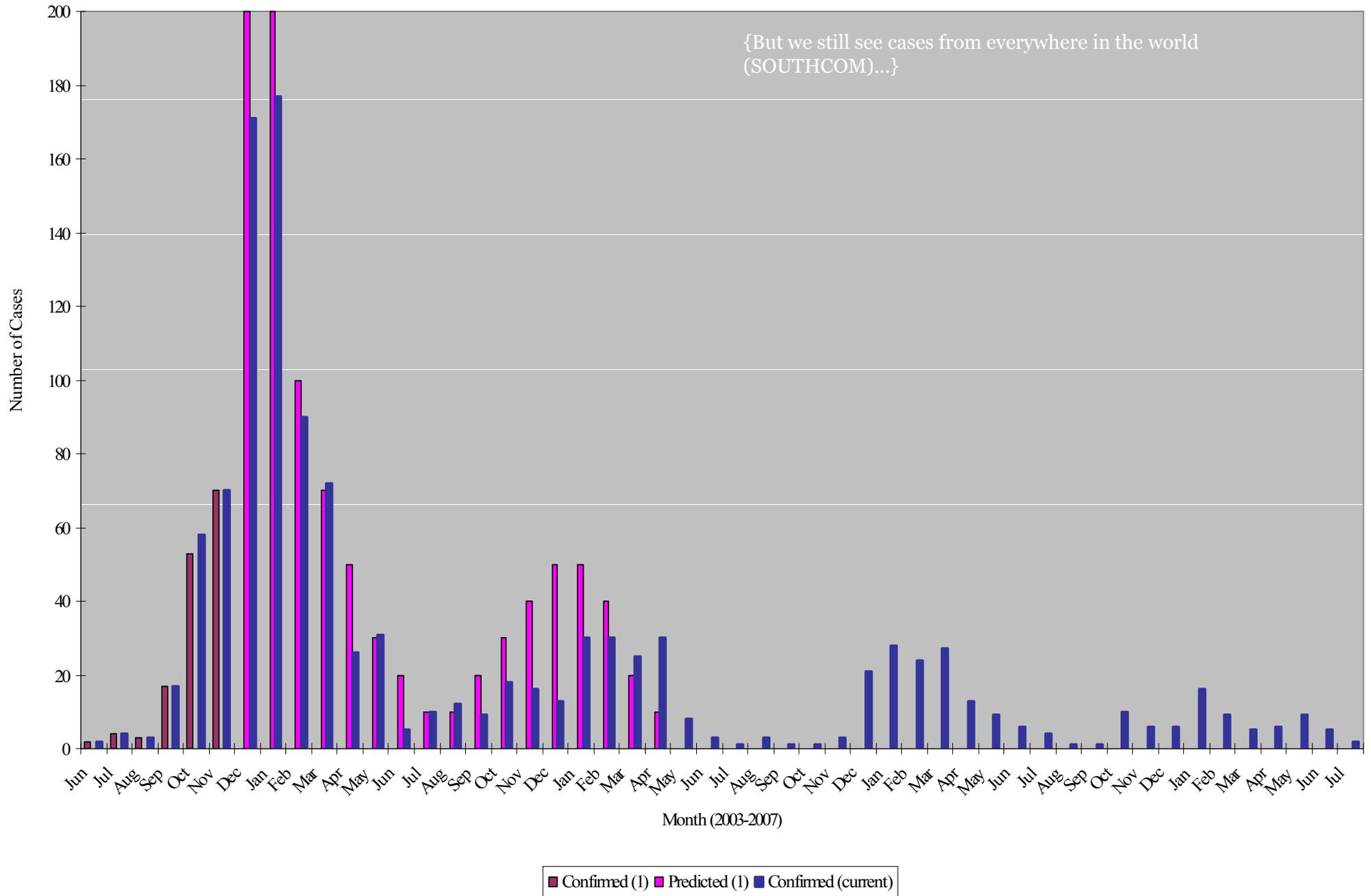
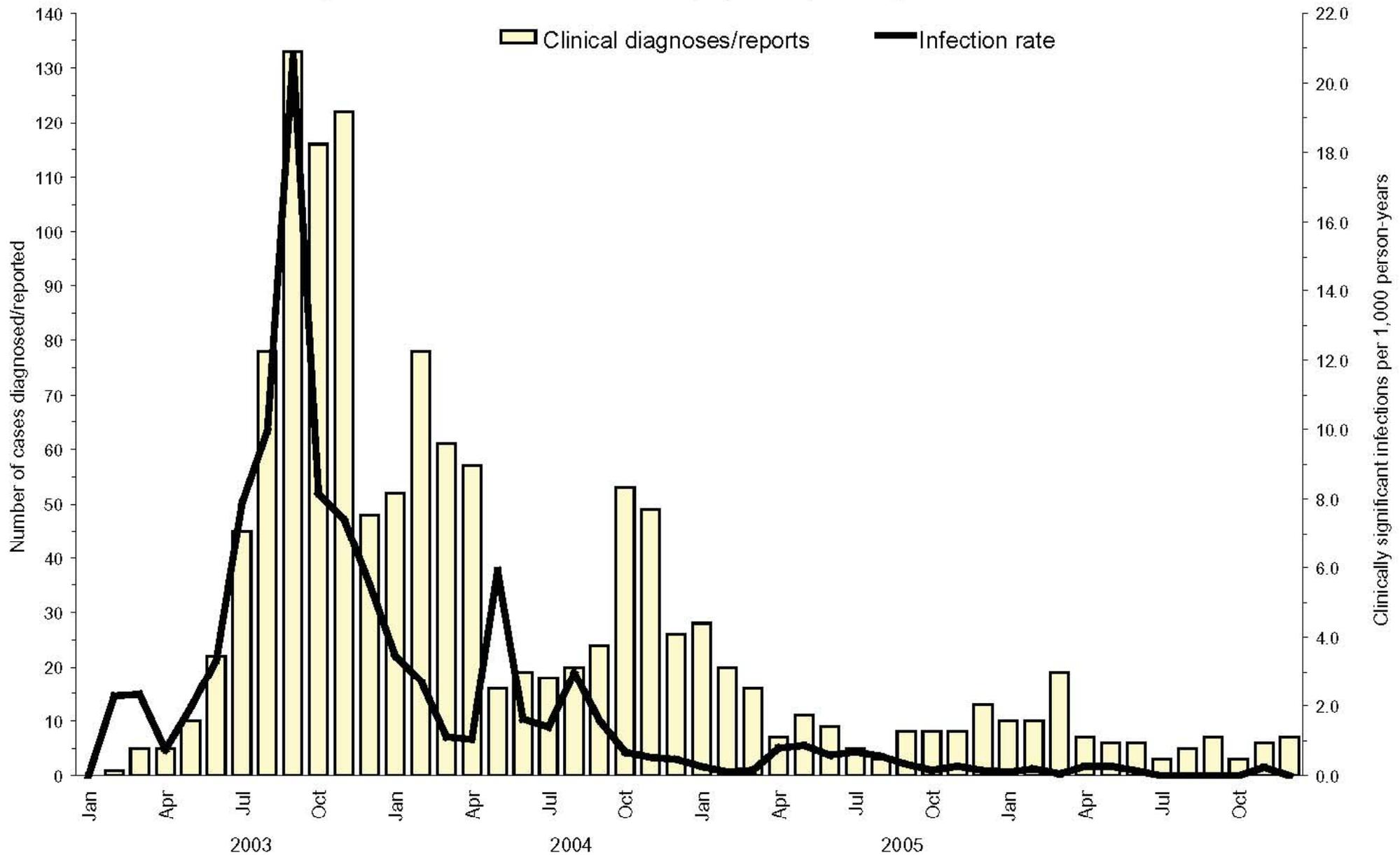


Figure 1. Clinical diagnoses/reports of leishmaniasis at U.S. military medical treatment facilities and estimated leishmaniasis infection incidence rates among U.S. service members in OEF/OIF, by month, January 2003-December 2006





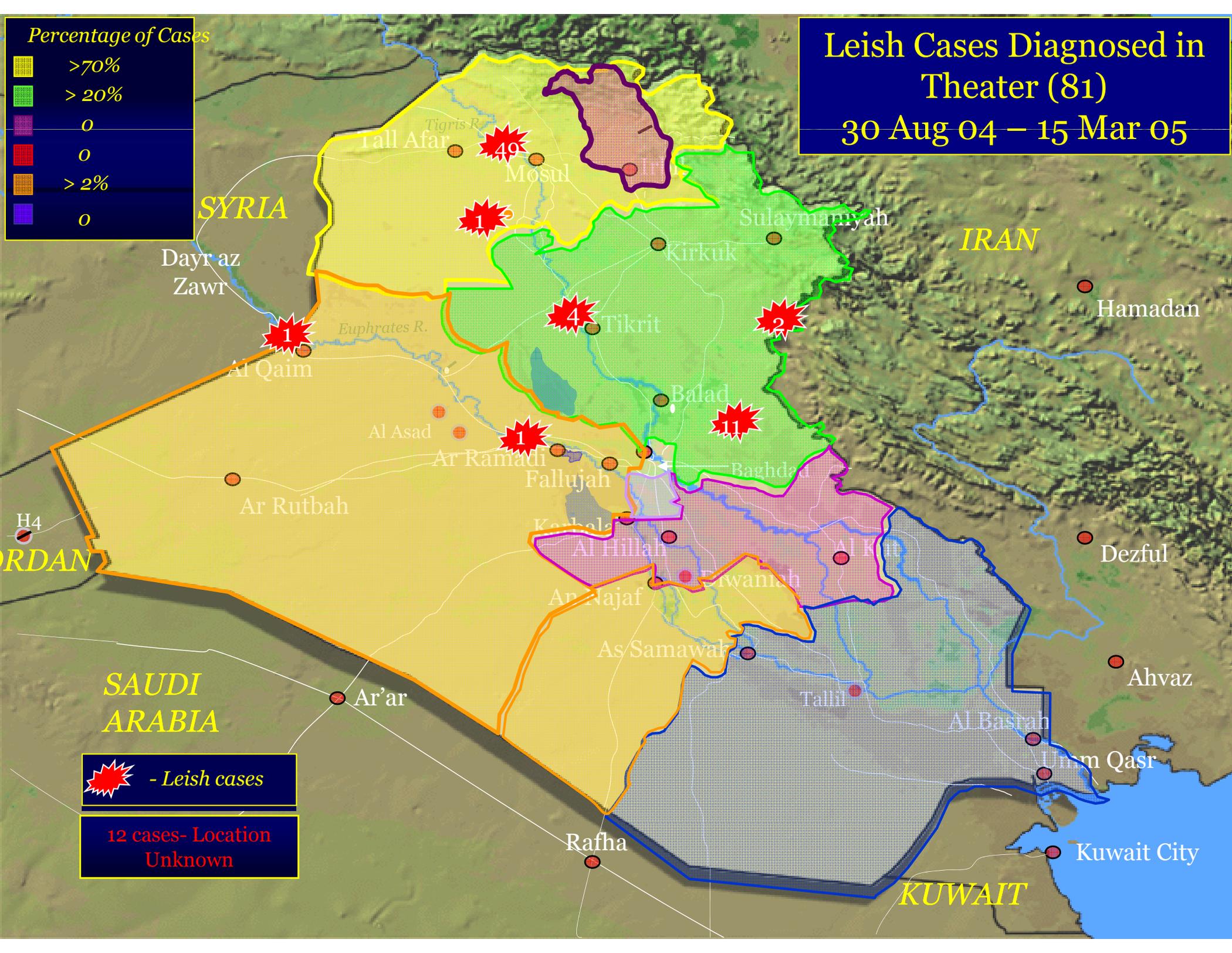
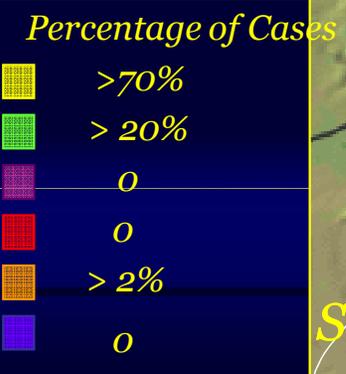




06/06/2006

Leish Cases Diagnosed in Theater (81)

30 Aug 04 – 15 Mar 05



- Leish cases

12 cases- Location Unknown

SYRIA

IRAN

JORDAN

SAUDI ARABIA

KUWAIT

Dayr az Zawr

Euphrates R.

Tigris R.

Tall Afar

Mosul

Sulaymaniyah

Kirkuk

Tikrit

Balad

Ar Ramadi

Fallujah

Baghdad

Ar Rutbah

Karbala

Al Hillah

Al Kut

An Najaf

Erwanah

As Samawah

Tallil

Al Basrah

Umm Qasr

Rafha

Kuwait City

Hamadan

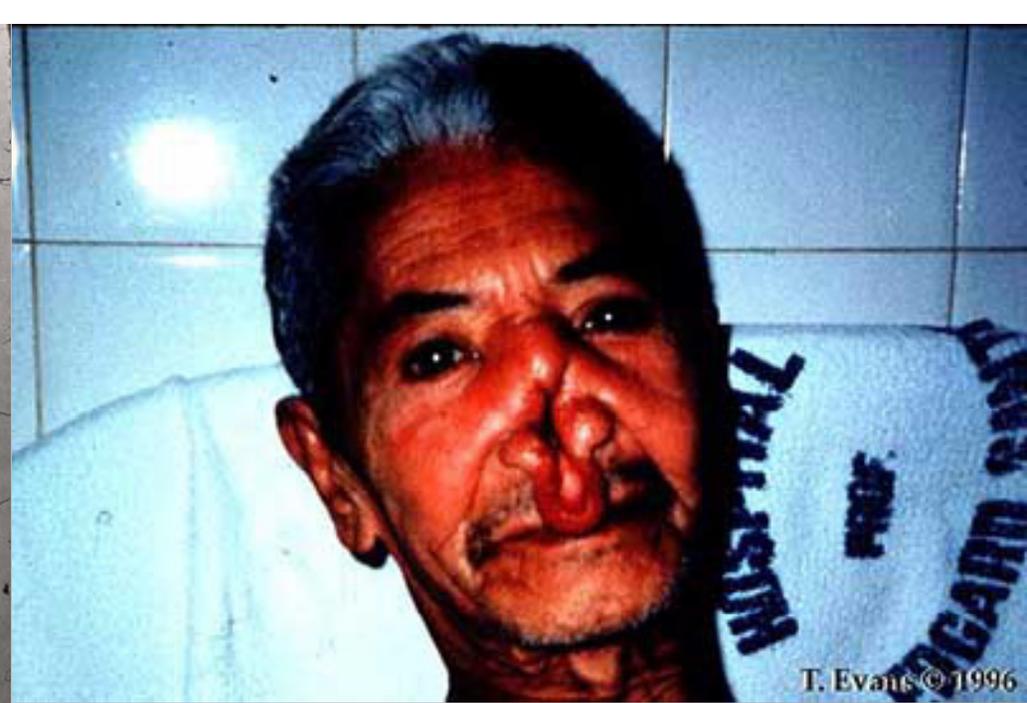
Dezful

Ahvaz

H4



Prof. Luis A. Leon
LAB. LEON Quito-Ecuador
Manson-Bahr, 1972°

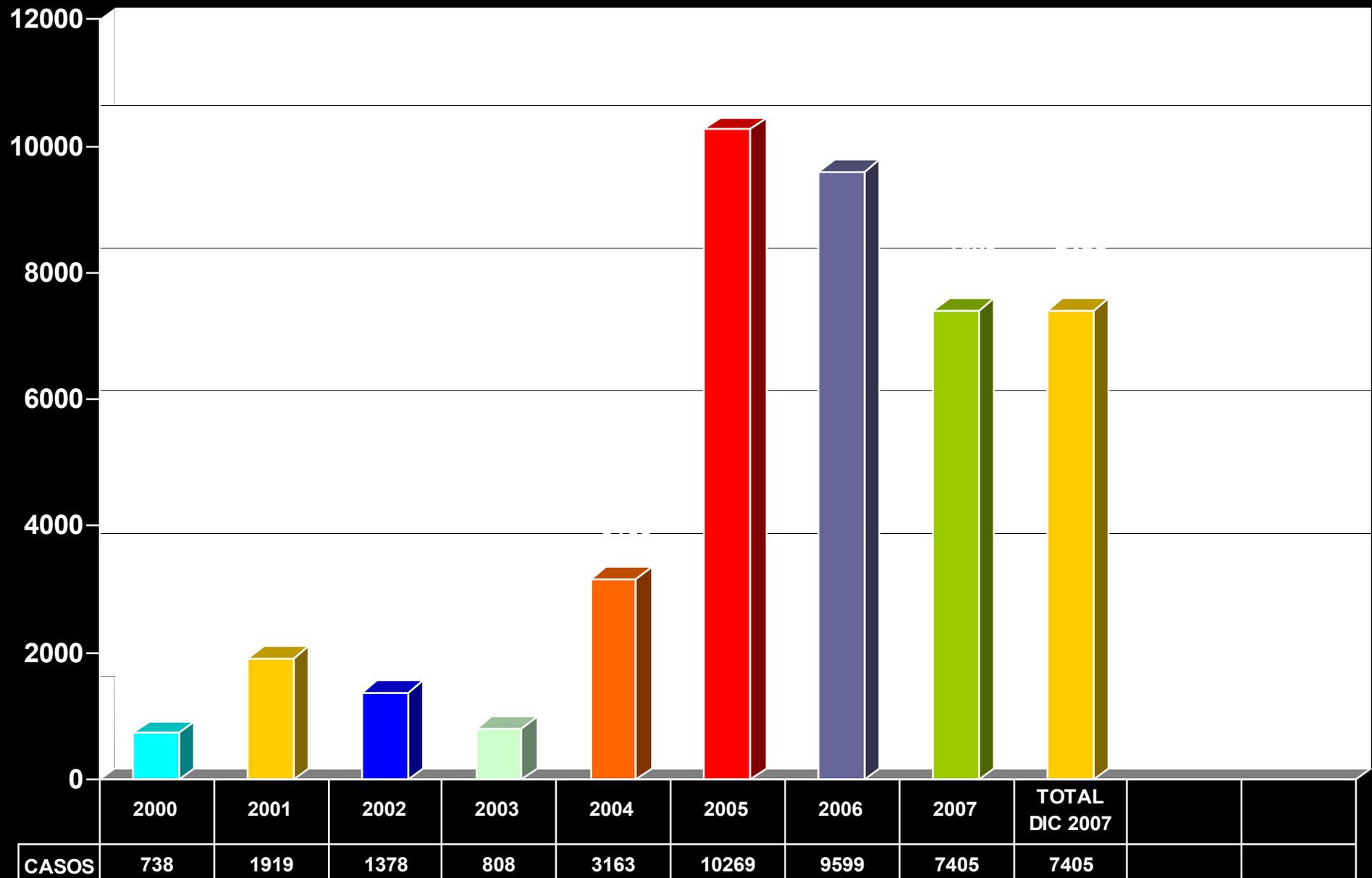


T. Evans © 1996

Long-standing cases



COMPORTAMIENTO COMPARATIVO CASOS DE LEISHMANIASIS 2000/2007





















San Jose del Guaviare



Diagnosis

Basic Diagnostic Principles

- Clinical Diagnosis
- Parasitologic Diagnosis
 - Amastigotes in a smear
 - Promastigotes in culture
 - PCR assessment for DNA
- Immunological Diagnosis
 - Serology (rK39 dipstick assay)

Diagnosis by Disease

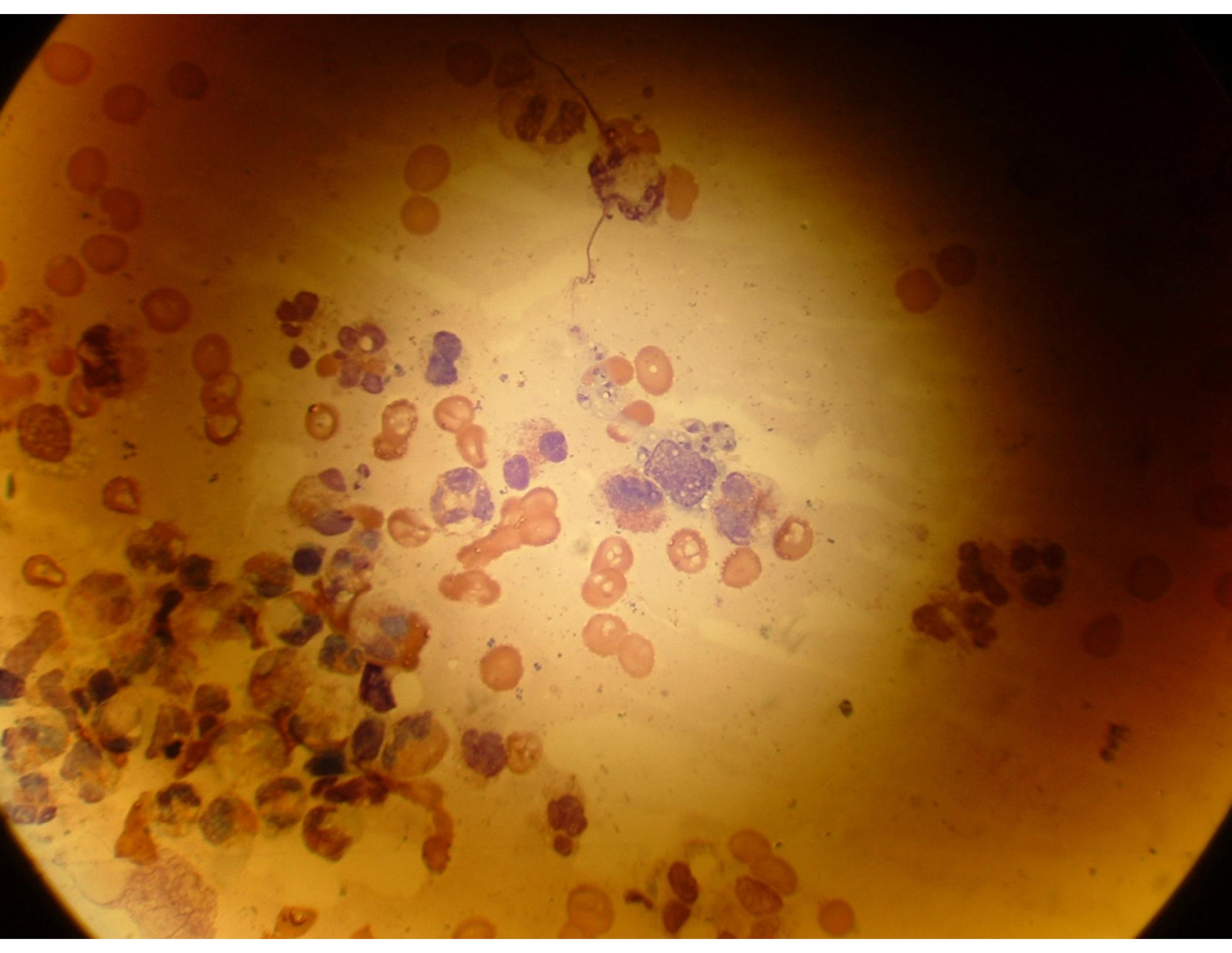
- Cutaneous Leishmaniasis
 - Biopsy/Aspiration/Scraping
 - Touch Prep, PCR, Culture
- Visceral Leishmaniasis
 - Biopsy of Bone Marrow or Spleen
 - Touch Prep, PCR, Culture
 - Immunologic
 - rK39 test strip
 - rK39 Direct Agglutination Test

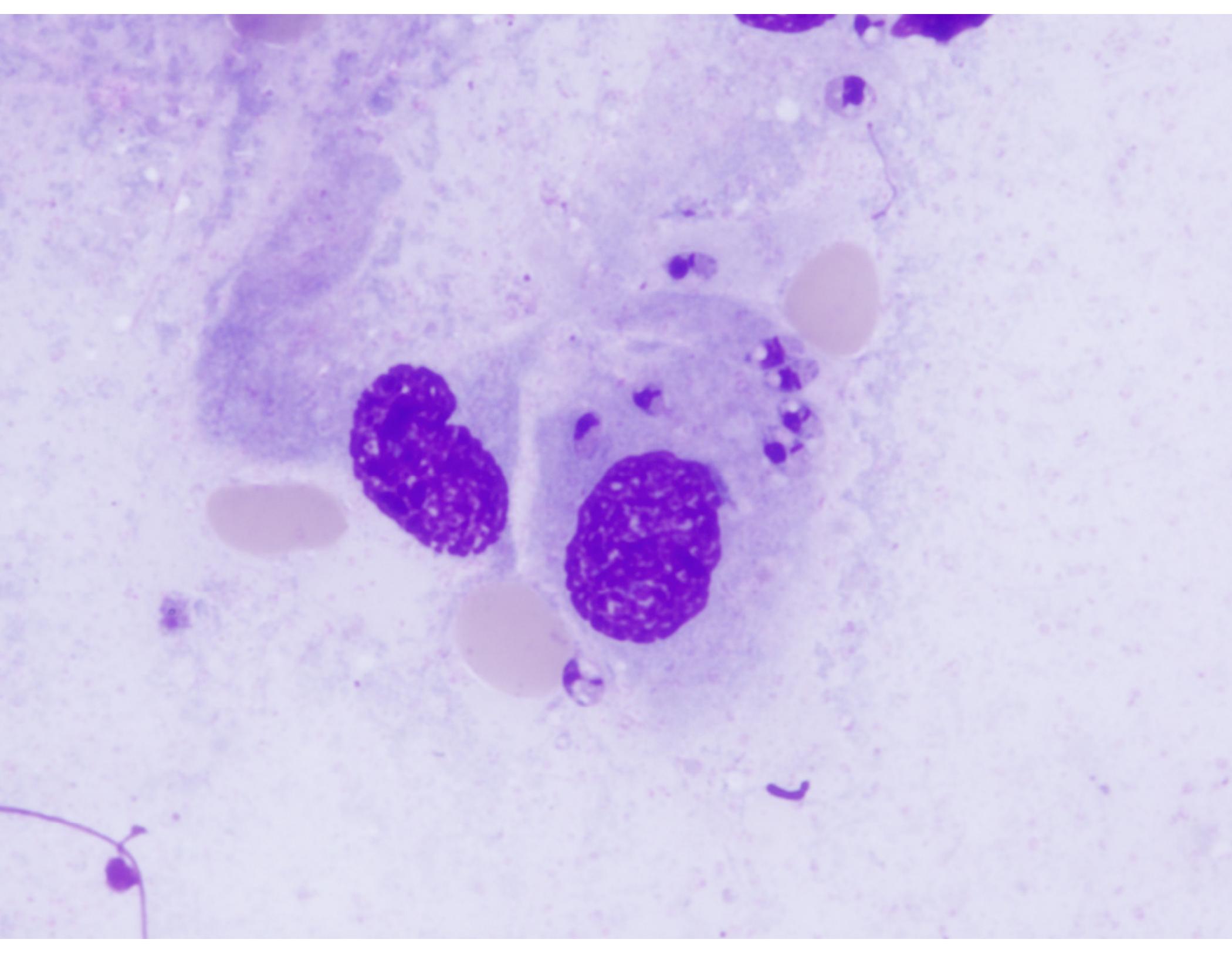


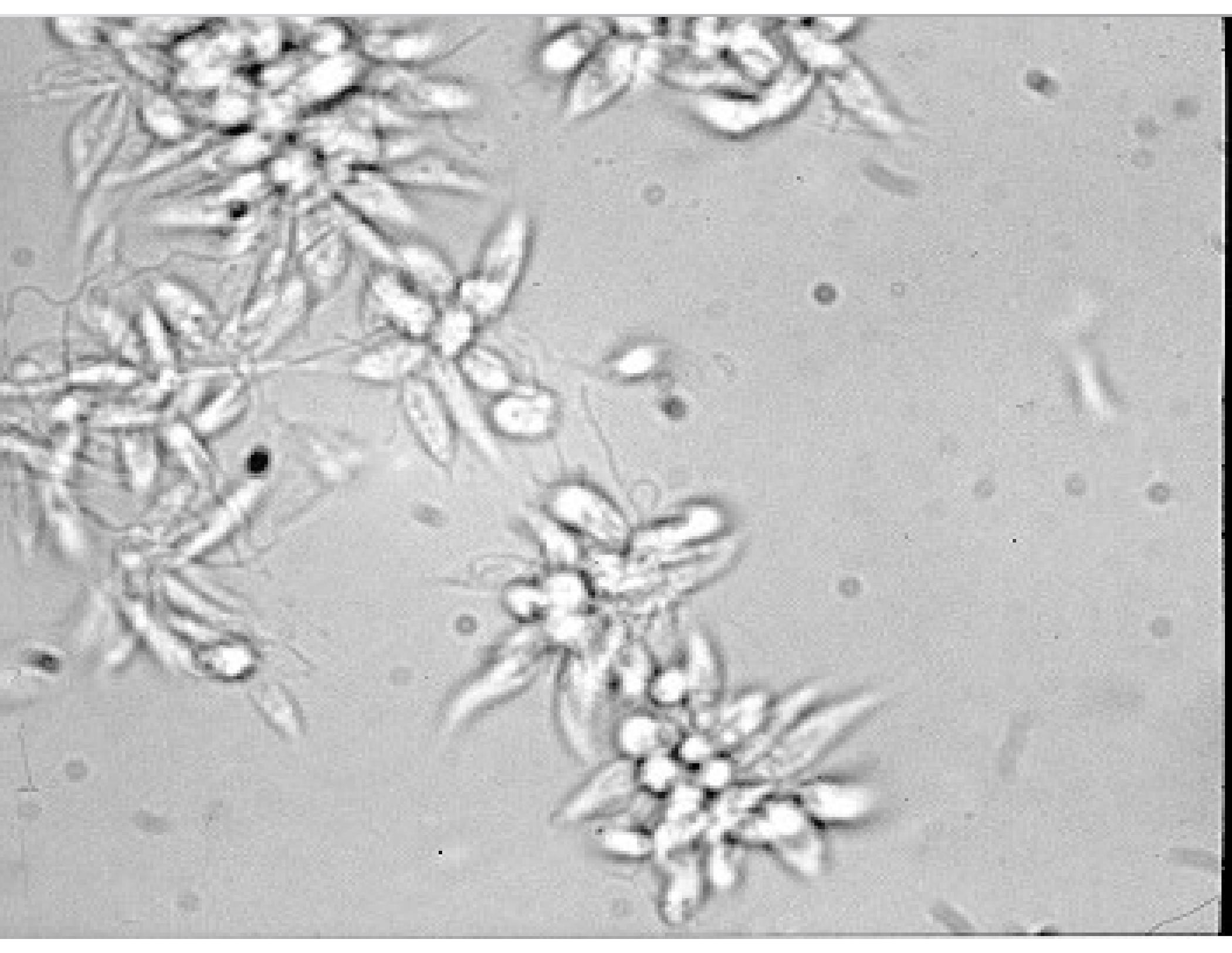
Biopsy should just catch edge of most affected tissue and should have relatively intact tissue adjacent to the lesion for at least one half of biopsy

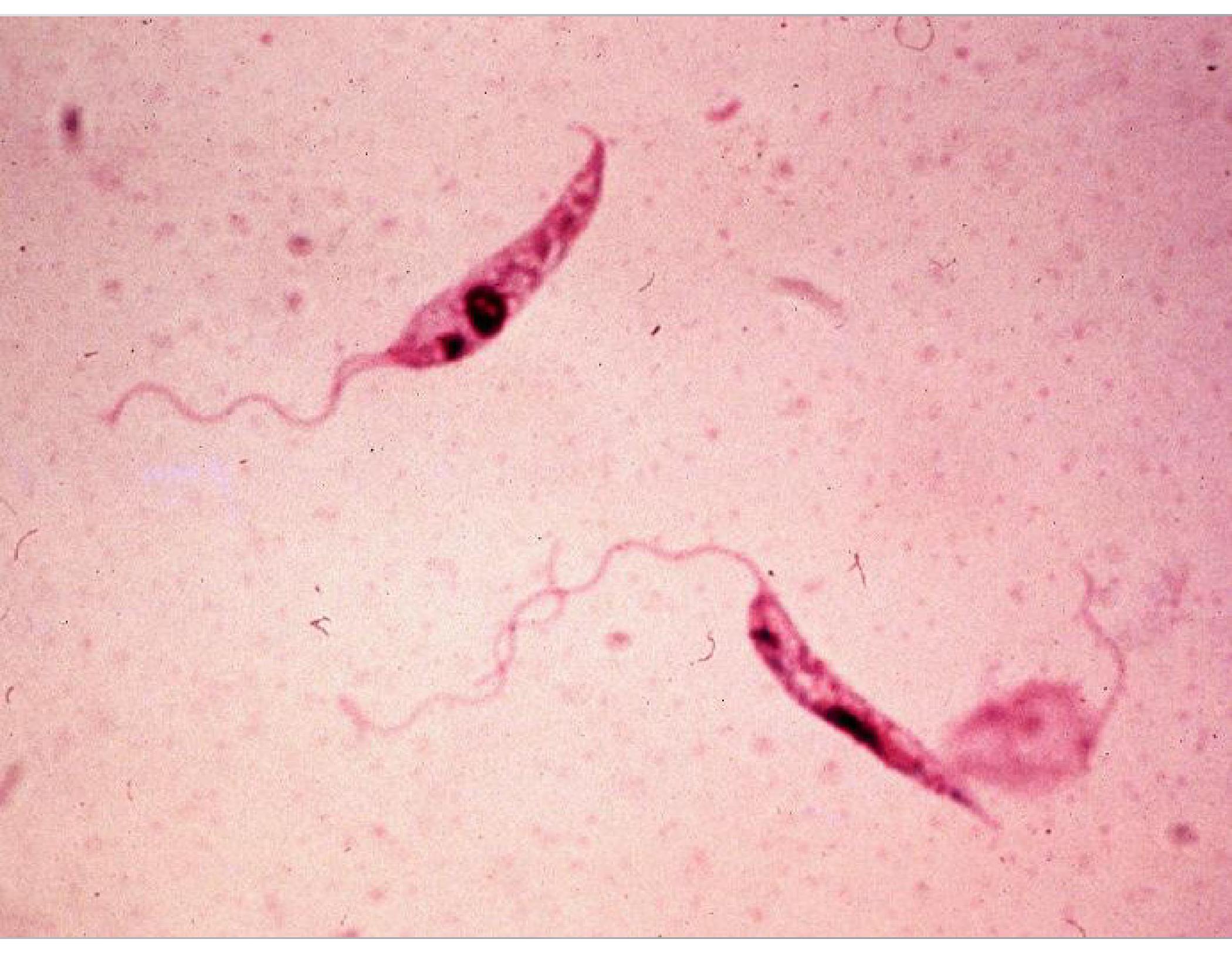
The kinetoplast!!!













InBios

Kalazar Detect

Lot #: DC1015 Exp: 08/2004
Store at Room Temperature
For Research Use Only

Manufactured in the USA by *InBios* International, Inc.
Seattle, Washington 98104

A close-up photograph of a patient's eye. The cornea is visible, showing a large, dark, circular lesion. The surrounding sclera and conjunctiva appear slightly red and inflamed. The word "Treatment" is overlaid in a gold, serif font across the center of the image.

Treatment

Treatment Modalities

Drug	Syndrome	Dosage regimen ^{5,12}	Comments
Parenteral			
Pentavalent antimony ³⁶ (intravenous or intramuscular)*	VL	20 mg Sb (V)/kg daily for 28 days	Longer courses of therapy may increase toxic effects. ³⁶
	CL	20 mg Sb (V)/kg daily for 20 days	Shorter courses may have merit in some situations.
	ML	20 mg Sb (V)/kg daily for 28 days	Longer courses do not necessarily improve effectiveness.
Amphotericin B deoxycholate (intravenous)	VL	0.5–1.0 mg/kg on alternate days or daily (total about 15–20 mg/kg)	Range, total dose about 7–20 mg/kg (varies by region and host status).
	CL	See comments	Infrequently used to treat CL; use if necessary and the toxic effects can be justified.
	ML	1 mg/kg on alternate days or daily (total about 20–40 mg/kg)	...
Lipid formulations of amphotericin B (intravenous)	VL	2–5 mg/kg daily (total about 15–21 mg/kg)	Range, total dose about 5–40 mg/kg (varies by region, drug, and host status). ^{14,37}
	CL, ML	Not currently recommended	Not clear whether useful for CL or ML; more theoretical basis for use in VL.
Pentamidine isethionate (intravenous or intramuscular)	VL	4 mg/kg on alternate days or three times per week for about 15–30 doses	Considered second-line therapy because of toxicity or suboptimal effectiveness.
	CL	3 mg/kg on alternate days×4 doses or 2 mg/kg on alternate days×7 doses	Based on studies in Colombia (most cases probably caused by <i>Viannia</i> subgenus, particularly <i>L [V] panamensis</i>).
	ML	2–4 mg/kg on alternate days or three times per week for 15 or more doses	Considered second-line therapy.
Paromomycin sulphate† (intravenous or intramuscular)	VL	15–20 mg/kg daily for about 21 days	Has been used as monotherapy in India and as adjunct to antimony compounds.
	CL	Not currently recommended	Ineffective against <i>L (V) panamensis</i> (Colombia) and <i>L (V) braziliensis</i> (Belize).
Recombinant interferon gamma (subcutaneous or intramuscular)		100 µg/m ² daily or on alternate days (adult dose)	Sometimes useful as adjunct for difficult cases of VL and other syndromes.
Oral			
Ketoconazole	CL	600 mg daily for 28 days (adult dose)	Consider for <i>L mexicana</i> and <i>L (V) panamensis</i> and possibly for <i>L major</i> .
Itraconazole	CL	200 mg twice daily for 28 days (adult dose)	Failure rate of at least 75% in Colombia (most cases probably caused by <i>Viannia</i> subgenus, particularly <i>L [V] panamensis</i>).
Dapsone	CL	100 mg twice daily for 6 weeks (adult dose)	Promising results obtained in India but not in Colombia (against mostly <i>L [V] panamensis</i>).
Allopurinol	CL	See comments	No better than placebo in Colombia (against mostly <i>L [V] panamensis</i>).
Local/topical			
Paromomycin sulphate ointment‡	CL	Apply twice daily for 10–20 days	Consider especially for <i>L major</i> and <i>L mexicana</i> .
Intralesional Sb (V)	CL	Weekly or alternate-day injections×multiple doses	Infiltrate four opposing sides of lesion until base completely blanched.§

VL=visceral leishmaniasis; CL=cutaneous leishmaniasis; ML=mucosal leishmaniasis; Sb(V)=pentavalent antimony. *Sodium stibogluconate=100 mg Sb(V)/mL and meglumine antimonate=85 mg Sb(V)/mL; locally made antimony preparations may have different antimony concentrations. Intravenous administration preferable for large volumes.³⁶ Children, particularly those weighing <20 kg, may benefit from dosing according to body surface area and treating with proportionately >20 mg Sb(V)/kg daily. †500 mg paromomycin sulphate corresponds to 350 mg base. ‡An ointment containing 15% paromomycin and 12% methylbenzethonium chloride in soft white paraffin is modestly effective. Much of the experience has been with *L major* infection. Methylbenzethonium chloride can cause local inflammation (eg, burning sensation, pruritus, vesicles). A product containing 10% urea instead is cheaper and better tolerated but less effective. §Depending on number and characteristics of lesions, intralesional therapy may not be practical. Much of the experience with intralesional therapy has been for old-world disease. Published regimens vary widely in total number of and interval between injections.

ANTIMONIALES PENTAVALENTES

	DOSIS	VIA	DIAS
CUTANEA	20 mg/ kg/ dia	IM	20
MUCOSA	20 mg/ kg/ dia	IM	28
VISCERAL	20 mg/ kg /dia	IM	28-40

“Standard of Care” - Therapy

➤ Cutaneous Leishmania

- Pentostam – 20 mg/kg IV x 10 -20 days
-
- But evolving as we speak.... Cryotherapy, ThermoMed, “Fluconazole”, Watchful waiting (not all cutaneous must be treated)...

➤ Visceral Leishmania

- Ambisome (liposomal amphotericin B) 3 mg/kg on days 1-5, 14, & 21
- or
- Pentostam – 20 mg/kg IV x 28 days











Visceral Leishmaniasis

- Traditionally thought all pathogenic
 - Now know subclinical/clinical ~ 30:1
- Characterized by:
 - fever
 - wasting (extreme weight loss)
 - splenomegaly (large spleen – left side)
 - hepatomegaly (large liver – right side)
 - pancytopenia (bone marrow depressed)
- Untreated 80-90% of symptomatic patients die
- Treatment – Antimony or Amphotericin B

The Washington Post

WEDNESDAY, NOVEMBER 13, 1991

c

Blood From Gulf War Vets Banned Because of Parasite

Associated Press

The Defense Department and the nation's largest association of blood banks yesterday banned blood donations from Persian Gulf War veterans and visitors to the region because 22 U.S. soldiers contracted a parasitic disease there.

The Pentagon and association policies apply to the half-million U.S. service personnel in Operations Desert Storm and Desert Shield and any civilians who were in Saudi Arabia, Kuwait, Iraq, Bahrain, Qatar, United Arab Emirates, Oman or Yemen. The ban goes back to Aug. 1, 1990, the day before Iraq invaded Kuwait.

The Pentagon expects a drop in military blood supplies and "we're doing everything we can to compen-

sate," said Virginia Stephanakis, a spokeswoman for the Army surgeon general.

The disease, leishmaniasis, is transmitted by sandflies and is treated by intravenous medication. The more serious form of the illness can be fatal if left untreated.

The American Association of Blood Banks will reassess its ban in January 1993, said Joel Solomon, the association's chief executive officer. The group represents 2,400 community, regional and Red Cross blood centers.

Fifteen infected Army servicemen have skin lesions from the less serious form of the disease, the Pentagon said in a statement. Seven have a more serious form which causes mild illness.

Viscerotropic Leishmaniasis from Desert Storm

- The following symptoms were found in eight visceral leishmaniasis patients returning from Desert Storm
 - Fevers: 6 of 8
 - Weight loss: 2 of 8
 - Nausea, vomiting, low-grade watery diarrhea: 2 of 8
 - Lymphadenopathy: 2 of 8
 - Hepatosplenomegaly: 2 of 8
 - Anemia: 3 of 8
 - Leukopenia or thrombocytopenia: 0 of 8
 - Elevated liver enzymes: 6 of 8
 - No symptoms: 1 of 8

Blood Supply Risk...

So what do we know?

- #1) Transfusion risk from Leishmania is unknown
 - (not zero, but certainly not high)
- #2) Time to disease manifestation from transfusion related infection is 6 to 12 months
 - (so it is not an immediate threat)
- #3) Visceral leishmaniasis is treatable
 - (and some might even argue, easier than cutaneous)
- #4) “Best” screening test for VL is arguably the rK39 test
 - (and this looks like there are potentially a large number of false positives. The question though is: ‘what do we do with a positive test result??’)



Emerging Blood Threats



- Testing currently done or recommended
 - HIV, HCV, WNV, Parvo B-19, HAV, HTLV I & II, HHV-8, CMV, T. pallidum, Chagas
- Recommended for 68 newly emerging agents
- XMRV – newly described virus
- human gammaretrovirus, xenotropic murine leukemia virus–related virus
- Because of concern over the potential for widespread infection and preliminary evidence that XMRV is transmitted similarly to HIV, officials are quickly trying to determine if action is needed to protect the blood supply



XMRV



- discovered in 2006
- found in tumor samples from men with a rare form of familial prostate cancer
- also linked the virus to chronic fatigue syndrome
- also found it in measurable levels in the blood of healthy people
- evidence isn't conclusive, as several other studies failed to find XMRV in the blood of people with chronic fatigue syndrome, and it isn't known how prevalent the virus is or whether it causes disease.



Case History - VL

- Sent an article on 15Mar05 by a friend who worked with the Theater Surgeon's Office at the Multi-National Headquarters in Baghdad
- Story was about an Iraqi child with fevers and an enlarged spleen who had no diagnosis
- Read the article and it immediately became apparent that the child potentially had Visceral Leishmania
- Requested that the child be tested with the rK39 test strips available to the Combat Support Hospitals in Iraq (message sent back 15Mar05)

Army doctor seeks stateside care for 3-year-old Iraqi boy

BY CHARLIE COON
Stars and Stripes

BAQOUBA, Iraq — Abbasi isn't like most 3-year-old boys.

He hardly ever smiles or talks. Abbasi often runs a fever of 106 degrees, and when he lays down on his back, the outline of his swollen spleen can be seen pushing through his stomach.

"I was with him the one time he smiled," said Spc. Penney Gainer. "It was my happiest moment since he has been here."

Qais Abbas, better known as Abbasi, is suffering from something that can't be pinpointed by the Iraqi doctors in Baqouba or the American ones at Forward Operating Base Warhorse.

So Dr. (Capt.) Matthew J. Carter, a pediatrician at the Teal Medical



Gainer

Aid Station, is pulling strings to have Abbasi flown for treatment to Walter Reed Army Medical Center in Washington, D.C.

Abbasi, the son of a coalition-friendly tribal sheik, or village leader, is thought to be suffering from leukemia or another disease that has caused his spleen and liver to swell and his blood counts to be dangerously low.

Abbasi's enlarged spleen gives his lungs less room to work, Carter said, making the boy work a little harder for every breath he takes.

Transporting Abbasi to the states for diagnosis and treatment has to be justified to the State De-

partment or Defense Department or both.

"We don't want to advertise that we can help every kid in town," he said. Doing so, Carter said, would undercut the Iraqis' own medical providers.

"But this is a very sick kid, and we care," he added.

Carter said he hoped a decision would be made within a week or two.

The Teal clinic is part of Company C, 203rd Forward Support Battalion, part of the 42nd Infantry Division's Task Force Liberty. Its Level 2 care capabilities enable the staff to treat everyday

sick calls, sprains and strains, dehydration and some casualties of war.

It has operating and trauma rooms. In its first three weeks of operation, the staff treated

392 patients, including 112 Iraqis.

Some of the staff have adopted Abbasi as one of their own. Gainer, of Cary, Ill., cradles Abbasi during the night shift, while Spc. Joy Maine of Snohomish, Wash., handles the day care.

"The first time I saw him I felt really bad because he looked really sick," Maine said. "Sometimes I'll take him outside for fresh air to get him out of his bed."

On Thursday the staff threw a little party for Abbasi, his third birthday. His gifts included a big, red stuffed bear, some clothes and other goodies.

Col. Steven Salazar, command-



PHOTOS BY CHARLIE COON/Stars and Stripes

Dr. (Capt.) Matthew J. Carter holds Qais Abbas, better known as Abbasi. Carter, a pediatrician at the Capt. John Teal Medical Aid Station at Forward Operating Base Warhorse in Baqouba, Iraq, is trying to get approval for Abbasi to be flown to Walter Reed Army Medical Center in Washington, D.C., for diagnosis of an undetermined medical condition.

er of the Warhorse-based 3rd Brigade Combat Team, said the request to transport Abbasi to Washington for treatment was a good use of U.S. taxpayer dollars.

"With all the dollars going into the overall fight, the dollars spent to take care of this boy is less than a drop in the bucket," Salazar said. "But it means a lot to the boy and a lot to a lot of people in (the province of) Diyala."

Abbasi is one of 22 children of

Sheik Ahmed Abdun al-Ahmeri of Bani Saad, located between Baghdad and Baqouba. He said he feels his son is part of his own body and is ready to do anything to make him feel better.

"I trust in God first," said Abdun, a Shiite, through a translator. "And then I trust the American physicians to help my son be better."

E-mail Charlie Coon at: coonc@mail.estripes.osd.mil



Article sent on
15Mar05 from
Iraq to the Leish
Diagnostics Lab



Follow-up

“...it was the suggestion that you forwarded to me in which I informed CPT Carter to initiated the testing here at the 86th that set it in motion. They had drawn the blood earlier that evening but did not run the test until the morning.”

-Message sent from the 86th to the entomologist who noticed the potential for VL-



Microbiology Laboratory Report

Accession #	A176
Collection Date	3/16/2005
Patient Name	1477
SSN or ID	1477
Sample Type	Serum
Patient Location	ICU-1
Provider	Unknown
Result Type	FINAL
<input type="checkbox"/> HIV Combo Test	
<input type="checkbox"/> HIV Rapid Antibody	
<input type="checkbox"/> Hepatitis B Surface Antigen	
<input type="checkbox"/> anti-Hepatitis B Surface Antigen	
<input type="checkbox"/> H pylori Antibody	
<input type="checkbox"/> Infectious Mononucleosis Antibody	
<input checked="" type="checkbox"/> Visceral Leishmaniasis Antibody	Positive
<input type="checkbox"/> Blood Parasite Exam	
<input type="checkbox"/> RPR	
Comments	Repeated x2

10

Laboratory report from the 86th CSH. Run on the 17th of March 2005.

18 Mar 05 Communication DCCS of the 86th CSH in Baghdad



“Follow up on our little patient. He had a rocky transport back to Baghdad (definitely would not have survived transport to US). Resuscitated him throughout the night and started amphotericin B (not liposomal which would be optimal). The drug seem to have taken an immediate effect. We are almost off all pressors and have weaned the vent from 100 % FIO₂ down to 60%. ...”





Monday, 21Mar05

Communication from 86th Combat Support Hospital



Response to a request for an update sent Sunday night to the 86th CSH:

“We did well on his nutrition but his oxygenation was poor, little guy’s saturation levels just kept dropping. He had gotten hypoxic when he bounced back to us, I was told he extubated himself on the return trip to us.”



“He had looked better to me on Saturday night,
but he died on Sunday morning...”

Case Study – Leish in a Ranger















E-7 Ranger

- Seen for lesions that started on the hand and neck and were there for several weeks
- Underwent standard Ambisome dosing (3 mg/kg) for 7 days... and then an additional 3 days
- Went back to full training and “suppliments”
- Came back because the lesions worsened
- Started on another course of Ambisome... 15 days total of 3 mg/kg... breaks due to elevated creatinine
- Total time “out of the fight” thus far.... 3 months...



Take Home Leish Points

- Threat is very real and ranges from cosmetic to disfiguring to fatal as well as acute to chronic
- The parasite is diverse and the disease is too
- Everything we know about it is continually brought into question the more we learn
- The best treatment is at times, poor at best, so preventive measures are key and vital
- Education is our best tool currently



Questions?