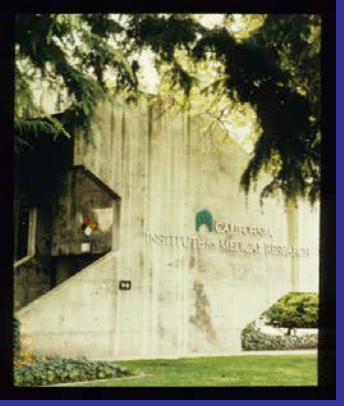


David A. Stevens, MD

Professor of Medicine, Emeritus, Stanford University

President, California Institute for Medical Research

Stanford and San Jose, California

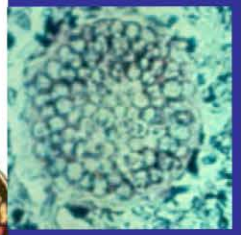
Coccidioidomycosis

Epidemiology/Clinical manifestations & as relates to Trial Endpoints/Latin America

USFDA

Aug. 5, 2020

Stevens, New England J. Med. 332:1077



Saprobic phase

Parasitic phase

Endospore

Tubular structure emerges

Mycelia

In soil

Arthro-conidia return to soil

Arthroconidia form as alternate cells along the mycelia

Arthroconidia

Arthro-conidia are inhaled

Spherule releases endospores

Endospores form in the spherule

In body

Spherule

Arthroconidia enlarge

Life cycle of *Coccidioides*.

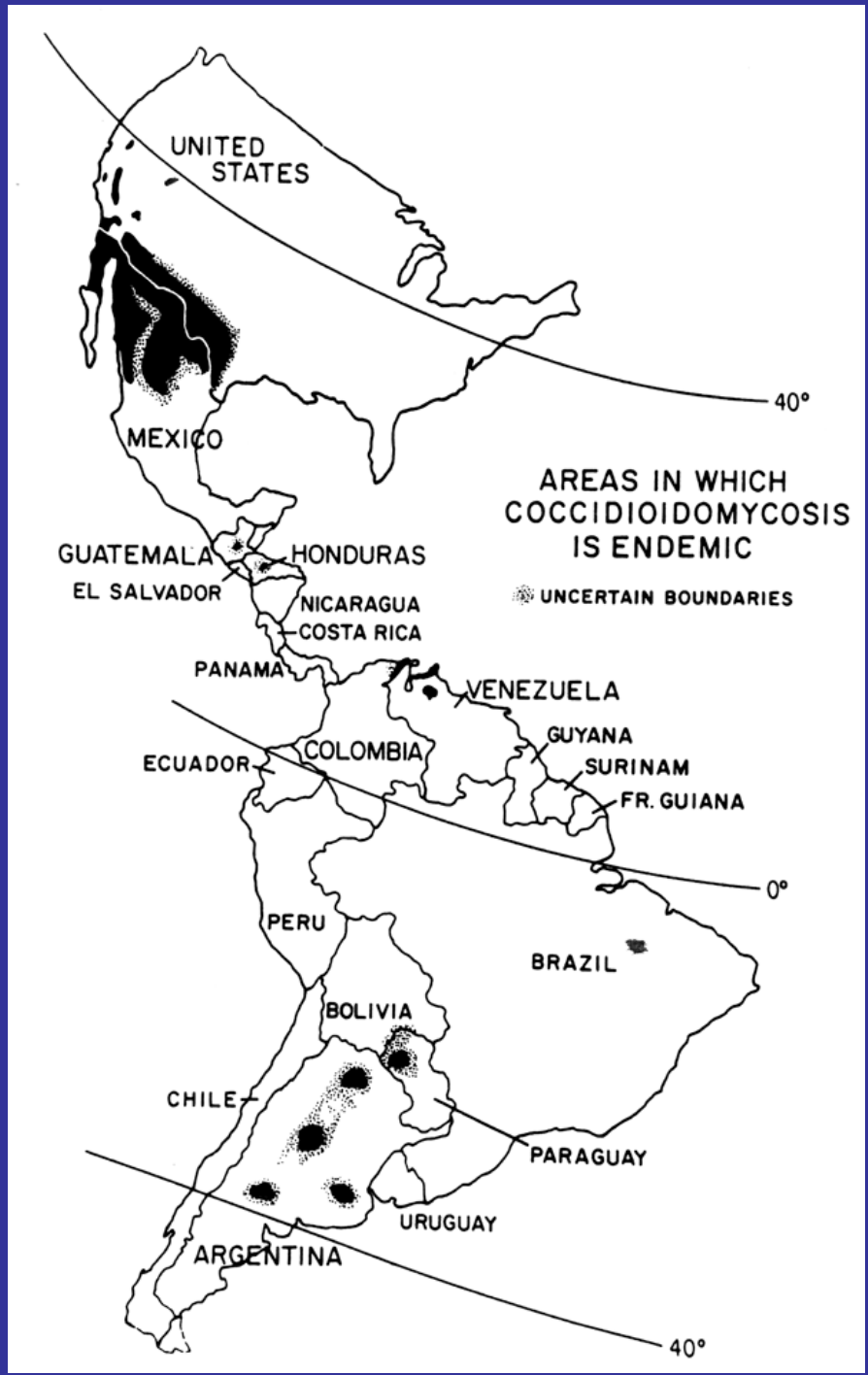
Why it's an infectious disease but not a contagious disease

Coccidioidomycosis

A "New World" disease

What's new- has been found in Brazil, Guatemala, Colombia, Oregon & Washington

With global warming, range of *Coccidioides* in soil will increase



Lower Sonoran Life Zone, which is a geoclimatic region of aridity associated with hot summers, mild winters, and alkaline soil

Sparse flora, low altitude


Lush central valley scenery, lush coccy Calif. prison

Two species?

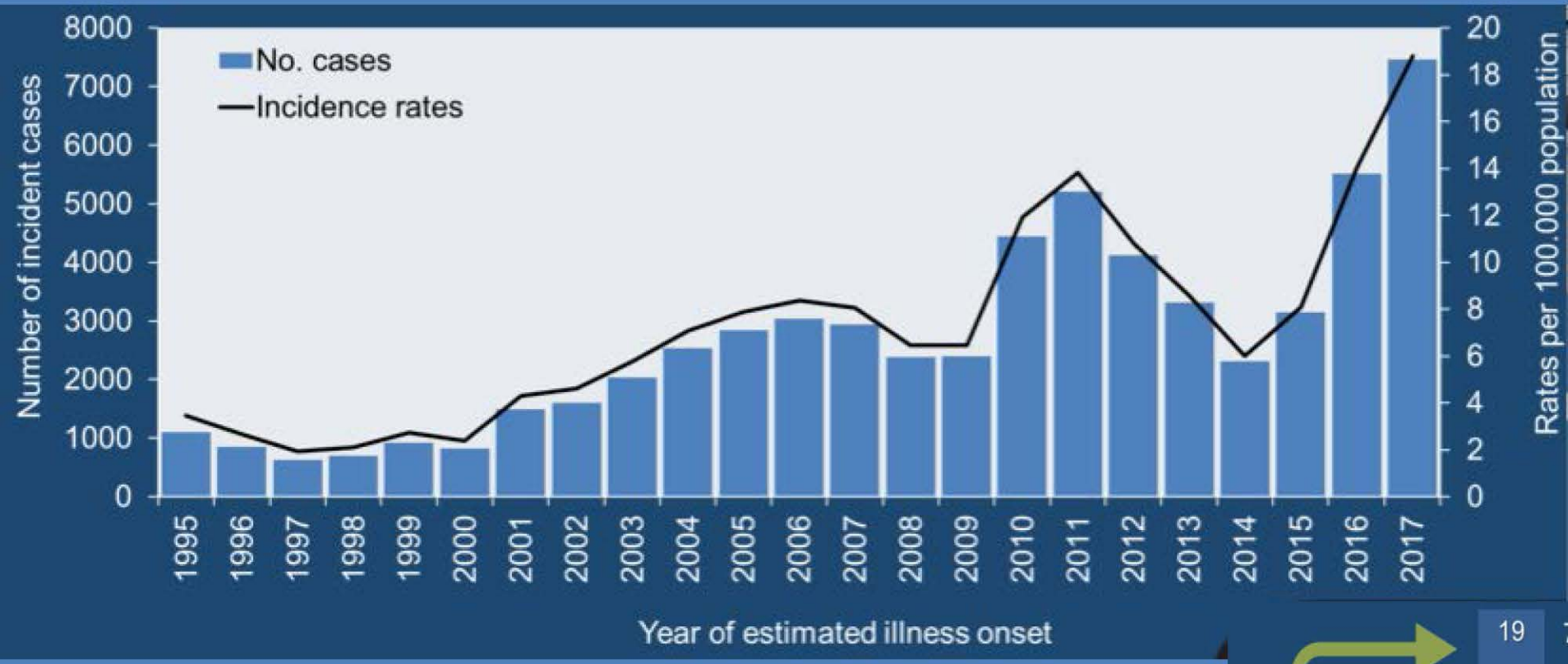
- *Coccidioides immitis* and *Coccidioides posadasii:* Calif. and non-Calif. species.

- Until recently, coccidioidomycosis was attributed only to *C. immitis* but microsatellite analysis allowed the distinction of at least two species.

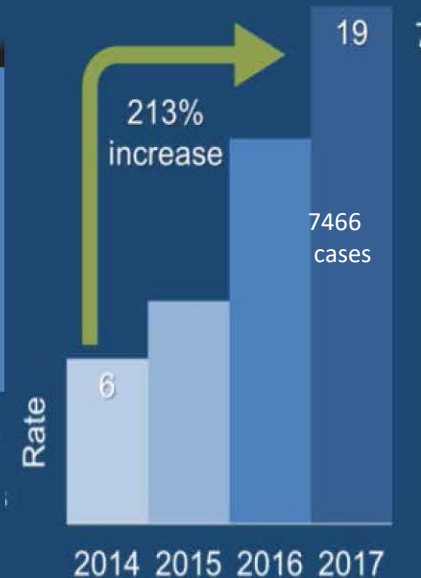
- Colony morphology, growth requirements and clinical disease appear identical.

Laniado-Laborin R. 2007. Ann N Y Acad Sc **1111:**19-34.
Pappagianis D. 1993. Seminars in Dermatology **12:**301-309.
Pappagianis D. 1994. CID. **19 Suppl 1:**S14-18.
Fisher MC, Koenig GL, White TJ, Taylor JW. 2002. Mycologia **94:**73-84.
Fischer MC et al. PNAS. 10 (98) 4558-4562

Coccy Epidemiology—on the rise



In 2011, more than 20,000 cases were reported in the US, twice as many cases as tuberculosis.



Preliminary data for 2018 report >8,000 cases

Estimated population at risk- up to 20 million
(residents, snowbirds, tourists, other travelers, military, etc.)

Estimated infections USA- 200,000/yr.
(3% conversion rate in the most endemic areas of CA, AZ, TX)
Under-reported disease

Estimated illness (1/3 of all exposures)- 67,000/yr.


Advancing Arthroconidial Storm
(Haboob)
New Homes of
Unsuspecting
Virgin Population


Northridge earthquake

Something to look forward to?

Construction work & construction workers for proposed high-speed “bullet” train through Central Valley of California?

Hint: don’t sign up for this work.

Transmission by fomites to nonendemic regions

Another source of infection- lab accidents

Expert Opinion: What To Do When There Is *Coccidioides* Exposure in a Laboratory

David A. Stevens,[1,2,3,4,5] Karl V. Clemons,[1,4,5] Hillel B. Levine,[4] Demosthenes Pappagianis,[7] Ellen Jo Baron,[5,6] John R. Hamilton,[3] Stanley C. Deresinski,[1,5] and Nancy Johnson[2]

Departments of [1]Medicine and [2]Infection Control and [3]Clinical Microbiology Laboratory, Santa Clara Valley Medical Center, and [4]California Institute for Medical Research, San Jose, [5]Division of Infectious Diseases and Geographic Medicine and [6]Clinical Microbiology Laboratory, Stanford University Medical School, Stanford, and [7]Department of Medical Microbiology, University of California, Davis, California

Clin. Infect. Dis. 49: 919-923

(Veterinary- Lisa Shubitz could discuss)

Impact on patients

Avg. # days ill= 202

Avg. # days missed work= 33

R. Sunenshine, Coccy Study Grp., 2008

Costs California- ~$2 billion, 2001-2011 (Assemblyman Rudy Salas, Jr., 2018)

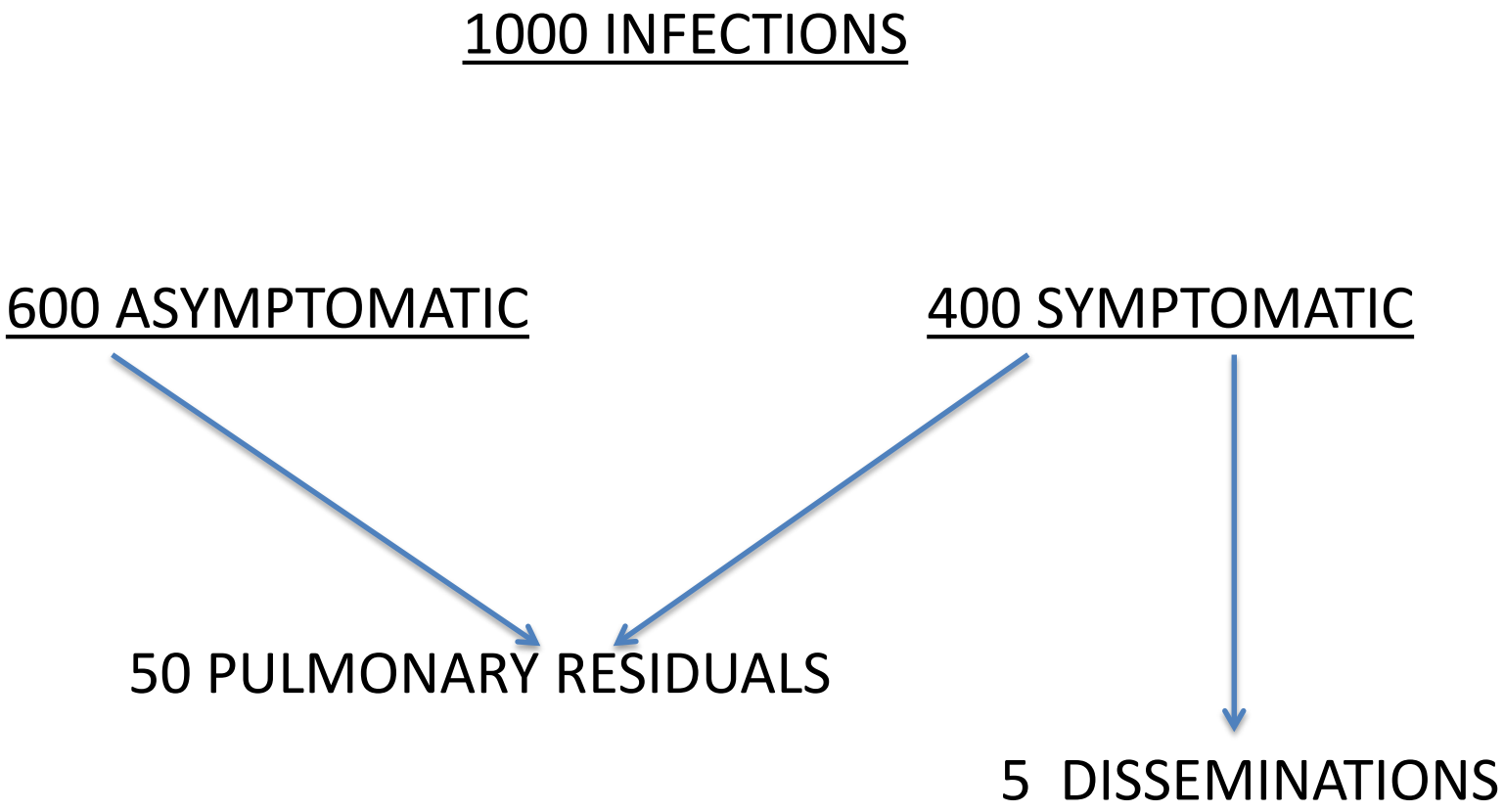
How much do docs in endemic areas know about coccy?

Range derived from various studies indicates only 3-52% docs test community-acquired pneumonia for coccy (*in AZ 29% of "community-acquired pneumonia" is coccy*)

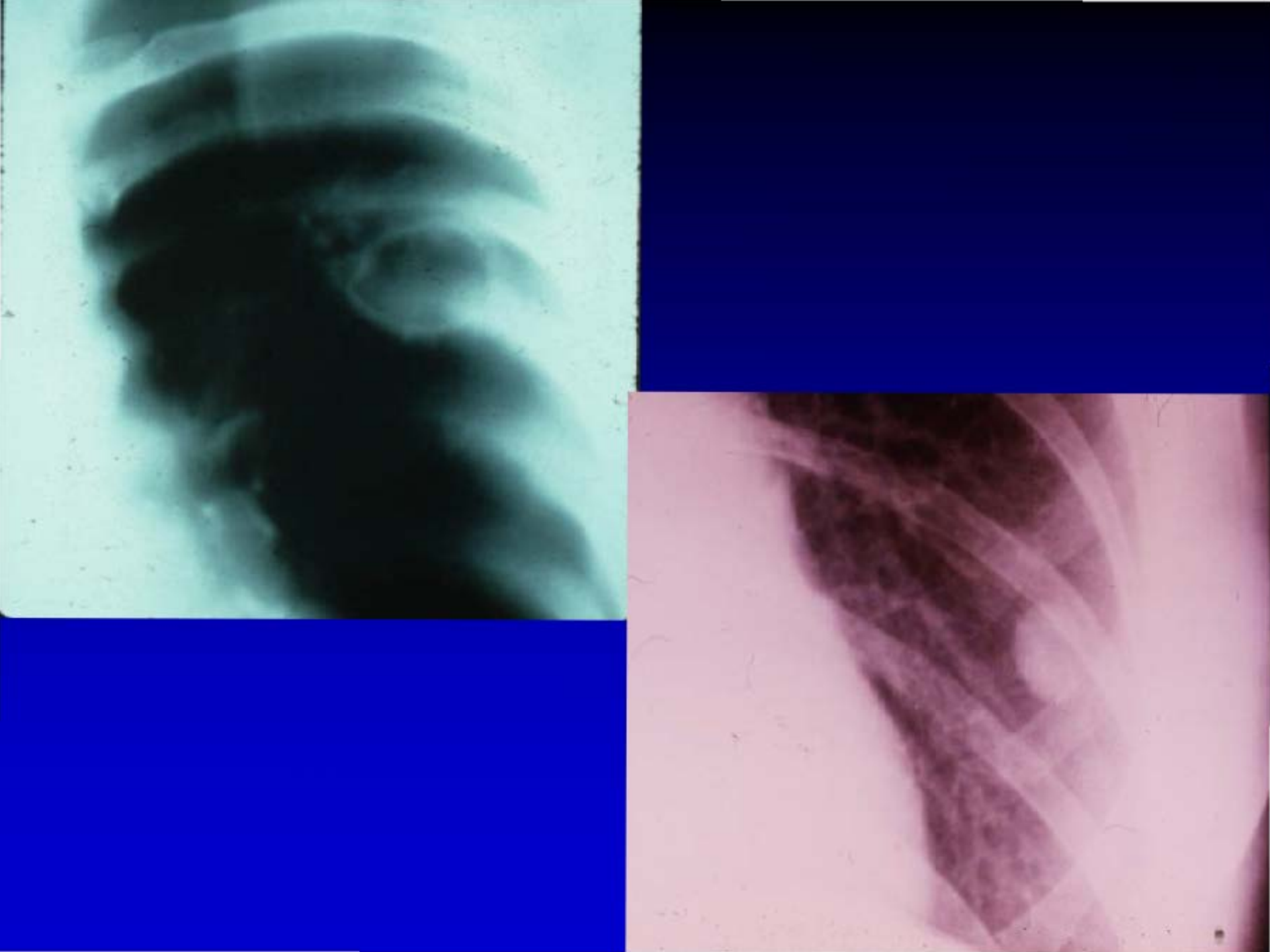
60% of coccy cases received antibacterials for it prior to dx.

Average # visits to doctors before dx. in a case of coccy is 3

Conversely, 43% of doctors treat a positive serology only, in an asymptomatic patient



(Calculations are largely based on healthy white males)



Primary Infection:

60% Asymptomatic or Subclinical/Mild

40% Spectrum of Respiratory Illnesses

--"Flu-like illness"

-- Community-Acquired Pneumonia: " Walking" to ARDS

May be accompanied by various skin eruptions (e.g. E. nodosum, E. multiforme)

- Onset generally 1-3 weeks post-exposure

Rx?

Primary Pulmonary Coccidioidomycosis

Erythema multiforme
in primary coccy

Erythema nodosum
in primary coccy

Primary Infection: Signs and Symptoms

- FATIGUE 40-100%
- FEVER 56-76%
- CHILLS 21-56%
- SWEATS 21-56%
- HEADACHE 20-40%
- MYALGIA/ ARTHRALGIA 23-70%
- RASH 12-30%
- COUGH 70-75%
- SPUTUM 22-50%
- PLEURISY 44-56%
- DYSPNEA 22-63%
- EFFUSION ~10%

Chronic "Active" Coccidioidomycosis = Progressive & Trouble

- CHRONIC PULMONARY
- DISSEMINATED
  EXTRA (META) PULMONARY

Chronic pulmonary coccy

Ddx. TB

Risk of dissemination

- Higher risk for extrapulmonary dissemination
  - healthy males
  - immune compromise*
    - AIDS (CD4 <250/µl)
    - immunosuppressive Rx, e.g, transplantation, corticosteroids, chemotherapy, anti-TNF-α drugs
    - malignancies
    - congenital immunodeficiency (IL-12 receptor β1, interferon gamma receptor 1)
  - pregnancy
    - 2nd and 3rd trimesters
  - certain racial groups
    - Filipino-Americans, African Americans, native Americans, Hispanics, and other Asians, are at greater risk than whites

Extrapulmonary = disseminated

- Almost always caused by dissemination due to hematogenous spread of the fungus.
- Usually a few months after the primary infection.
- Nonmeningeal
  - Skin
    - Plaques, superficial abscesses, pustules, and granulomatous lesions
  - Bone
    - Osteomyelitis, abscesses and sinus tracts
  - Joints
    - synovitis
  - Other sites

  Meningeal

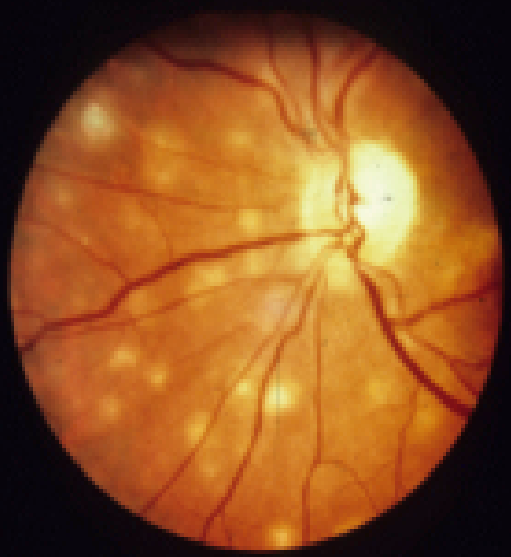
  Tendency to relapse

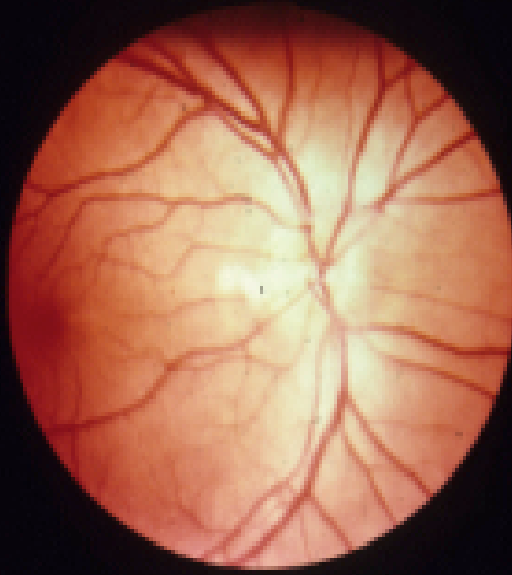
Soft tissue abscess
& ulcer

Bone Scan

Mutifocal choroiditis
spares retina

Juxtapapillary retinochoroiditis



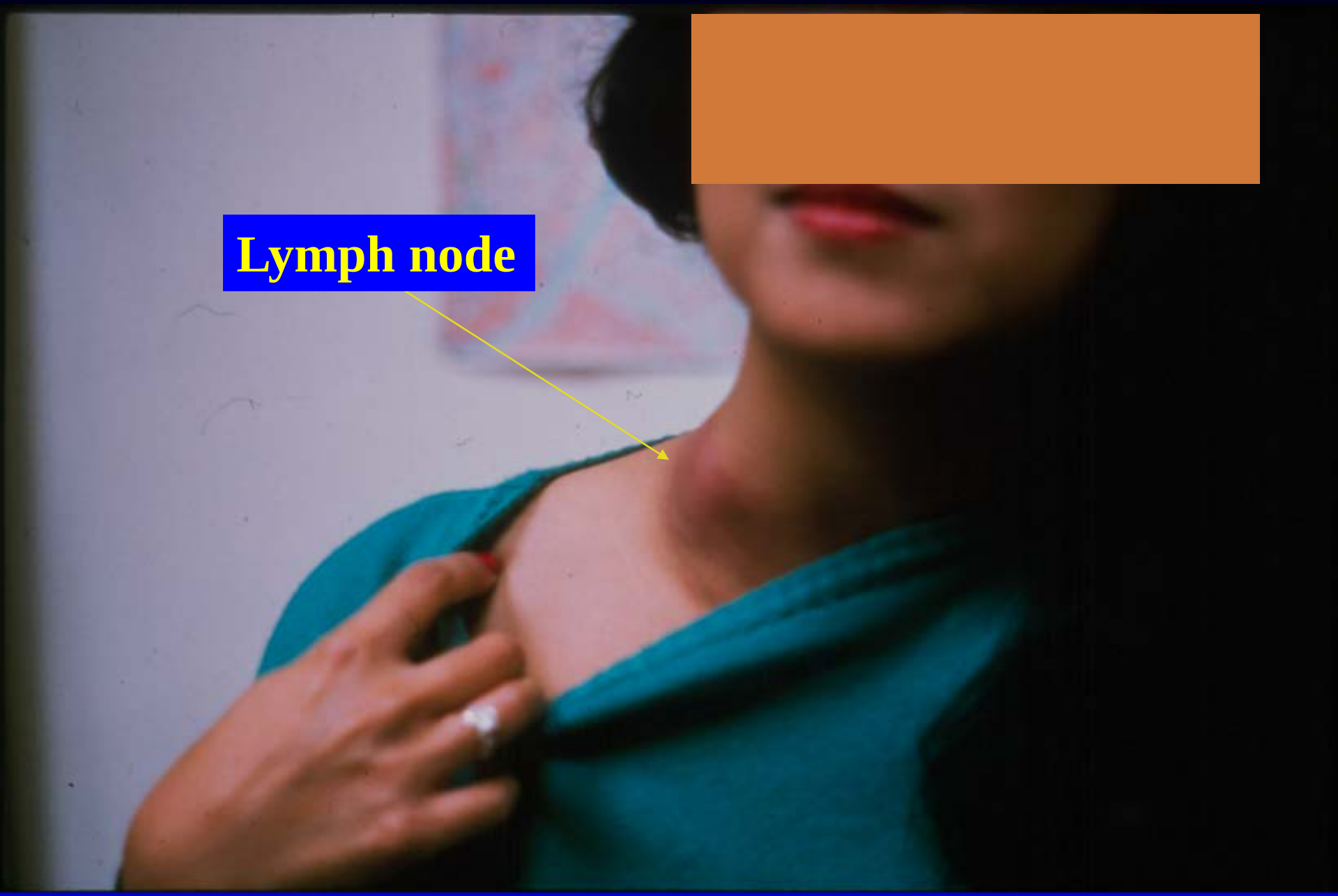


Blumenkranz, M.S., Stevens, D.A. Endogenous coccidioidal endophthalmitis.

Ophthalmology 87:974-984

Spherical infiltrates at retina & Bruch's

Punctate peripheral retinal infiltrates


Lymph node

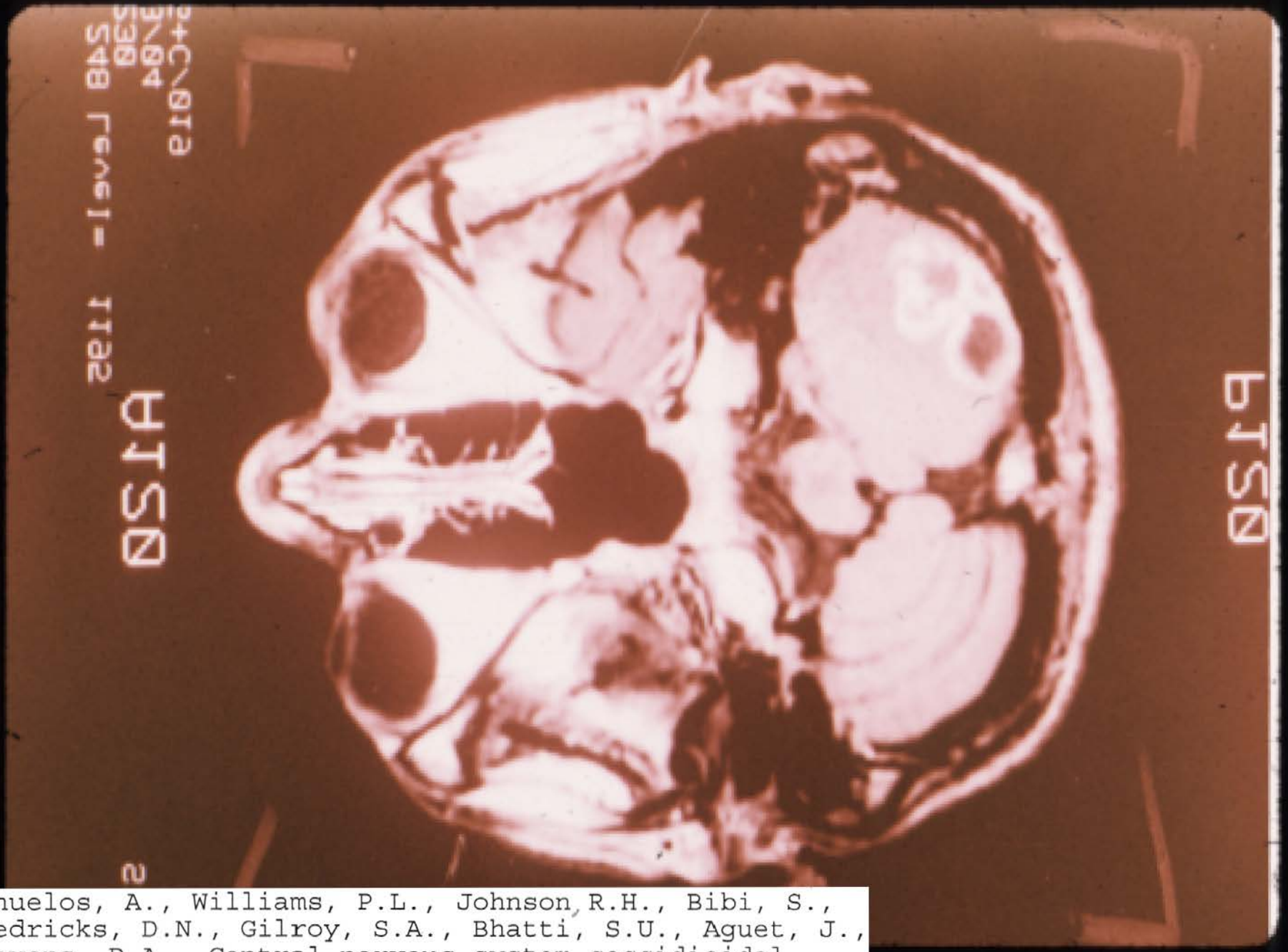
Coccy meningitis

Worst complication of coccy.

200-500 new cases of meningitis/year.

Fatal within 2 yrs. left untreated.

Even with Rx, many stroke events associated; hydrocephalus; cord compression



Banuelos, A., Williams, P.L., Johnson, R.H., Bibi, S., Fredricks, D.N., Gilroy, S.A., Bhatti, S.U., Aguet, J., Stevens, D.A. Central nervous system coccidioidal abscesses. Clin. Infect. Dis. 22:240-250

Deresinski, S.C., Stevens, D.A. Coccidioidomycosis in compromised hosts. Medicine 54:377-395. 1975.

Reviewed all cases of coccy at Stanford Univ. Hosp., from its opening.
Found 13 cases in immunocompromised hosts.

46% were disseminated (100 times rate in noncompromised)

Risk of reactivation for persons receiving immunosuppression or experiencing immunosuppressive diseases.

Viable coccy must be living in you after initial infection even after successful resolution or successful Rx

Iatrogenic Immunocompromised hosts 2020

With massive increase in transplant as Rx modality:
(Hem. stem cell, kidney, lung, liver, etc.)

+

Massive increase in use of immunosuppressives:
(Oncology, rheumatology, dermatology, etc.)

=

Huge problem in endemic areas

(Janis Blair could discuss)

HIV & coccy -epidemiology

- Active coccidioidomycosis is a common occurrence among the HIV infected living in the endemic area
  - ≈20x more common than in non-compromised patients
- A CD4 lymphocyte count <250/µL is the major risk factor for the development of disease
- Cases are mixtures of new infections and reactivation of old disease

(Neil Ampel could discuss)

Disseminated Coccy Rx

- Nonmeningeal
  - Oral azole therapy, min. 1 yr.
  - Continue Rx for at least 6 months after disease becomes inactive
  - Amphotericin B if lesions in critical locations, if worsening rapidly
  - Surgical debridement of bone sequestra; drain pus from soft tissue lesions

Scoring system for Rx trials- useful, and experience

Patients initially were scored according to culture-confirmed sites of disease (soft tissue, osteoarticular, or pulmonary), serologic titer, and extent of lesions.

Later revisions allowed for scoring symptoms and signs and lesion size or severity.

The sum of points pretreatment was the baseline score.

A successful response was considered a reduction of the baseline score by 50% or more within a set period of time.

Because coccidioidomycosis tends to improve relatively slowly, scoring was done at 3-month intervals.

The scoring system, although far from ideal, allows physicians to estimate a total body burden of disease and follow that index.

MSG/CCTG Scoring system

- Points are assigned as follows:
- (1) symptoms:
  - 1 point is given for each symptom;
- (2) examination
  - score: 2 points are given for each lesion at each site of infection
- (3) serology: 0 points if immunodiffusion complement furation (IDCF) is 1:2 or less, 1 point if IDCF is 1:4 or 1:8, 2 points if IDCF is 1:16 or 1:32, 3 points if IDCF is 1: 64 or greater
- (4) cultures: 4 points for each site from which C immitis is isolated
- All had to have score of >=4

(Tony Catanzaro will discuss trial endpoints)

Stevens, D.A., Restrepo-M., A., Cortes, A., Betancourt, J., Galgiani, J.N., Gomez, I. Paracoccidioidomycosis (South American Blastomycosis): Treatment with miconazole. Amer. J. Trop. Med. Hyg. 27:801-807, 1978.

Borelli, D., Bran, J.L., Fuentes, J., Legendre, R., Leiderman, E., Levine, H.B., Restrepo-M, A., Stevens, D.A. Ketoconazole, an oral antifungal: laboratory and clinical assessment of imidazole drugs. Postgrad. Med. J. 55:657-661, 1979.

Restrepo-M., A., Stevens, D.A., Leiderman, E., Fuentes, J., Arana, A., Angel, R., Mejia, G., Gomez, I. Ketoconazole in paracoccidioidomycosis: Efficacy of prolonged oral therapy. Mycopathol. 72:35-45, 1980.

Retrepo-M., A., Stevens, D.A.,Gomez, I., Leiderman, E., Angel, R., Fuentes, J., Arana, A., Mejia, G., Vanegas, A.C., Robledo, M. Ketoconazole: A new drug for the treatment of paracoccidioidomycosis. Rev. Infect. Dis. 2: 633-642, 1980.

Diaz, M., Negroni, R., Montero-Gei, F., Castro, L.G.M., Sampaio, S.A.P., Borelli, D., Restrepo, A., Franco, L., Bran, J.L., Arathoon, E.G., Stevens, D.A. A Panamerican five year study of fluconazole therapy of deep mycoses in the noncompromised host. Clin. Infect. Dis. 14 (Suppl. 1): S68-S76, 1992.

Castro, L.G.M., Belda, W., Cuce, L.C., Sampaio, S.A.P., Stevens, D.A. Successful treatment of sporotrichosis with oral fluconazole-a report on three cases. Brit. J. Derm. 128:352-356, 1993.

Dewsnup, D.H., Galgiani, J.N., Graybill, J.R., Diaz, M., Rendon, A., Cloud, G.A., Stevens, D.A. Is it ever safe to stop azole therapy for Coccidioides immitis meningitis? Annals Intern. Med. 124:305-310, 1996.

Stevens, D.A., Diaz, M., Negroni, R., Montero-Gei, F., Castro, L.G.M., Sampaio, S.A.P., Borelli, D., Restrepo, A., Franco, L., Bran, J.S., Arathoon, E.G., and other investigators of the Fluconazole Pan-American Study Group. Safety evaluation of chronic fluconazole therapy. Chemother. 43:371-377, 1997.

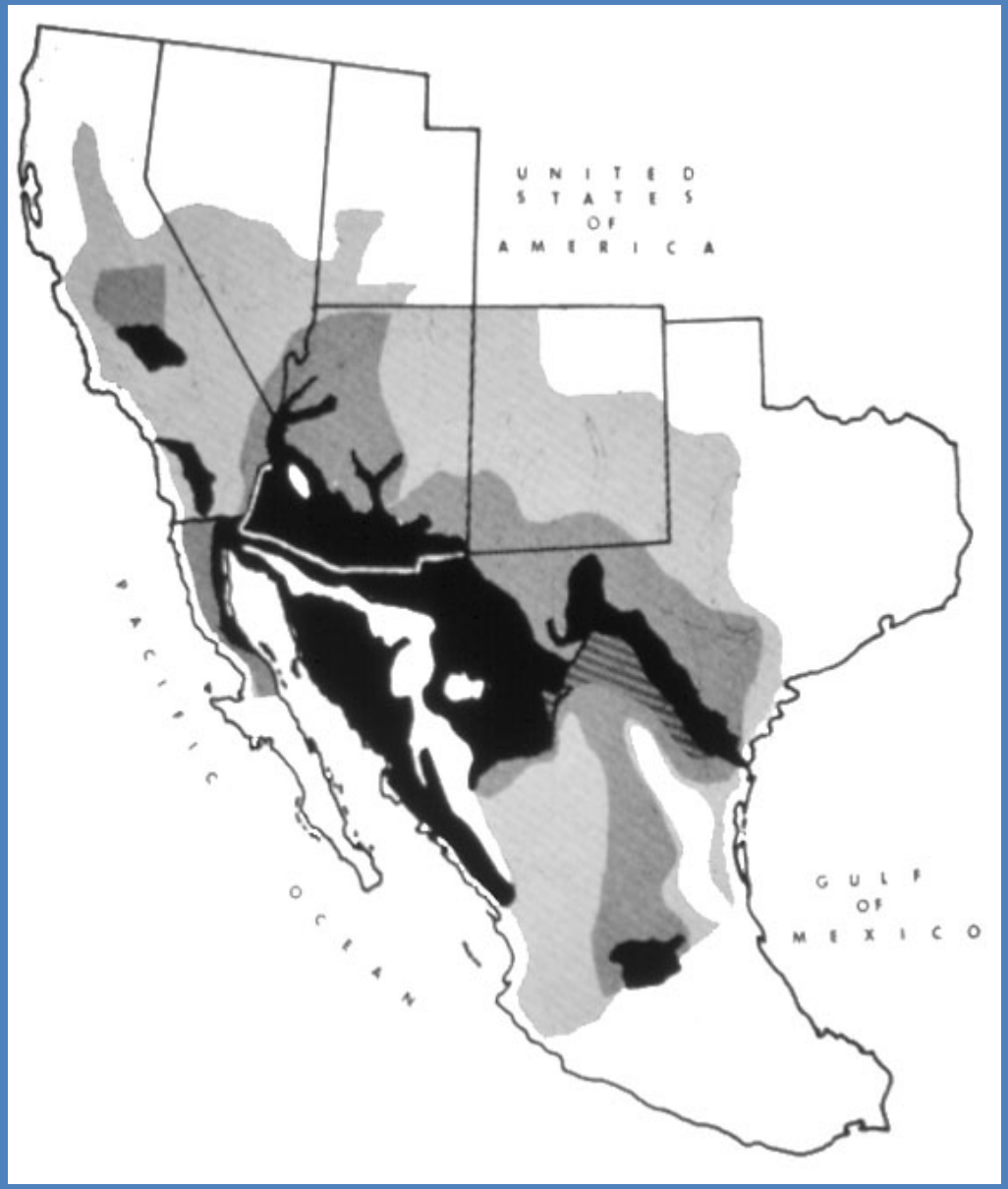
Stevens, D.A., Rendon, A., Gaona, V., Catanzaro, A., Anstead, G.M., Pedicone, L., Graybill, J.R. Posaconazole therapy for chronic refractory coccidioidomycosis. Chest 132:952-958, 2007.

Is productive collaboration in clinical trials with Latin American centers possible?

A <u>personal</u> perspective: yes!

← 9 papers

(In my opinion: direct, individual connections are key to success)



Latin American potential collaborating sites

My opinion:
Best bet= Mexico

-Number of cases
-Proximity to US
-Past hx. of success
-Ties to US investigators
Baja, Monterrey

(Rafael Laniado Laborin & Luis Ostrosky-Zeichner could discuss)

Questions?