Coccidioidomycosis

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Abstract 1: Clinical Predictors of Relapse in Coccidioidomycosis after Therapy with Fluconazole

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Relapse in active coccidioidomycosis is a common event, occuring in up to 40% of patients once therapy is stopped. In order to determine if there are clinical predictors of relapse, we examined results from a previously reported study (Mycoses Study Group #9,Catanzaro et al., Am J Med 98:249, 1995) which treated patients with chronic pulmonary or disseminated coccidioidomycosis with 200 to 400 mg ol fluconazole. In that study, 15 of 41 patients (37%) relapsed after therapy was discontinued. Age, entry score and clinical score at time of discontinuation were not significantly associated with relapse (for all, $p > 0.05$). In addition, there was no association with relapse and length of therapy, sex, race or type of coccidioidomycosis, and presence of underlying disease (for all, $p > 0.05$). P-values were closest to significance for white race and high final clinical score. Because of the small number of sublects for analysis, the power of this study was low. Future studies or different parameters will be required to determine risk factors for relapse in coccidioidomycosis.

Abstract 2: Efficacy of SCH 56592 in Murine Model of Systemic Coccidioidomycosis

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By broth dilution testing, SCH MIC and MFC of the Sil. isolate of *C. immitis* was 0.4 and 3.1, and for 4 other clinical isolates 0.4-3.1 and 1.6-3.1 mcg/ml respectively. Female CD-i mice were infected IV with 220 viable anthroconidia of Sil. Groups of 10 mice either received no treatment, methylcellulose diluent, fluconazole (FCZ) 10 or 100 mg/kg/d, itraconazole (ITZ) 10 or 100 mg/kg/d, SCH 0.5, 2, 10 or 25 mg/kg/d. Therapy began 2 d post-infection P0 QD for 19 d. Surviving mice were killed 49 d post-infection and infectious burdens determined by culture. All drugs were superior to untreated or diluent-treated controls (p<.0O1) in prolonging survival, but were not significantly different. ITZ 100 mg/kg was superior to either dose of FCZ or ITZ 10 mg/kg in reduction of CFU in the spleen, liver and lung (p<.0l-.0Ol). SCH at 0.5 mg/kg was superior to either dose of FCZ or ITZ 10 mg/kg in reduction of CFU in all 3 organs (p<.05-.OOl), but inferior to ITZ 100 mg/kg in the liver. SCH at 2 mg/kg was not significantly different than ITZ 100 mg/kg in all 3 organs. SCH at 10 and 25 mg/kg were superior to either dose of both FCZ and ITZ and to SCH 0.5 mg/kg in all 3 organs (p<.05-.OOl) and to SCH 2 mg/kg in the liver only. In terms of reduction of CFU, SCH is approx. 700-20,000-fold as potent as FCZ and approx. 50-200-fold as ITZ on a weight basis. There was a clear dose-responsive relationship with SCH in each of the organs. It is noteworthy that SCH effected cures (no detectable *C. immitis* in any organ) in 1/9, 6/10, and 9/9 surviving mice in the 2, 10, and 25 mg/kg groups respectively. Neither FCZ nor ITZ cured any survivor. SCH has potent activity against *C. immitis*.

Abstract 3: Activity of LY 303366, a Beta Glucan Synthase Inhibitior against Coccidioides immitis in vitro

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LY303366 is an echinocandin derivative which inhibits synthesis of cell wall beta glucan by action on the synthase enzyme. It was tested in vitro vs. *C. immitis* clinical isolates in their mycelial form by a broth macrodilution method, and compared to other, clinically active, anti-coccidioidal drugs. As the table below shows, LY303366 MICs = MFCs and ranged from C.8-6.3 mcg/ml. Values for current drugs are shown. *C.immitis* is susceptible to LY303366, and should be studied in vivo in coccidioidomycosis.

C. immitis	**Fluconazole**		**Amphotericin**		**Itraconazole**		**LY303366**	
	MIC	**MFC**	**MIC**	**MFC**	**MIC**	**MFC**	**MIC**	**MFC**
Silveira	6.25	>100	1.0	4.0	0.78	1.56	6.25	6.25
94 - 178	12.5	100	2.0	2.0	0.39	3.13	6.25	6.25
94 - 208	>100	>100	1.0	>8	0.20	3.13	6.25	6.25
93 - 110	6.25	>100	1.0	1.0	0.39	0.39	3.13	3.13
93 - 154	25	>100	2.0	2.0	0.78	>12.5	0.78	0.78

Abstract 4: Current Status of Nikkomycin Z in Coccidioidomycosis

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Nikkomycin Z, a fermentation product of S. tendae, is a specific inhibitor of fungal chitin synthase. Both in vitro and in mouse models of coccidioidomycosis, blastomycosis, and histoplasmosis, the results demonstrate that the compound, when given by the oral route, has marked activity relative to that seen with azoles, and compares favorably with amphotericin B. Indeed, in organ burden assays in a mouse model of coccidioidomycosis, the compound was able to sterilize the lungs of a majority of treated animals, indicating a fungicidal mechanism of action. The status of the project was reviewed, including a summary of the preclinical results, the toxicology profile, and manufacturing considerations. Possible scenarios for phase II clinical trials were presented, together with a tentative timetable for initiation of studies. It is anticipated that clinical trials will begin in coccidioidomycosis under the auspices of the NIH Mycoses Study Group early next year.

Abstract 5: Progress in the Development of a Rabbit Model of Coccidioidal Meningitis

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A Subcutaneous reservoir system(RS) was placed over the cranium of 3 to 4 kg. anesthetized, New Zealand white male rabbits (R) with the exit catheter placed into the cervical subarachnoid space at Cl-C2. After a 3-week recovery period, the RS was accessed using sterile technique by percutaneous puncture. R were inoculated with 3 different doses of arthroconidia (A). R were immunosuppressed with 2 mg~kg intramuscular injections of cortisone acetate administered the day prior to inoculation and continued daily for 3 days after inoculation. 3 R were inoculated with 2×10^1 A, 3 R were inoculated with 2×10^2 A, and 3 R inoculated with 2×10^3 A. Systemic consequences including anorexia, weight loss, lethargy, and labile temperature occurred as early as 3 days after inoculation and occasionally did not develop for 6 weeks. All R were euthanized within 6 weeks of inoculation. Systemic symptoms tended to presage neurological manifestations and tended to correlate with the severity of the subsequent histopathology (HP). Neurological sequelae included ataxia, head shaking, and episodes of falling with difficulty "righting". Temporal development of systemic and neurological consequences of inoculation tended to be somewhat more uniform in the group administered 2×10^3 A. HP studies of the brain and spinal cord demonstrated chronic basilar meningitis in 8 of the 9 R with 1 R demonstrating normal brain findings. Extension of infection into the brain (cerebritis) was identified in 5 R. Spinal cord involvement closely paralleled HP findings in the brain. Vasculitis (V) either involving the spinal cord, brain or both was identified in 4 R. Focal infarction was identified in 5 R, all of whom had V including endarteritis obliterans. The most notable areas of infraction involved the mesencephalon, thalamus, and anterior spinal cord. Severity of HP findings were not correlated with serologic response (quantitative immunodiffusion for IgG). Positive serologies were documented in 7 of 8 R tested with titers ranging from positive undiluted to 1:32. 2 instances of hydrocephalus were identified. Because of difficulty in sampling spinal fluid through the RS, additional studies are being planned which will involve blind cisternal puncture.

Abstract 6: Valley Fever in Arizona: Morbidity and Mortality

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Objective: The study was designed to provide an epidemiologic profile of valley fever in Arizona.

Methods: Morbidity data were compiled from the Arizona Department of Health Services' (ADHS) general communicable disease reporting system. Mortality data were collected from immediate cause of death data compiled from Arizona death certificates. The 1993 Arizona Hospital Discharge Database (HDDB), which documents all non-federal Arizona hospital discharges, was utilized to evaluate the ADHS reporting system. Patients were differentiated by date of birth, sex, and zip code.

Results and Conclusions: The number of valley fever cases, more commonly known as cocci, reported to ADHS remained relatively stable duiring the 1980's. However, between 1990 and 1995 the number of reported cases increased from 190 cases (5.2 per 100,000) to 635 cases (11.9). Between 1990 anl 1994, mortality related to cocci also increased from 21 deaths to 37 deaths. County specific rates showed temporal and geographic shifts over the five-year time penod (range, 1.0 to 35.2) with the highest rates in Southern Arizona. During this time period, the majority of the reported cocci cases in Arizona were among white individuals. However, race specific rates for blacks were more than two times the rates for whites. Arizona residents over the age of 60 were disproportionately affected by cocci. Specifically, during 1995, the age specific rate for individuals over the age of 60 was 39. Age specific rates for the younger age groups ranged from 2, for those individuals under the age of 19, to 26, for those individuals between 50 and 59 years of age. In 1993, 698 patients were discharged with a cocci-related ICD-9CM code in their first five discharge diagnoses. In contrast, a total of 580 cocci cases were reported to ADHS in 1993. The majority of the 698 patients (83.9%) were only hospitalized one time. In 1993, hospital costs related to cocci totaled more than 20 million dollars. The average cost per hospitalization was $23,720. The average length of stay was 10 days. The range was between one and 125 days. There were 881 diagnoses related to cocci. The majority of the diagnoses were primary, pulmonary cocci (58.8), other progressive cocci (22.9%) and cocci meningitis (6 8%). Cocci-related adissions showed a bi-phasic peak during the winter and the summer. The hospitalization rate per 100,000 was highest (42 per 100,000) for individuals 60 years of age and older. There were 73 cocci-related deaths for a case fatality rate of 10.5% for the 698 patients. The case fatality rate for cocci-related hospitalizations was highest (17%) among the 30 - 39 years of age group. A co-morbid diagnosis of HIV infection was found in 43.8% of the 73 deaths. Other co-morbid conditions in the 73 deaths included chronic lung disease and status post transplant/graft.

Abstract 7: 58 years of Coccidioidin skin testing in Kern County

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Over 17,000 skin tests given to adults and children since 1937 indicate that the rate at which people were infected bv Cocci in the Bakersfield area (the Infection Rate) dropped from over 10% per annum in the '30s-'40s to around 2 1/2% by 1980 and to less than 2% in 1995 (with a 'blip" to 3% early in the curve due to the epidemic). Judging from the student figures, the plateau came in the mid 1960's, after long increasing irrigation and cultivation made the soil less "friendly" to Cocci.

Although the number of Cocci cases rises with population growth, the likelihood of any one person here being infected is much less now than it was 60 years ago (with the exception of the '77 windstorm and 3+ years in the early '90s).

A person who had lived here for 30 years in J937 had about a 96% chance of having encoun-tered Cocci (indicated by a positive skin test). By the 1970-80's around 50% of those people would have been infected, with the number now down to about 40%. That's why many (still susceptible) long term residents got Cocci during the '91-93 epidemic.

Since it would be ideal to be able to compare such studies to each other more directly we have long encouraged using a standard form for a study done periodically in each part of the endemic area. Form will be provided on request.

Abstract 8: Economic Burden of Chronic Coccidioidomycosis

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The economic impact of acute coccidioidomycosis was recently described. Over the past five years in Kern County, California, numerous cases of chronic coccidioidomycosis have required management. The economic burden of providing care for such patients was evaluated. Forty cases were randomly selected from the referaal clinics at Kern Medical Center. Costs were determined from adjusted charges and were averaged based on disease presentation (skin, bone, CNS, or pulmonary) and treatment. Utilization of services was evaluated over three years.

Results: Eleven patients with pulmonary disease, 14 with skin or bone disease, and 15 with meningeal disease formed the study population. Year one costs totaled S1,085,000; in year two, 30 patients remained and accumulated totaled $403,000 in medical care costs; twenty-three remained in year three and incurred $299,000. Costs for pulmonary and non -meningeal disease decreased substantially in successive years. However, meningeal disease decreased by 50% between year one and year two and then remained stable in year three. Based upon the cumulative incidence of new cases in Kern County between 1991 and 1994, there were projected to be 177 chronic cases receiving management by 1995. The cost of chronic care in 1995 was estimated at 2.19 million representing 30% of the total cost of caring for patients with coccidioidomycosis in 1995.

Conclusions: The chronic nature of non meningeal and meningeal disseminated coccidioidomycosis results in an increasing burden of medical management in endemic regions. In 1995, 30% of the costs for caring for coccidioidomycosis was represented by chronic disease.

Abstract 9: Kern County Valley Fever Task Force Report on the Control of *Coccidioides immitis*

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The Following is a summary of a report given to the Kern County Board of Supervisors in August 1995. Findings of the 29 member Task Force include the following: (1) Fungus grows in small sites along foothills and in **undeveloped** (virgin) soils of the San Joaquin Valley (2) Fungus grows only in top few inches of soil (3) Extensive soil testing for the fungus is not reliable nor practical (4) Transmission of Valley Fever is primarily caused by naturally occurring winds and dust storms, secondarily by dust-creating activities on undeveloped soils, earth moving (land development), earth tilling (agriculture), mining (oil drilling), recreation (off road vehicles), home gardening (landscaping) (5) Drought conditions followed by heavy rainfall in late winter and spring months each year (1991 - 1994) caused abundant growth of ftingus in virgin soils resulting in increased human and animal infections in the Southern San Joaquin Valley (6) Land development/construction activities declined during this 1991 - 1994 epidemic period (7) Construction and agricultural activities reduce fliture risk of Valley Fever by paving over or planting on infected soil areas ("hot spots") (8) **NO** state of California policy or Cal-O.S.H.A. regulations for protection or education of workers (9) 50% of Kern County residents already immune due to previous Valley Fever infection (10) Cost of 1991-94 epidemic-$66.6 million.

Recommendations of task force: (Dust Control) (1) Monitor and enforce dust control rules and ordinances currently in place: A. Rule 8020-Regulation VIII (APCD) B. Kern County grading, land division and zoning ordinances C. Include Valley Fever in "Risk of Upset" section of Environmental Impact Reports (E.I.R.) **(Education and Protection)** (2) Public information campaigns (3) DustiMist mask use advisory for dusty' conditions and voluntary skin testing (4) Industries provide information to workers "At Risk" **(Research)** (5) Support Kern County Health Department in the following on-going Valley Fever research: A. Occupational surveys B. Skin Testing surveys C. Epidemiology studies D. Soil studies **(Vaccine Development)** (6) Support vaccine flind raising and development activities ($7-10 million): A. Elected officials B. Medical/research community C. Kern County industry D. New media E. Community-at-large.

Summary:(1) Kern County is a highly endemic area for Valley Fever. (2) Valley Fever infections are an environmental phenomenon. (3) Dust control and education may reduce infections. (4) A vaccine will produce a significant reduction in cases.

Abstract 10: Recent comparison of serologic tests for Coccidioidal antibody with emphasis on detection of "precipitin" IgM

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Since the demonstration by C.E. Smith et al of production by patients with coccidioidomycosis (CM) of precipitin (later identified as IgM) and complement fixation (CF) antibody (primarily IgG), additional serologic procedures -immunodiffusion ('D), latex agglutination (LA) and enzyme immunoassay (EIA) - have provided means of testing for coccidioidal antibodies. The recent commercial availability of the sensitive EIA has led to its use as a qualitative screening test by numerous laboratories. Kaufman et al (1995) J.C.M. 33:618) and Martin et al (Ibid 33:940) described some discrepancies between the rate of EIA positive human sera and results by ID, LA, or CF. Specimens positive by EIA at several clinical laboratories have been submitted to us for additional testing. Among these we noted that some reported positive for IgM by EIA were negative by our ID using previously (evaporatively) concentrated sera. Based on successive samples from the same 49 patients or recovery of *C. immitis*, 29(59%) were negative by ID and probably negative for coccidioidal antibody. The total number (64) of patients was small but the rate of false positive EIA for IgM exceeded that noted by Kaufman and Martin and their colleagues. Therefore, especially for sera positive onlv for IgM by EIA microbiologic or serologic confirmation of CM is essential. (Detection of Ig(i by EIA has not produced a significant disparity with ID tests.)

Recent experience in our lab indicates that sera from patients with cystic fibrosis but without evidence of CM may yield by ID a deceptive reaction resembling that given by coccidioidal IgM.

Abstract 11: Frequency of antigen-reactive cells in subjects with quiescent and active coccidioidomycosis

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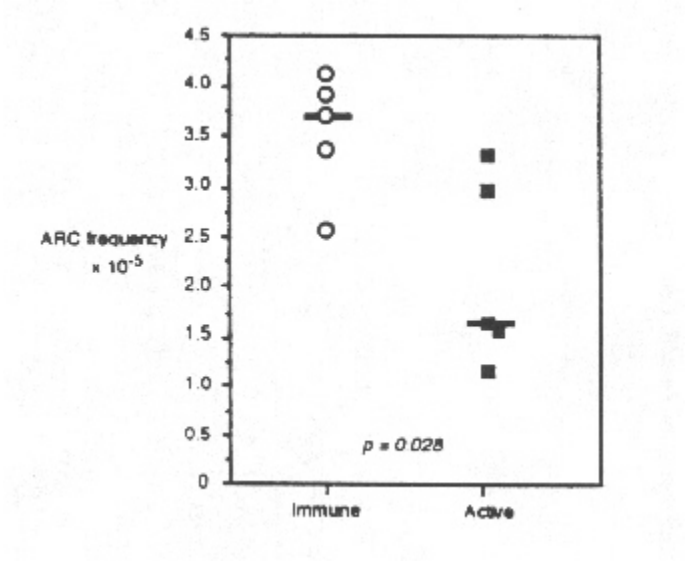
We hypothesized that patients with active coccidioidomycosis would have a lower frequency of antigen-reactive cells (fARC) in peripheral blood than healthy, asymptomatic subjects with coccidioidal delayed-type hypersensitivity (DTH). Peripheral blood mononuclear cells (PBMC) were isolated by density centrifugation. A standard lymphocyte transformation (LT) was performed. To determine fARC, a variation of LT using limiting dilution analysis (LDA) was performed comparing 5 healthy donors with coccidioidal DTH to 5 donors with active coccidioidomycosis without DTH. As shown below, there was a marked and significant difference in fARC between healthy, immune donors and donors with active coccidioidomycosis without DTH ($p < 0.03$).



When the fARC results were compared to clinical score, CF titer or absolute LT count, there were no significant associations (for al, $|r| < 0.5$, $p > 0.05$). These data indicate that fARC distinguishes patients with active coccidioidomycosis without coccidioidal DTH and healthy donors with DTH. Future studies will be needed to establish the clinical utility of this assay.

Abstract 12: Cloning and expression of the *Coccidioides immitis* complement fixation antigen-chitinase

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The characterization and production of specific antigens could enhance the effectiveness of cerain serological tests for coccidioidal antibody or antigen in body tissues and fluids. We have cloned, characterized, and expressed in *E. coli* a *C. immitis* chitinase that is the coccidioidal complement fixation (CF) antigen. A bacteriophage lambda cDNA library was screened with a chitinase specific probe and positively hybridizing clones converted into plasmid form. Cultures of *E. coli* containing the plasmid clones were induced and clones producing a functional recombinant chitinase were selected. One clone, pCTS 4-2A, was chosen for further study. Polyacrylamide gels of total protein extracts from induced cultures of pCTS 4-2A showed an approximately 48-kDa protein that was not present in uninduced cultures. When tested on immunodiffusion (ID) plates the same induced extracts produced a line of identity with the DCF antigen control and had chitinase activity. Recombinant chitinase that was purified by a chitin affinity method produced the same results and was able to function as the coccidioidal CF antigen in a conventional CF assay. To determine the temporal expression of the chitinase gene, blots of total RNA fiom various time points during spherule-endospore (SE) development and actively growing hyphae were hybridized to a probe synthesized using clone pCTS 4-2A DNA. Autoradiographs showed that RNA complementary to the chitinase probe was undetectable during early spherule development, present at high levels by 36-hr of development just prior to endospore release, and present at low levels in actively growing hyphae. These results are in good agreement with results that show the temporal appearance or presence of active chitinase and CF antigen in SE culture filtrates, extracts of developing spherules, and hyphae. The results demonstrate that a functional CF antigen can be produced in *E. coli*, used in serological diagnostic applications, and suggests a functional role for this chitinase in SE maturation.

Abstract 13: Use of a Recombinant CF Antigen in Serological Assays

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We have isolated a clone from a *Coccidioides immitis* developing cDNA library that encodes the coccidjoidal chitinase/CF antigen. The 13-galactosidase fusion protein from this clone (pCTS 4-2A) was expressed in *E. coli* and the fusion protein released by an osmotic lysis procedure. The recombinant chitinase-CF antigen was isolated from the lysate by affinity adsorption-desorption to chitin. The reactivity of 41 human sera containing coccidioidal complement fixing antibodies ranging in titer from <1:2 to >1:128 were studied using the enzyme-linked immunosorbant assay (ELISA). The reactivity of 19 sera containing no detectable coccidioidal antibodies using conventional serological methods were also studied. The mean absorbance of the negative sera was 0.061 and the standard deviation was 0.050. The absorbance of the sera contalning CF antibodies ranged from 0.118 to 2.999 and appeared to cluster into 3 groups: low positive, CF titer between <1:2 and <1:4; middle positive, CF titer between 1:4 and 1:16; and high positive, CF titer> 1:64. A cutoff value of 0.161 was calculated (mean + 2 standard deviations) to determine the sensitivity and specificity of the assay. The specificity of the assay was 100% and the sensitivity was 96.6%. Forty three of the above specimens were also evaluated using the Meridian Premier *Coccidioides* EIA. The Meridian EIA likewise demonstrated a specificity of 100%, however the sensitivity was 84.4%. These results indicate that the ELISA using the recombinant CF antigen has good potential for use in detecting coccidioidal CF antibodies.

Abstract 14: Cloning and Sequence Analysis of the cDNA for a Proline-rich Protein from *Coccidioides immitis* with Immunogenic Potential

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We have cloned and sequenced the cDNA encoding an immunoreactive protein from the pathogenic fungus *Coccidioides immitis* which stimulates human T cells and has been associated with protective vaccines in mice. The transcript contained an open reading frame encoding 194 amino acids with a calculated molecular weight of 19.5 kDa, a 151 base 5' untranslated region (UTR), and a 468 base 3' UTR. A four member repeat motif, usually thr-ala-glu-pro, exists for amino acids 98 through 141. Deduced amino acid sequence derived from the cDNA was identical with previously determined internal amino acid sequence from the native protein, and goat antiserum raised against the purified fungal protein reacted with an inducible fusion protein translated from this cDNA. Using this cDNA to produce recombinant protein will allow direct testing of its role in human immunity to coccidioidomycosis and may lead to new diagnostic tests.

Abstract 15: Outcome of Primary Pulmonary Coccidioidal Infections: Analysis of Armed Forces VA Collaborative Study Group Records, 1955-1958

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The 905 patient charts included in this collaborative study were reviewed and 199 (22%) were identified as having a primary illness defined as evidence of either a positive culture 99 (50%) or serology 166 (83%). An additionaj 99 patients (14%) presented with symptoms suggestive of coccidioidal infection. Of these patients 40 (40%) had an abnormal radiograph and 95 (96%) had a positive skin test.

Of the 199 patients with definite diagnosis 66 (33%) had a self limiting illness, 47 (24%) developed a pulmonary nodule, 30 (15%) developed a pulmonary cavity, 31 (16%) disseminated, 5 (3%) developed residual pulmonary fibrosis, and no follow-up was available for 20 (10%). The suggestive diagnosis group had 46 (46%) patients with self limiting illness, 30 (30%) with a nodule, 7 (.07%) with a cavity, 5 (.05%) with dissemination, 5 (.05%) with residual fibrosis, and 6 (.06%) whose outcome is not known.

Abstract 16: *Diabetes mellitus* (DM) and coccidioidomycosis (CM) - brief view from the serologic laboratory

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Cavitary CM was apparently first described in a publication by Farness and Mills in 1939 followed by descriptions of the entity in the 1940s by several authors. C.E. Smith et al, from data of the 1940s ancf 1950s, described cavitary coccidioidomycosis in up to 8% of all diagnosed cases of CM. Baker and Waskow in the 1960s found that 52% of 23 patients (candidates for resection of pulmonary tissue) who had DM and CM had pulmonary cavities. Among 23 patients with ruptured pulmonary CM cavities reported by Cunningham and Einstein in 1982, 2 had DM. In 1975 we presented data on 47 patients with DM and CM: 49% had pulmonary cavities, and 13% had disseminated CM. More recently, of 515 patients with DM and CM, we found that 166 (32%) had cavities and 74 (14%) had disseminated CM. (For the same period of review, we had recorded a total of 1,051 cases with cavitary CM.) The proportion of patients with DM and cavitary CM may actually he higher than 32% based on incomplete reporting of the presence of DM by physicians who submitted specimens to us. The high rate of pulmonary cavitation (and dissemination) in patients with DM and CM has important implications in their management such as whether and when to resect pulmonary tissue.

Abstract 17: Airway Obstruction due to Endobronchial *Coccidioides immitis*

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Divisions of Respiratory Medicine and Infectious Diseases, Santa Clara Valley Medical Center and Stanford University School of Medicine

A 48 year old Pakistani man came to clinic because of cough, fever and chills for 2 weeks. He had been in Bakersfield, California for 4 weeks and returned to San Jose just at the time he became ill. The patient had a porcine mitral valve replacement in Pakistan 1 year previously. He had a new left upper lobe infiltrate on chest film and was treated as an outpatient for "community-acquired" pneumonia with oral erythromycin and cephalexin for 2 weeks. The patient was admitted to hospital with a temperature of 104° F and a new right calf skin lesion. A chest film showed bilateral infiltrates. He ultimately required tracheal intubation for respiratory failure and hypoxemia. Bronchoscopy showed an endobroncial mass occluding the left upper lobe bronchus. Endobronchial biopsies were not done because of a coagulopathy, but the skin biopsy, blood cultures and endobronchial brushings grew *Coccidioides immitis*. The patient was treated with a total of 2.5 gm of intravenous amphotericin and a repeat bronchoscopy showed complete resolution of the endobronchial mass after 4 weeks of therapy. Serum HIV antibody was undetected, IgG CF titer was negative on admission, 1:8 after 6 weeks and 1:2 after 10 weeks of therapy.

A 38 year-old black woman presented with cervical lymphadenopathy which was resected and which grew *Coccidioides immitis* on culture. A chest CT scan showed a precarinal mass eroding into the airway and there were no pulmonary parenchymal infiltrates. Fiberoptic bronchoscopy showed an obstructing mass involving the lower trachea, main carina and the right mainstem bronchus. Endobronchial biopsies grew *Coccidioides immitis*. Serum CF titer was 1:128.

Laryngeal and subglottic masses and a soft tissue neck abscess with tracheal compression due to *Coccidioides immitis* have been described. There are only 2 previous case reports describing endobronchial obstruction due to *Coccidioides immitis* and both involved the right mainstem bronchus.

Abstract 18: Coccidioidal Meningitis in Fluconazole Treated Patients

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Patients have previously been described that have developed coccidioidal meningitis while taking either intravenous Amphotericin B or Ketoconazole. This paper describes four patients, ages 14, 17, 30, and 49 years that developed symptomatic coccidloidal meningitis while taking fluconazole. The HIV status of all four individuals were negative; all were males, two Caucasian and two Latino. The primary presentation of these four patients were universally respiratory with an abnormal chest x-ray. One out of four additionally had disseminated skin disease; all four patients had a negative skin test and all have a serum CF titer of ≤ 1:32. The premeningeal fluconazole course was 4OOmg given for 5 to 21 months before the onset of symptomatic central nervous system disease. Symptoms at the time of central nervous system presentation included headache in all cases, fever and sweats in two of four cases. CSF pleocytosis at CNS presentation ranged from 82-423 WBC/cmm, CSF CF titers at CNS presentation ranged from 1:8 to 1:64. CSF protein at presentation varied between 122 and 222 mg/dl.

Conclusion from analysis of these four cases would indicate the following: 1)Persistent elevated titers of CF antibodies are not benign and may progress to dissemination, 2)fluconazole 4OOmg QD does not assure protection from CNS dissemination, and 3)symptoms of CNS dissemination are similar in fluconazole treated and untreated patients.

Abstract 19: Comparative incidence and contrasting mortality of coccidioidomycosis in Arizona and Kern County California, 1989-1994

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Perusal of data kindly provided by the section on Epidemiology and Disease Control, Arizona Department of Health Services and by the Kern County-California Department of Health provided a marked contrast in the mortality rate of coccidioidomycosis in these two geographic areas. Thus, for the period 1989-1994 the mean deaths per 100 cases of coccidioidomycosis reported in Arizona was 7.5 (range 4.8 to 11.1) and in Kern County it was 0.7 (range 0.37 to 1.09).

Comparative incidence and mortality of coccidioidomycosis: Arizona and Kern County, California 1989 - 1994

Year	Population	#Cases	Rate/ 100,000	Annual Deaths	Deaths/ 100 cases
ARIZONA					
1989	3,617,300	268	7.4	25	9.3
1990	3,665,228	190	5.2	21	11.1
1991	3,767,000	286	7.6	20	7.0
1992	3,858,850	436	11.3	28	6.4
1993	3,958,875	580	14.7	28	4.8
1994	4,071,650	573	14.1	37	6.4
	Mean	389		Mean	7.5
KERN COUNTY					
1989	529,438	276	52.1	1	0.37
1990	549,600	275	50.0	3	1.09
1991	574,600	1181	205.5	10	0.85
1992	595,100	3342	561.6	25	0.75
1993	609,800	2608	427.7	10	0.38
1994	622,900	1304	209.3	10	0.77
	Mean	1498		Mean	0.70

The basis for this striking, persistent tenfold difference has not been determined but poses an interesting coccidioidal conundrum

Abstract 18: Prediction of Relapse after treatment for Coccidioidomycosis

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Relapse has been a problem in the treatment of Cocci with both amphotericin B (AMB) and the azoles. We reviewed the records of 34 patients who required therapy for Cocci between 1973 and 1993, 10 relapsed (R) and 25 did not relapse (NR) during follow-up (one patient had 2 courses of therapy). Duration of followup was a mean of 9.4 yr in R and 3.5 yr in NR. Total dose of AMB for R was a mean of 3.8g and two patients received additional ketoconazole for 17m each. Total AMB for NR was a mean of 2.1g and 5 patients received additional azoles for a mean of 15.4m. Ten NR received azoles only for a mean of 10.7m. Time to relapse was 7.3m (1-21m).

All 34 patients had a clinical response to therapy. A four-fold or greater fall in CF during therapy was seen in 7/9 (78%) of R and 17/20 (85%) NR (p =0.956). Using a nonparametric test (Wilcoxon Rank Sums), there was no significant difference between R and NR for the lowest complement fixation (CF) titer during therapy, the end of therapy CF or the peak CF. A peak CF $\geq$ 1:256 was seen in 5/10 who relapsed and 3/25 (12%) NR (p=0.048). For serial coccidioidin skin tests (SCST), 2/19 (11%) who had consecutive positive skin tests during therapy relapsed as compared to 7/14 who had negative skin tests (p=0.034). Univariate logistic regression modelling revealed an odds ratio (OR) for relapse of 8.5 (95% CI 1.4-51.5) and 7.3 (95% CI 1.3-41.4) for negative SCST and a peak CF $\geq$ 1:256, respectively. Stepwise-logistic regression determined that negative SCST and peak CF $\geq$ 1:256 were independently predictive with an OR of 5.7 (90% CI 1.1-28) and 5.4 (90% CI 1.1-27.1), respectively.

We conclude that clinical response, lowest CF, end of therapy CF, and decrease of CF $\geq$ 4 fold are not predictive of relapse. The best predictors of relapse are negative serial coccidioidin skin tests and a peak CF titer $\geq$ 1:256.

Abstract 18: The relationship of serum and cerebrospinal fluid fluconazole levels to treatment outcome in thirty cases

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During the past two years thirty cases of coccidioidal meningitis (CM) presented as part of an unprecedented epidemic. Previous fluconazole experience at Kern Medical Center and studies reviewed by others led to therapy being offered as an alternative to IV and IT Amphotericin B for CM.

The data to be discussed is an evaluation of patients treated with oral fluconazole at doses ranging from 400 to 1400 mg/day. The demographics, presenting symptoms, and laboratory findings will be summarized and an analysis of the clinical and cerebral spinal fluid parameters will be reviewed.

The relationship of serum and cerebral spinal fluid fluconazole levels to clinical and laboratory response will be presented and the therapeutic implications discussed.

Abstract 19: 54 Years of Cocci skin testing in Kern County (11,500 skin tests revisited)

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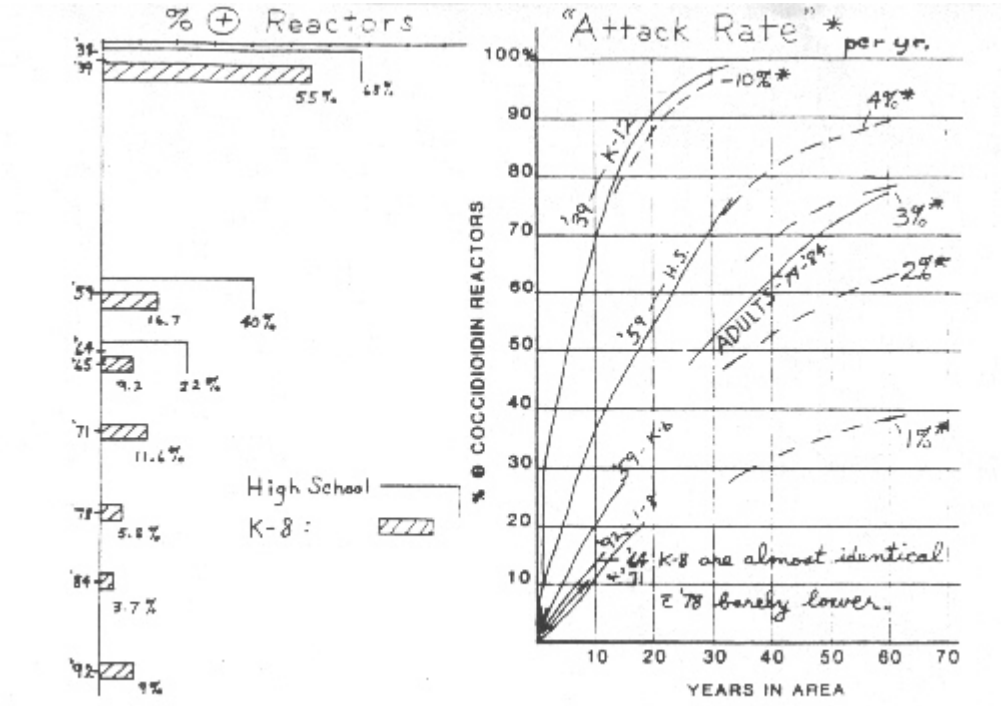
We have previously reported here ('61, '64, '79 and '86) the 50% drop in Cocci skin test reactivity in our students from '39 to '59, presumed due to major changes in irrigation and cultivation, with another 50% drop by 1965 (less well explained). It then tended lower, with a small rise in 5/92, early in the recent Cocci epidemic.

The annual attack rate (gross figures aren't much use unless you factor in how long your subjects have been exposed) had gone from about 10% in 1939 to around 1% in 1-8th graders. Adult figures have consistently shown a higher attack rate of 2-4% per annum (a rough figure) before the current epidemic. The attack rate now seems headed back toward where it was before.



Presentations of unusual cases of coccidioidomycosis competing for an annual award:

This year's competition was won by **Hans Einstein** of Bakersfield, CA for his presentation *"Feline Fungus Fells Female Friend"*. A 30 year old female veterinarian sustained a deep needle stick iniury from a syringe filled with pus just aspirated from a cat's coccidioidal arthritis. In spite of immediate institution of Fluconazole therapy, she developed fever in a miliary type infiltrate twelve days later. She made an uneventful recovery on amphotericin, no other lesions became manifest (bone scan and LP were negative).