Coccidioidomycosis

STUDY GROUP

PROCEEDINGS OF THE ANNUAL COCCIDIOIDOMYCOSIS STUDY GROUP MEETING

Meeting Number 41

April 5, 1997

San Diego, California

Published By: The Valley Fever Center for Excellence, Tucson, AZ

Editor of Proceedings: John Galgiani MD

Production Editor: Robert J. Brauer, Jr., M.A.

Appreciation is expressed for the support of the California Thoracic Society.

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Abstract 1: An Outbreak of Coccidioidomycosis in Travelers Returning from Mexico to Washington State

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Recognizing acute travel-related coccidioidomycosis (CM) in adolescents can be challenging for clinicians, particularly in non-endemic areas. In July 1996 the Washington State Department of Health was notified of a cluster of cases of influenza-like illness associated with rash in a 126-member church group, at least two-thirds of whom were adolescents. This group had recently returned from a six-day stay in Tecate, Mexico where members had participated in several construction projects. After CM was diagnosed in one member, we conducted a retrospective cohort study and skin-test survey of trip participants. All available participants had a spherulin skin test (ALK Laboratories, Berkeley, CA) applied, and read 48 hours later. Group members with positive skin tests or symptoms were serologically tested by immunodifiusion and complement fixation assays. A case-patient was defined as a church group member who had traveled to Tecate in July 1996, had a positive skin test or any symptoms after returning, and had a positive serologic test for CM.

Completed questionnaires and skin test results were obtained from 59 (47%) of 126 group members. We identified 21 case-patients, giving a minimum attack rate of 17%. Of the 21 case-patients, 95% were 14-18 years old, 71% female, 95% white, and 95% symptomatic; 86% had fever, 85% had headache, 81% had myalgias, and 67% had cough. Although uncommon in adults, 13 (62%) of these case-patients had rash; 11(85%) were female. Sixteen symptomatic case-patients saw a total of 20 health care providers - all of whom aware of the group's travel history. CM was diagnosed in only one case. On univariate analysis, persons who had helped dig a swimming pool had an increased risk of infection (relative risk =2.5; 95%Confidence Interval = 1.0 - 6.2) This investigation emphasizes the risks to non-immune person who participate in activities with high dust exposure in areas where *C. immitis* is endemic, the difference in presentation between adolescents and adults, and the difficulties physicians unfamiliar with CM have in diagnosing the disease. Travelers to areas endemic for *C. immitis,* particularly those at increased risk for disseminated disease, should be educated about the risks of such travel. Physicians should consider CM in persons returning from endemic areas with respiratory or influenza-like symptoms and should be aware that adolescents with acute CM disease are more likely to have rash than adults.

Abstract 2: Coccidioidomycosis in Arizona: Are the Elderly at Increased Risk?

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The incidence of coccidioidomycosis (CM), an airborne fungal infection endemic to the southwestern U.S., more than doubled in Arizona among persons > *65* years between 1990 and 1995 (14.9 to 35.0/100,000 pop.). The role of recent migration to Arizona in predisposing elderly residents to CM was unclear. We conducted a case-control study of risk factors for CM in persons > 60 years in Arizona. A case was defined as laboratory-confirmed clinical diagnosis of incident CM. We systematically selected cases occurring from January 1, 1996, to February 15, 1997, from state surveillance. We enrolled two control groups, the first via random-digit dialing (group 1), and the second using 1996 lists from three major Arizona laboratories of subjects with negative serologic results for CM (group 2). A total of 89 case-patients *(65%* male, 92% white, median age=73 years), and 91 group 1, and *58* group 2 controls were enrolled. The median duration of Arizona residence among case vs. control groups 1 and 2 was *6.5* vs. 19.5 and 11.0 years, respectively. Compared with control groups, case-patients spent significantly less time in Arizona ($p<0.005$ for group 1; *$p<0.05$* for group 2). Controlling for time spent in Arizona, case-patients were also more likely than group 1 controls to have histories of congestive heart failure (OR 8.3, 95% Cl 1.3 -54.7), cancer (OR 3.2, 95% CI 1.1-9.0), smoking (OR 3.7, 95% CI 1.4-9.6) or taking corticosteroids (OR 6.8, 95% CI 12-39.7). Most patients (89%) presented with upper respiratory symptoms. Elderly migrants to Arizona had increased risk of developing CM. This risk was not due to selective testing of newcomers to Arizona; risk persisted when case-patients were compared with other persons undergoing serologic testing. Underlying illnesses were independent risk factors for CM. Elderly migrants to Arizona should be made aware of the increased risk of developing CM, and should be considered for vaccination when a safe, effective vaccine becomes available.

Abstract 3: Coccidioidomycosis: Risk Factors for Severe Pulmonary and Disseminated Disease, Kern County, California

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Coccidioidomycosis (CM) has a spectrum of clinical manifestations including asymptomatic infection, self-limited flu-like illness, pneumonia, and disseminated disease. To identify risk factors for severe pulmonary and disseminated disease in adults, we conducted a case-control study among persons> 1 8years of age with laboratory-confirmed CM identified through population-based surveillance in Kern County, CA (population 624,000) between 1/1/95 and 9/30/96. Cases were defined as severe pulmonary disease (pneumonia requiring hospitalization) or disseminated disease (extrapulmonary or miliary CM). Controls were persons with CM who had mild, flu-like illness. We enrolled 380 patients identified by surveillance: 77 with severe pulmonary disease, 33 with disseminated disease, and 270 with mild disease. Independent risk factors for severe pulmonary disease included diabetes (adjusted odds ratio [OR] 2.7,95% confidence interval [CI] 1.1-6.7), smoking cigarettes in the previous 6 months (OR 2.8, CI 1.2-5.7), income <$15,000 per year (OR 1.8, CI 1.0-3.6), and older age (OR 1.04 per year, CI 1.0-1.1); oral antifungal therapy before hospitalization was protective (OR0.4,Cl 0.2-0.8).

Independent risk factors for disseminated disease were black race (OR 28, CI 2-385*),* income <$15,000 per year (OR 19, Cl 2.2-168), and pregnancy (OR 9, CII .0-79). No environmental or occupational exposures were associated with either severe pulmonary or disseminated disease. Early treatment of CM with oral antifungal agents may be appropriate to prevent severe pulmonary disease in high risk groups such as persons with diabetes and smokers. A vaccine to prevent CM would be useful for persons at high risk for severe pulmonary or disseminated CM.

Abstract 4: Epidemiology Of AIDS-Related Coccidioidomycosis in California

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Objectives: To describe the epidemiology of coccidioidomycosis in AIDS patients in California.

Methods: We reviewed AIDS cases reported to the California Department of Health Services from 1987 to August 31, 1995. We compared patients with and without coccidioidomycosis as an AIDS-defining illness by age, sex, race and ethnic group, transmission category and county of residence.

Results: Of the 58,926 AIDS patients reported during this time period, 158 (03%) had coccidioidomycosis as their first AIDS-defining illness, and 159 (03%) had it reported as a subsequent opportunistic infection. The number of AIDS patients diagnosed with coccidioidomycosis as an AIDS-defining illness rose from 3 (0.05%) in 1987 to 39 (0.6%) in 1993 (p<.001). AIDS patients presenting with coccidioidomycosis were more likely to be 30-39 years old (56% vs. 45%, p=.006) and to be intravenous drug users (18% vs. 9%, p<.00l). Non-whites were no more at risk for coccidioidomycosis than Whites. The risk of coccidioidomycosis was greatest in a four-contiguous-county area in Central California, with the highest rates in Kern (16/456,3.5%), Tulare (4/139, 2.9%), San Luis Obispo (4/181, 2.2%) and Kings (1165, 1.5%) counties. In these four counties, AIDS patients presenting with coccidioidomycosis did not differ from AIDS patients presenting with other opportunistic infections and malignancies by sex, age group, race and ethnic group and transmission category.

Conclusion: We conclude that coccidioidomycosis is a relatively rare AIDS-defining illness in California, even in areas endemic for *Coccidioides immitis.* Intravenous drug users and AIDS patients residing in the southern San Joaquin Valley are at highest risk for coccidioidomycosis.

Abstract 5: Epidemiologic Characteristics of Cocci in the Semi-desert Zones of the State of Queretaro

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As a result of the study of Dr. Gonzalez Ochoa, conducted in the early 1960's, the State of Queretaro has been considered as a non-endemic zone of coccidioidomycosis. However, this state is surrounded by three states which do have endemic areas of Cocci and the bioclimatic characteristics of the semi-desert zones of Queretaro fit the lower Sonoran Life Zone. In this study we try to identify potential areas of endemic Cocci in the State of Queretaro.

At the time of this report we had applied 225 tests with Spherulin (ALK Labs) and 225 with coccidioidin (INDRE) in 3 different communities of the State of Queretaro. We had information on and had read 182 skin tests from the total applied (0.1 ml. intradermally, read 48 hours later).

The town of	**Esperanza**	**Victoria Popular**	**Chichimequillas**
# Applied	100	75	50
# Read	76	57	49
%Positive (Spherulin or coccidioidin)	15%	19%	14%
# Positive / #read	12/76	11/57	7/49
+ to both Spherulin & coccidioidin	6	9	5
+ to only Spherulin	6	0	1
Total % + to Spherulin:	15%	16%	12%
+to only coccidioidin	0	2	1

These preliminary results indicate that there are potential endemic zones of Cocci in the state of Queretaro with positive skin tests of 14% or more in mostly life-long residents of the 3 initial areas tested.

[85 tests done since in 2 other sites showed 2% and 8% positive reactors.]

Abstract 6: MR Imaging of Coccidioidal Spondylitis

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Purpose:To characterize the MRI features of coccidioidal spondylitis.

Materials and Methods: From 1999 - 95, 9 patients with biopsy-proven coccidioidal spondylitis underwent pre- and post-contrast MRI examinations of the spine. These studies were retrospectively analyzed for sites of involvement and signal changes. Post-treatment follow-up scans were available in 5 cases.

Results: Four patients had initial involvement of a single vertebral body with sparing of the adjacent intervertebral disks; 3 of these had radiographic progression of their disease despite medical management. Three individuals had contiguous multilevel involvement. Two others had multiple skip lesions. On T1 -weighted images (T1 WI) the signal intensity of the lesion(s) was decreased in 5 patients, increased in 2 patients, and isointense in one. All lesions enhanced with Gd-DTPA. Ring-enhancing intraosseous lesions were seen in 2 cases. Six of the 9 cases had paraspinous masses. Five had epidural spread, and one had spinal cord compression. Seven had little or no evidence of disk involvement at presentation.

Conclusion: Findings suggestive of coccidioidal spondylitis include vertebral body destruction, paraspinous mass, and relative sparing of the intervertebral disk space despite involvement of the adjacent endplates. The appearance of coccidioidal spondylitis may mimic that of tuberculous spondylitis. Lesions confined to the vertebral bodies often resembled metastases.

Abstract 7: Tc-99m Sestamibi To Distinguish Cancer from Benign Pulmonary Nodules In A Population With A High Prevalence of Coccidioidomycosis

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It has been demonstrated that cancerous tissues take up more Tc-99m Sestamibi (MIBI) than noncancerous tissues. 37 patients were injected with 592-740 MBq of Tc-99m MIBI and underwent imaging prior to biopsy. Images were obtained using a dual detector, continuous, planar acquisition for 30 minutes followed by a triple detector SPECT acquisition. Both acquisitions were evaluated by a blinded experienced Nuclear Medicine physicians for a qualitative assessment of increase activity in the nodules. ROIs (Regions Of Interest) were defined in the region of the nodule and a symmetric region of the contralateral lung. The regions were defined in the anterior and posterior projections. Geometric mean (GM) corrections were applied to the ROI data. The GM ROI over the nodule was then divided bv the normal lung ROI to give the ROI ratio. An ROI ratio of> 1.3 was considered to be positive for malignancy. 17 patients had cancer on biopsy. 20 patients had nonmalignant lesions of which 14 were CM, I Nocardia and 5 benign inflammation. The table below demonstrates the results of our study.

	Visual planar	Visual SPECT	ROI ratio> 1.3
sensitivity	70%	75%	94%
specificity	80%	82%	95%

The ROI qualitative method appears to have an excellent sensitivity and specificity for distinguishing cancer from noncancerous pulmonary nodules in a population with a high prevalence of CM.

Abstract 8: The Non Invasive Differentiation Between Malignant and Non-Malignant Causes of Pulmonary Nodules Using a SSTR Binding Peptide-Technetium

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Unlike granulomatous and other non-malignant processes, many neoplasms including small cell and non-small cell lung cancers are known to express Somatostatin Type Receptors (SSTR). P829 is a unique low molecular weight somatostatin type receptor binding polypeptide. Technetium Tc-99m P829 is a peptide radiopharmaceutical under investigation for the non-invasive detection of a variety of malignancies known to express SSTS. The purpose of this study was to determine the ability of P829 scintigraphy to differentiate malignant from benign pulmonary nodules, the latter primarily resulting from granulomatous diseases, including coccidioidomycosis. Nine patients with pulmonary nodules greater than 1 cm in size underwent simultaneous Computed Tomography and P829 scintigraphy, including Single Photon Emission Computed Tomography (SPECT). The patients underwent tissue biopsy, wither transthoracic needle biopsy or thoracotomy. In five patients there was intense uptake in the pulmonary nodules seen on chest film, and all of these patients had a final diagnosis of malignancy as the etiology of the nodules. Four patients with no P829 uptake in the region of the radiographic nodules had demonstrated granulomatous changers without malignancy on tissue pathology. In eight of the nine patients, the nodules were solitary on radiographs. One patient had two adjacent nodules, both failing to take P829 and demonstrated necrotizing granulomatous inflammation on biopsy of one of the nodules. One additional patient with a non-diagnostic needle biopsy and with no P829 uptake remains clinically and radiographically stable at 4 months of follow-up. It is hoped that with larger series confirming this initial experience, P829 scintigraphy will prove to be a valuable, non-invasive technique for the differentiation of granulomatous and malignant causes for pulmonary nodules.

Abstract 9: Therapy of Coccidioidal Meningitis in the 90's

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Initial treatment of newly diagnosed coccidioidal meningitis July 1991 to January 1997 included 78 patients. Four received intrathecal amphotericin B, 16 received Fluconazole 400mg (Flu400), 28 received Fluconazole $\geq$800mg (Flu$\geq$800), 30 additional patients received Fluconazole with dose variations making these unevaluable. Sex distribution in all treatment groups was approximately 2/3 male and mean ages of all treatment groups were in the mid 30's. There was a modest preponderance of caucasians in the Flu4OO, where as Latinos were most numerous in the Flu $\geq$ 800 and the nonevaluable Fluconazole group. The Flu $\geq$ 800 group had approximately 50% skin test positivity during the first 90 days of illness as compared to a minority in the Flu400 and Flu nonevaluable group. In all Fluconazole treated patients (n=74), there were 18 deaths. 14 of these deaths occurred at $\leq$ 90 days. Response to therapy was measured with the NIAID MSG meningitis score system. 31% were responders, 69% nonresponders in the Flu400. In the Flu $\geq$ 800, 75% were responders and 25% nonresponders.

Conclusion: Fluconazole $\geq$800mg in medication compliant patients appears to be more efficacious than Fluconazole 400mg in the improvement of clinical and cerebrospinal fluid parameters as measured by the NIAID MSG score. Initial therapy of coccidioidal meningitis in the 90's is either high dose Fluconazole or intrathecal amphotericin B.

Abstract 10: A Rabbit Model of Coccidioidal Meningitis

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We used a blind cisternal tap technique for entering the subarachnoid space (SAS) of the anesthetized rabbit (R) for purposes of inoculating arthroconidia of *C. immitis* (c.i.) And for purposes of sampling cerebrospinal fluid (CSF) during the course of infection. We were successful in 100% of R (7) in allowing for a successful inoculation of 4 x $l0^3$ and 1 x 10^6 arthroconidia. In all R (4) given 4 x $l0^3$ arthroconidia, serial sampling of CSF could be accomplished with demonstration of marked pleocytosis, lowering of CSF glucose, and increased CSF protein. CSF sampling of R given 1 x 10^6 arthroconidia could not be accomplished due to severe inflammation within the SAS with a resultant obscuring of the SAS. All R demonstrated illness, histopathologic evidence of subacute or chronic coccidioidal meningitis (CM) and significant growth of c.i. on quantitative fungal brain and spinal cord cultures. No c.i. was recovered from the CSF implying attachment of c.i. to receptor sites within the central nervous system, comparable to what is observed in humans. All R inoculated with 1 x 10^6 arthroconidia developed significant neurological abnormalities. Histopathologic studies demonstrated changes comparable with human histopathologic studies of fatal CM including frequent cerebritis and, less commonly, infarction involving both brain and spinal cord. Serologic response (serum) when present, was minimal. The current rabbit model of CM will allow the study of the pathogenesis of CM as well as allowing for study of novel antifungal therapies.

Abstract 11: Assessment of the Pharmacokinetics, Safety and Efficacy of Nikkomycin Z in Chimpanzees with Naturally-Acquired Coccidioidomycosis

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Nikkomycin Z is an antifungal drug produced by Streptomyces which competitively inhibits chitin synthetase in the fungal cell wall. Two juvenile chimpanzees at the Primate Foundation of Arizona were chosen to participate in this study. There were 3 phases:

Phase I: This phase was designed to determine the appropriate oral dose level of Nikkomycin Z. Incremental increases in dosage (15, 30, 60 and 90 mg/kg) were given once daily for 7 days. Both chimps showed no changes in CBC and chemistry panels and remained clinically normal throughout this phase. The Nikkomycin Z was well absorbed and as expected, levels were greater as the dose increased.

Phase 2: This phase allowed determination of drug blood levels and half-life. Blood samples were taken at varying times from 0.5 hour to 24 hours after the drug was administered. Both chimps achieved drug blood levels within the fungicidal range of 1000-4000 ng/ml. The first chimp peaked at 3500 ng/ml (with a half life for elimination of 1.5 hours) and the second at 2000 nglml (with a half life of 1.8 hour.) For both chimps, the plasma levels of Nikkomycin Z returned to nearly zero by 24 hours post dosing suggesting little accumulation of the drug from day to day.

Phase 3: This phase involved dosing at 2 levels - 33 mg/kg and 100 mg/kg TID. At the low dose, plasma levels stayed within the fungicidal range for most of the day and returned to near zero by 24 hours post-dosing. With the high dose, plasma levels also stayed within the fungicidal range for most of the day but a residual level (>6OOngIml) was seen at 24 hours post dosing. Net accumulation of the drug was apparent at both the third dosing and at the 24 hour sample. Since there was no accumulation seen with the low dose, this suggests that the rate of uptake of Nikkomycin Z saturates somewhere between 33 and 100 mg/kg.

Abstract 12: Results of Human Phase Ia Trial with Nikkomycin Z

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In a randomized, open, placebo-controlled, single rising dose study, the safety and tolerability of nikkomycin Z was evaluated over a dose range of 250-2,000 mg in a human study. The drug was studied in 2 groups of 6 male subjects at dose levels of 250, 500, 1000, 1500, 1750 and 2000 mg and placebo. Nlkkomycin Z was well tolerated at the dose levels studied, up to 2000 mg. All 12 subjects recruited completed the study. The majority of adverse events reported during this study were those that could be expected over the course of a 6 week study, such as URTI, migraine and toothache which occur with frequency in the community. Only three adverse events were classified as possibly drug related; i.e., abnormal LFTs, one headache and one episode of lightheadedness. There was no evidence of any dose-related trend in adverse event reporting. All the physiological measurements and safety blood and urine parameters were considered to be within clinically acceptable limits and no trends were identified. Plasma samples assayed for PK revealed that the drug is absorbed, with the 1750 mg dose resulting in a Cmax of 6.2 ug/ml by 4 h, with a $T_{1/2}$ of 2.2h.

Results from a rat balance study revealed that the drug is rapidly and essentially completely eliminated via the renal route.

Abstract 13: Preliminary Study of a Glucan Synthase Inhibitor (LY 303366) and a Chitin Synthase Inhibitor (Nikkomycin Z) for Inhibition and Killing of *C. immitis*

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***C. immitis* isolate Silveira, mycelial form:**

Nikkomycin Z MIC 800, MFC >800 mcg/ml

LY303366 MIC 12.5, MFC 12.5 mcg/ml

Interaction: FIC index 0.008

Powerful synergy, e.g., no growth in 0.05 LY if 3.13 NZ present.

No potentiation of LY killing.

***C. immitis*, Silveira, parasitic form:**

Nikkomycin Z MIC 0.78, MFC 0.78 mcg/ml

LY303366 MIC ≥25 MFC, ≥25 mcg/ml

NB: 1000-fold NZ susceptibility for parasitic, >1000 fold for killing LY increased.

Interaction: FIC index <0.129

FFC index <0.129

Strong synergy, extends to killing.

Abstract 14: Enzymes of *Coccidioides immitis*

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Enzymes are of significance in various aspects of the biology of *C. immittis* including morphologic development, host-fungus interactions and potential or demonstrated targets for antifungal therapy. In some instances both hyphal (H) and spherule/endospore (SE) phases appear to share some enzymes though some differences are demonstrable. The Embden-Meyerhof glycolvtic enzvmes are present in both, but the SE phase can produce from glucose ethanol and $C0_2$ scarcely produced by H cells. Enzymes of the pentose-phosphate shunt are present. Absence of -oxoglutarate dehydrogenase of the Krebs cycle is offset by presence of isocitrate lvase and malate svnthase providing a glyoxylate bypass, absent from the mammalian host and thus a potential target for antifungal therapy.

Chitin and glucan svnthases and chitinases and glucanases acting on cell wall polysaccharides, participate in synthesis and breakdown of cell walls. The synthases are targets for nikkomycin Z and echinocandin-like antifungal agents. Chitinase is the antigen eliciting an IgG (complement fixing) antibody response and, perhaps complexed with antigen, an inflammatory response. (A second chitinase has been inferred from genetic studies.) Proteases e.g. elastase and collagenase may contribute to the pathogenesis by acting on host tissues or on leukocytic enzymes, or to shaping/reshaping of fungal cells directly or by influencing enzymes such as chitinase. Miscellaneous enzymes include catalase (possibly protective to fungus), alkaline phosphatase (role unknown), a T-cell stimulant (inferred to be 4-OH phenylpyruvate dioxygenase), and arginase (inferred) which can contribute urea for urease with possible role in alkalinizing and thus reducing effectiveness of the usually acidic phagocytic vacuole.

These and other enzymes are or may be useful in the diagnosis, prevention, or improved management of coccidioidomycosis.

Abstract 15: Molecular Population Genetics of the Pathogenic Fungus, *Coccidioides immitis*: Recombination, Distinct Populations, and Cryptic Speciation

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Understanding the reproductive mode (clonal or recombining), and the population structure of fungi is important to studies of their identification, molecular development, epidemiology, and control. With the ascomycete pathogen, *Coccidioides immitis*, we used phylogenetic and population genetic analysis of 14 loci (defined as base substitutions or small length mutations in usually arbitrary DNA), to show that Arizona *C. immitis* recombine in nature. Using 11 of these loci and population genetic analysis (Wright's Fst), we now show that gene flow among *C.immitis* from Arizona, California and Texas is significantly reduced, particularly to and from California. Subsequent analysis of ca. 2400 nucleotides from parts of five genes in 17 widespread *C.immitis* confirms recombination among *C.immitis* individuals in-California and out-of-California, and demonstrates genetic isolation of the two groups over an estimated 8 myr. Eight fixed nucleotide differences between the groups facilitate group-specific identification and make it desirable to include representatives of both groups (species?) in efforts to control this fungus by drugs or vaccines.

Abstract 16: DNA Vaccination of Mice to Immunize against *Coccidioides immitis*

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Life-long immunity follows most coccidioidal infections and vaccination with killed spherule vaccine protects mice from later infection. Indirect evidence implicates a proline-rich antigen (PRA) as a stimulus of cellular immunity. To study this directly, a 597 bp PCR amplimer encoding PRA was inserted into plasmid vectors VRIOI2 and VR1020 (Vical, San Diego CA). DNA sequencing verified orientation and reading frame. Female Swiss-Webster mice, 6-8 weeks old, received 100 ug i.m. of plasmid DNA. ELISA with recombinant PRA was used to detect a humoral response. After a single vaccination with either vector, PRA-specific IgO was detected by 2 wks (mean$\pm$SEM OD of 0.347$\pm$0.038 versus 0.128$\pm$0.004 for vector control mice, serum diluted 1:320, $p<0.004$). Antibodies were elevated for over 2 months. Vaccination repeated at 4 wks boosted IgG levels in 6 of 7 mice studied. In a preliminary study of intranasal *C. immitis* infection, 8 surviving mice had higher preinfection IgG levels in serum diluted 1:640(0.939$\pm$0.162) as compared to 4 mice who died before day 21(0.494$\pm$0.167). DNA vaccination will be a useful tool for studies of coccidioidal immunity.

Abstract 17: Expression of a Proline Rich Antigen (PRA) from *Coccidioides immitis* as a Potential Immunodiagnostic Reagent

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Previous work has demonstrated diagnostic and prognostic value in detecting antibodies against PRA isolated from spherules of *C. immitis* in the serum and CSF of patients with coccidioidomycosis. We have sub-cloned the cDNA encoding this 19.5 kDa protein into pET32 (pPRA.BI 5) and expressed it in *E. coli* at high levels as a thioredoxin fusion protein. Immunoblots of induced cell lysates consistently showed two immunoreactive protein bands, which appeared to differ by 4-5 kDa on SDS-PAGE. After removal of the fusion partner, the 12 N-terminal amino acids of the two proteins were identical by Edman degradation. Two [35S]-labeled protein bands also resulted following *in vitro* transcription / translation using rabbit reticulocyte lysate with either pPRA.B15 or a pBluescript-derived plasmid as template. In a direct ELISA, we compared the ability of a goat antibody previously raised against native PRA to recognize 30 ng native or 30 ng rPRA, and found the lgG responses at a dilution of 1:1280 to be essentially equivalent (OD0.7). lgG from a pool of human patient serum also recognized both antigens equally well at a dilution of 1:1280 (ODl.8), and lgG binding to rPRA was evident in a pool of human patient CSF. Preimmune goat antiserum binding was undetectable at 1:80. Primers have been constructed which produce PCR amplimers encoding four overlapping peptides spanning PRA. Expressed in a fashion similar to the whole protein, these peptides will be used to map immunodominant regions. The availability of rPRA may allow development of laboratory aids to the management of coccidioidomycosis.

Abstract 18: Historical Outcome of Primary Coccidioidal Pneumonia

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The VA-ARMED FORCES Cooperative Study Group abstracted case records from 905 patients with coccidiodomycosis from 1955-1958, prior to effective antifungal therapy. An initial review identified 172 patients with complete records of primary coccidioidal infection (a respiratory illness with either *Coccidjoides immiris* recovered in culture or the presence of coccidioidal antibodies in sera). All but 3 patients were male, reflecting a military population. Age at onset ranged from 1 8 to 81 years (median 34). Racial distribution was: 62% Caucasian, 18% African American, 10% Filipino, 9% Hispanic, and 2% other. Frequent symptoms included fever 80%, cough 69%, chest pain 68%, sputum production 32%, malaise 32%, weight loss 29%,and chills 29%. Initial chest radiograph (CXR) revealed infiltrate 85%, adenopathy 23%, both infiltrate and adenopathy 20%, pleural effusion 12%, cavity 9%, nodule 2% and normal 1%. Spread beyond the chest occurred in 18.5%, an unusually high rate compared to published studies. Follow-up CXRs were available for 92% of patients and outcomes were: completely resolved 27%, cavities 1 8%, residual nodule or fibrosis 28%, active but improving 22%, or disease progression 5%. Diabetes mellitus was present in 3% of the patients with primary coccidioidal pneumonia and only one of these patients developed cavitary disease. Since prior studies indicated only an 8% incidence of cavity formation in male college students, our higher incidence may reflect an age dependent or acquired susceptibility to pulmonary complications. We conclude that older individuals appear to have a greater susceptibility to both pulmonary and extrapulmonary complications following a coccidioidal pneumonia

Abstract 19: Hypercalcemia and Coccidioidomycosis

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Hypercalcemia has been described in various granulomatous diseases such as sarcoidosis, tuberculosis and occasionally in disseminated coccidioidomycosis. In sarcoidosis. the best studied granulomatous disease associated with hypercalcetnia, the pathogenesis of hypercalcemia is felt to be related to increased 1-alpha hydroxylase activity in activated macrophages. This mechanism has been adapted to account for hypercalcemia in other granulomatous disorders. In the previous literature, evaluating hypercalcemia in coccidioidomycosis when 1.25 dihydroxy Vitamin D was measured. the vatues were low contrary to what would have been expected.

To help clarify this clinical problem, we retrospectively evaluated 13 patients who presented with progressive coccidioidomycosis and had concomitant hypercalcemia. These patients represented approximately 20% of the patients who were referred to our specialists for severe diseases. All patients had hypercalcemia greater than 10.5mg/dl on 3 or more occasions. Mean serum calcium was 12.7 mg/dl. The median duration of coccidioidomycosis was 4 months, and the mean complement fixation titer was 1:256. Immobility was a factor in 46% of the patients as was bone disease. Serum 1.25 dihydroxy Vitamin I) was in the normal range or low in 7 patients in whom it was measured. 25 hydroxy Vitamin D was normal or low in 7 of 8 patients in whom it was measured, and the parathyroid hormone was in the normal range or depressed in ~ patients.

In 3 patients in whom pharmacologic therapy was indicated treatment with etidronate (1 patient) or pamidronate (2 patients) was instituted. Patients treated with either 30 mg or 80 mg of pamidronate had satisfactory reversal of hypercalcemia within one week after treatment.

Conclusion: In disseminated cases of coccidioidomycosis, hypercalcemia may occur in up to 20% of patients. Hypercalcemia can range from mild to severe, and unlike sarcoidosis was not associated with elevated 1.25 dihydroxy Vitamin D. Reversal of hypercalcemia occurred with pamidronate and antifungal therapy. Immobilization and bone dissemination were inadequate explanations for hypercalcemia. Hypercalcemia in coccidioidomycosis is mediated by an unknown process that appears to activate osteoclasts.

Abstract 20: Coccidioidal Arachnoiditis

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PN	**ZK**	**DR**	**RE**	**MW**	**MP**	**MR**	**DP**	**PA**	**OB**	**JO**
35, M, L	28, F, C	17, M, C	32, M, C	50, M, C	19, M, L	44, M, L	54, M, C	39, M, L	23, M, C	32, M, C
M 93 A 96	M 92 A 94	M 93 A 93	M 93 A 96	M 95 A 95	M 92 A 94	M 93 A 94	M 92 A 93	M 93 A 94	M 93 A 96	M 92 A 96
sciatica, neuro- bladder	backpain R legpain radiation	backpain groin p b weak sciatica	neck pain	disorient Ha	back ache weak	back ache, Ha	back ache, sciatica, vertigo	leg weak ataxia	R leg pain	back ache
Cistern C_5	A C_4, T_8 T_{12}	A L_4, S_1	Smfocus A C_2 L hemi paresis aphasia	AC_{2-3},L_{4-5} block $T_{11,12}$ w/prog. A to L_1	MR enhance ment L_4-S_2	T_1-S_1	T_1-L_5	C_1-C_3 with stenosis	T_{12}-L_{4-5}	T5-S1
flu 1.0 hylase 3X	intracist intra vent AB	ICIL cist om.AB, VPshunt itra 0.4	flu 0.8 VP shunt	Cist om. flu 1.2 VP shunt hylas 10	flu 1.0, AB IT x2	VP shunt, flu 1.0	om.39, flu 1.0, Cist AB	C1 lamin- ectomy	flu 1.0- 1.6, Cist AB 3 mos	VP shunt
ommaya improve	remission	full time student, no pain, neuro bladder	death 8/96 mul infarcts 2 to CM & arteritis	flu 0.2, ha neuro bladder, sp para- paresis backpain	active dz functional w/ back pain, flu 1.0	active dz flu 1.0	active dz flu 0.8	active dz flu 1.0 walker	?active dz no f/u 4m flu 1.6	active dz back ache flu 0.8

1. Coccidioidal arachnoditis is a syndrome of coccidioidal meningitis, perhaps related to longer survival.
2. Cocci arachnoditis appears unrelated to intrathecal treatment.
3. Treatment should be for the basic meningitis.
4. Surgery does not appear helpful.
5. Coccidioidal arachnoditis may be self limited in some cases.

A (arachnoditis)	CM (coccidioidal meningitis)
S (sex)	R (race)
ha (headache)	om (ommaya)
IT (intrathecal)	AB (amphoB)
L (Latino)	C (Caucasian)