Coccidioidomycosis

STUDY GROUP

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Abstract 1: THE 25 YEAR COMMEMORATION OF THE COCCIDIOIDO-MYCOSIS STUDY GROUP

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Shortly after streptomycin was discovered, the first large scale Cooperative Study Group was initiated under Barnwell's leadership to determine its value in TB. The Group included the VA and Armed Forces hospitals and clinics. Not only was therapy evaluated, but other facets such as resistant organisms, sputum-negative cavities, and epidemiology and immunology. Despite the faults of large cooperative researches, they are extremely valuable; and we learned that the evaluation of small numbers of cases by various hospitals could add much to our knowledge and enable us to develop better clinical research. We learned that large studies required: Proper protocols, adequate numbers of cases, diverse geographic distribution to include the varying characteristics of both the disease and the observer. In 1955, Gold and his associate's isolated Amphotericin B, and a number of us felt that it was an ideal time to evaluate the hopeful beginning of a series of specific drugs for coccy and, in addition, to learn about other aspects of the disease. We in the VA and Armed Services started a Cooperative Coccidioidomycosis Study Group. This group, with its conferences, meetings and research studies, added much to our knowledge of the pathogenesis, mycology and clinical aspects of the disease. The Group was centralized at the San Fernando VAH, but the earthquake of 1971 not only destroyed the hospital, but almost destroyed the group. Fortunately, many came to the rescue and we have again viable group.

Where do we go from here? Fortunately, the past few years have produced such developments as: New immunological studies, the spherulin skin test, vaccine, and new antibiotics, such as miconazole and ketoconazole. What we need now is a return to our original intent and start a Cooperative Research Group!

Abstract 2: COCCIDIOIDES IMMITIS IN URINE CULTURES

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Coccidioiduria (Cu+) has been infrequently reported and its significance is uncertain. Since 1972, 19 patients have had Cu+ at the Tucson VAMC. From 1976, 74 patients had C. immitis cultured from any site, 28 had urine; cultured for C. immitis, and 6 (21%) had Cu+. Patients whose urines were cultured were more seriously infected than those not cultured (immunocompromised, 26 vs. 7%; disseminated, 25 vs. 9%; treated, 51 vs. 34%), but no difference was found between Cu+ and Cu- patients with regard to extent of disease, treatment, or culture. Four Cu+ patients had no other findings of extrathoracic spread. Of these, 2 (1 renal transplant recipient, the other with Crohn's disease, receiving prednisone) resolved their disease without treatment. Another patient demonstrated variability in CFU/culture prior to treatment; treatment with ketoconazole reduced CFU/ culture but counts increased after treatment were withdrawn. Of 14 patients with Cu+ quantitated, 5 of 8 with progressive disseminated disease had >10 CFU/specimen; 6 with pulmonary or self limited disease had <5 CFU/specimen.

We conclude: 1) Cu+ is common; 2) repeated culturing improves yield of Cu+; 3) Cu+ can resolve spontaneously without treatment; 4) when associated with progressive infection Cu+ can respond to systemic antifungal agents such as oral ketoconazole; 5) Quantitation of positive cultures may help identify those in need of treatment.

Abstract 3: FLEXIBLE FIBEROPTIC BRONCHOSCOPY FOR DIAGNOSING PULMONARY COCCIDIOIDOIMYCOSIS

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To assess the diagnostic yield of flexible fiberoptic bronchoscopy (ffb), we reviewed records of 30 patients having 1) microbiologic and/or histologic evidence of coccidioidomycosis; 2) abnormal chest roentgenograms; and 3) undergone 40 ffb examinations. Evaluation involved sputum collection followed by ffb. Needle aspiration or thoracotomy was performed if ffb was nondiagnostic.

Diagnosis resulted from: prebronchoscopy sputum 20% (6/30); bronchoscopy specimens 33% (10/30); needle aspirate specimens 3% (1/30); Thoracotomy specimens 33% (10/30); and extrathoracic specimens 10% (3/30). All 8 patients with a solitary pulmonary nodule (SPN) had nondiagnostic ffb, and comprised the majority of patients requiring thoracotomy.

Excluding patients with SPN, 69% (20/29) of ffb procedures provided microbiologic or microscopic evidence of coccidioidomycosis. Sixteen percent (7/44) of prebronchoscopy sputum collections compared to 59% (17/29) of ffb procedures produced C. immitis cultures. Seven percent (1/14) of prebronchoscopy sputum smears and biopsies from 28% (8/29) of ffb procedures provided microscopic evidence of coccidioidomycosis. Ffb uncovered coexisting pulmonary pathology in four patients.

Airway findings associated with + C. immitis specimens were either acute inflammation in the area of chest roentgenogram abnormality or small submucosal or granular changes of the bronchial mucosa.

Ffb is a valuable procedure for documenting pulmonary coccidioidomycosis when sputum specimens are nondiagnostic except in patients with SPN.

Abstract 4: ENDOGENOUS COCCIDIOIDAL ENDOPHTHALMITIS

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Coccidioidomycosis is generally a self-limited respiratory illness. The literature indicates ocular involvement is rare, usually confined to the anterior segment and adnexa. Ten consecutive patients with chronic pulmonary and disseminated disease referred for chemotherapy represent the first prospective study of ocular involvement. Four demonstrated presumed coccidioidal dissemination to the posterior segment without significant vitreous or anterior segment involvement. Juxtapapillary choroiditis was seen in three, including one who demonstrated retinal infiltrates, telangiectatic capillary change, and macular edema on fluorescein angiography. Another developed a coccidioidal lid granuloma. Correlation between intraocular involvement and systemic outcome was poor. Systemic amphotericin B appeared more effective than miconazole for intraocular disease in two patients. Intraocular involvement in progressive coccidioidomycosi appears more common than previously reported.

Abstract 5: INCIDENCE AND RISK FACTORS FOR DISSEMINATED COCCIDIOIDOMYCOSIS IN RENAL TRANSPLANT RECIPIENTS

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Renal transplantation increases the risk of extra thoracic spread of a coccidioidal infection. We reviewed the records of 260 transplant recipients to assess the incidence of symptomatic infection and dissemination after renal replacement while residing in Arizona. Also, those with and without dissemination were compared for the following characteristics: sex, ethnic background, presence of pretransplant diabetes mellitus, ABO blood group and HLA type (1977 WHO classification). In addition to tabulating this data, infection rates were statistically compared for the different groups over time with respect to each characteristic.

Eighteen patients developed symptomatic coccidioidal infection, of which 12 had progressive dissemination. Time at risk was greater than 8 years in some patients but no infection was detected after 4 years:

Year of risk	1	2	3	4	>4
% Incidence of dissem	4	2	2	1	0

No increased risk of dissemination was observed in non-Caucasians (8/181 Cauc.; 2/62 Mex.-Am.; 2/37 other), diabetics (2/24 with; 10/126 without) or those with either HLA-type A9 or B5. However, 11 of 164 males disseminated compared to 1 of 96 females ($p<.05$). Also B blood group antigen (either alone or as AB) was more prevalent ($p<.05$) in disseminators:

	O	A	B	AB
Dissemination	.25	.33	.25	17
No dissemination	.50	.39	.08.	.03

We conclude that the incidence of severe coccidioidal infection is greatest in the first year of risk and appears increased in males and those with either B or AB blood groups.

Abstract 6: PULMONARY CAVITIES DUE TO COCCIDIOIDOMYCOSIS WITH SPONTANEOUS RUPTURE

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Hans Einstein, M. D.
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This is a review of 22 patients that have had a spontaneous rupture of a Coccidioidomycosis cavity. Statistical information is included along with a discussion of medical and surgical treatment.

The ages varied from 11 to 47 years, with 16 male and 6 females. There were 18 Caucasians, 2 Chicanos and 2 Orientals. Sixteen of the patients did not know they had a coccidioidomycosis infection until the cavity ruptured. A large percentage had negative skin tests, although serology titers were elevated in all 22 cases. Positive culture of the pleural fluid was present in 20 of the 22 patients.

Surgical treatment included 7 lobectomies, 12 sublobectomy resections, one pneumonectomy and two patients did not have surgical treatment. There were 16 requiring some degree of decortication. Ten patients were treated with Amphotericin B. There were no deaths.

All patients should be operated upon as soon as possible. Causes for delay are listed. The extent of surgical resection is limited due to the contaminated pleural space. Also listed are indications for Amphotericin B therapy.

Abstract 7: KETOCONAZOLE IN EARLY AND LATE MURINE COCCIDIOIDOMYCOSIS

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Ketoconazole (KTZ) (35 mg/kg) was administered po to mice BID beginning at different intervals after infecting them intranasally with arthrospores of C. immitis. When treatment was begun on the 4th day, before extensive extrapulmonary dissemination had occurred, the drug preserved life in all animals and prevented extension of pulmonary disease from lungs to livers, spleens and kidneys. There was 90% mortality in the controls. Lung lesions, however, were not rendered free of the fungus after 21 days KTZ in most animals. The initiation of treatment on the 12th day of the infection, as a picture of moribundity began to emerge in the group, was again life-preserving. However, lesions of peritoneal organs in 30-60% of the surviving animals and pulmonary lesions in approximately 90% of the group harbored viable fungi after an 82 day treatment course. Comparable prevention of death among survivors of a challenging dose lethal to 28% of animals within 30 days was shown by beginning treatment on the 35th day and ending it on the 120th day after infection.

The data above, in conjunction with earlier findings, indicate that the strong antifungal attributes of the drug in vitro also operate in vivo. When infections were treated early, results were optimal for biological cure. Once the fungus became entrenched in lesions of the peritoneal organs or the lungs, its eradication became difficult, possibly the result of restricted access of the drug to organisms within focal cellular infiltrates.

Abstract 8: THERAPY OF DISSEMINATED OR PULMONARY COCCIDIOIDOMYCOSIS WITH KETOCONAZOLE

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Oral therapy with ketoconazole for active disseminated or progressive pulmonary coccidioidomycosis was evaluated according to defined criteria of objective improvement for 39 patients, most of whom had received other antifungal chemotherapy. Minimal inhibitory concentrations of ketoconazole for isolates of Coccidioides immitis were below mean peak serum concentrations. Eighteen patients responded at all sites of disease, one patient failed to respond, and the others either are being evaluated or cannot be evaluated. Most patients who responded to therapy required more than three months of treatment before the response was clearly noted. Responses were seen with skin, soft tissue, skeletal, and pulmonary infection as well as other conditions. Reversions of cultures for C. immitis to negative and decreases in titers of complement-fixing antibody were common. One patient relapsed after a course of therapy of only four months. In general, patients with skin disease who responded required only 200 mg per day, whereas those with skeletal disease required 400 mg per day. Adverse effects were uncommon despite extensive monitoring and were generally limited to transient nausea (with vomiting in patients receiving 400 mg per day). The data show that ketoconazole appears to be a promising new drug for coccidioidomycosis.

Abstract 9: THERAPY OF CUTANEOUS COCCIDIOIDOMYCOSIS WITH IMIDAZOLES: COMPARISON OF RESULTS WITH MICONAZOLEAND KETOCONAZOLE

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In two open non-randomized studies of cutaneous C. immitis infections, 30 patients were treated with intravenous miconazole and 20 patients were treated with oral ketoconazole. Disease had been present an average of 2 years, and most patients had failed prior chemotherapy. Patients receiving miconazole responded (improvement or complete resolution) in 44% of the 18 evaluable treatment courses of ≥30 day's duration. Patients receiving ketoconazole responded in 83% of the 18 evaluable treatment courses of ≥60 days duration ($p < 0.05$). For neither regimen were differences noted between responders and non-responders when compared by sex distribution, age, ancestry, duration of therapy, or total dose. Six patients responding to miconazole relapsed at the previously involved sites within 4 months of completing therapy. While only 3 patients have completed ketoconazole therapy, none have relapsed in 1-6 months follow-up. Eighty two adverse effects were noted during miconazole therapy ($p < 0.001$). The more favorable clinical response rate, potential for fewer relapses, convenience of oral therapy, and lower incidence of toxicity all suggest that ketoconazole may be superior to miconazole in treatment of cutaneous coccidioidomycosis.

Abstract 10: Miconazole Therapy for Disseminated Coccidioidomycosis 5 year Follow-Up

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After amphotericin-B failure, 13 patients with disseminated coccidioidomycosis were treated with intravenous miconazole. Six of these patients with coccidioidal meningitis also received miconazole intrathecally.

Of the 13 patients three were black, two were Mexican, one was Filipino and 4 were Caucasian. All the patients had nonreactive skin tests (coccidioidin 1:10 and 1:100). All of them had other concurrent serious illnesses, including severe renal impairment. There were six deaths; three died from disseminated disease and three were disease free (death due to other causes).

Seven patients are still alive and disease free including three meningitis patients; two over five years, four over four years, and one over three years since completion of miconazole treatment. Miconazole can be a safe al tentative to amphotericin-B for the treatment of disseminated coccidioidomycosis, including those patients with impaired renal function.

Abstract 11: Intrathecal Amphotericin Therapy Following Ventricular Decompression

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The continuation of intrathecal Amphotericin treatment following ventricular peritoneal shunting for noncommunicating internal hydrocephalus is reviewed. The incidence of cisternal puncture related complications had been high, particularly bleeding following decompression. Two cases are presented where treatment was continued in spite of bleeding noted with the initial cisternal puncture& Careful persistence of therapy caused decrease in bleeding with complete disappearance approximately two months following surgery. Bleeding would recur only sporadically and it was possible to treat these two patients in the usual manner with initial improvement noticed over the five month follow-up period. It is concluded that persistence of cisternal treatments is feasible following decompression.

Abstract 12: IMMUNOLOGIC RESPONSIVENESS AND SAFETY ASSOCIATEDWITH THE C. IMMITIS SPHERULE VACCINE IN VOLUNTEERSOF WHITE, BLACK AND FILIPINO ANCESTRY

P.L. Williams, S.P. Sorgen, D.L. Sable, D. Pappagianis, H.B. Levine, S.K. Brodine, D.A. Stevens

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A trial with the killed C. immitis spherule vaccine was undertaken in healthy skin test negative adults re its safety, to evaluate its induction of humoral and cell-mediated immune responses and to determine if there were race or sex differences in these responses. The vaccine was given as 3 intradeltoid doses over 8 weeks. Hematologic, renal and hepatic function were assayed. Fifty-six were given three 3.5 mg doses of the vaccine. Two dropped from the study after the first dose due to severe local reactions. Four received 3.5 mg doses for the first 2 doses but 1.75 mg for the booster due to untoward local reactions to the former. Moderately severe to severe local reactions occurred in 29% of subjects in these groups (12% of all 3.5 mg doses). No systemic or laboratory abnormalities were identified. Several sterile abscesses developed and some required therapeutic aspiration. Of those completing the series & the 3.5 mg dose, 61% converted their skin test, 42% showed boosting of their lymphocyte transformation (LT) in vitro to spherulin and 16% converted their serology.

Forty-seven received three 1.75 mg doses over 8 weeks. 15% developed moderately severe to severe local reactions (6% of doses). No sterile abscesses requiring aspiration were found in this group. This dosage was associated with a 55% skin test conversion rate and 100% had boosting of LT response. There were no serologic conversions. There were no differences in local morbidity or immunologic responsiveness to vaccination on the basis of race or sex. The 1.75 mg dose of the vaccine appears to be best for a future efficacy trial.

Note: This communication is not necessarily the official opinion of the US Navy.

Abstract 13: CHITIN IN THE STRUCTURE OF C.IMMITIS

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Studies on the ultrastructure of C. immitis with emphasis on the role of chitin in-the cell wall have revealed a good deal of information about the cell wall architecture. Some of the major conclusions are as follows. Chitin serves as one of the key cell wall components for maintaining the structural integrity of the spheru1e. Chitin can be found as a distinct layer in the spherule, next to the cytoplasmic membrane. During the process of endosporulation in the spherule, chitin is one of the first polymers made, and may serve as the endosporulation initiator. This is suggested by the observation that inhibition of the synthesis of chitin by polyoxin D either blocks or severely interferes with endosporulation. Chitin is also one of the first polymers made during arthrospore germination and is probably important to hyphal growth and septum formation.
(Supported by NIH Grant 5ROl AI-13336)

Abstract 14: SKIN TESTING IN THE DIAGNOSIS OF COCCIDIOIDOMYCOSIS: A COMPARISON OF COCCIDIOIDIN AND SPHERULEN

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Spherulin is an antigen prepared from the spherule phase of Coccidioides Immites. It as been demonstrated to detect more reactions than coccidioidin in epidemiologic studies, in this study the reactivity to spherulin is compared with coccidioidin in patients suffering from coccidioidomycosis. Cases were divided into four groups. Skin test reactions were measured in mm, 48 hr after antigen was injected. Reactions were as follows: Active pulmonary disease - coccidioidin 1:100 N = 21, mean 9.8 ± 2.2mm, 67% >5mm, spherulin 2.8) ugm N = 13, mean 9.6 ± 3.4mm, 54 %:> 5mm; Inactive pu1monay disease - coccidioidin 1:100 N = 13, mean 10.2 ± l.7 mm, 83% :>5mm, spherulin 2.8 ugmN = 4, mean 6.2 ±4.7mm, 50% >5mm; Unifocal dissemination – coccidioidin 1:100 N = 8, mean 6.5 ± 2.Omm, 62% 5mm, spherulin 2.8 ugm N = 7, mean 6.5 ± 2.5mm, 57% >5mm; Mu1tifocal dissemination - coccidioidin 1:100 N=26, mean 4.5 ± 1.2, 38% >5mm, spherulin 2.8 ugm N = 23, mean 2.9 - 0.7mm, 43%>5mm, coccidioidin 1:10 N=14, mean 10.4 ± 3.0mm,64%>5mm (coccidioidin 1:100 and spherulin skin test reactions were not significantly different from each other. Both were significantly smaller in the multifocal dissemination group than other groups, $P < 0.05$). Thirty-one percent of patients reacted to both antigens. Discordance was observed in 14% and was equal in both directions. Many patients (45%) with coccidioidomycosis fail to react to skin test antigens from C. immitis. Thirty-four percent of patients with reactivity to at least one noncoccidioidal skin test antigen failed to react to either coccidioidin or spherulin.

In clinical cases there is no significant difference between the rate or size of reactions when I tested with spherulin or coccidioidin 1:100. Lack, of reactivity appears to be due to defects in immune function and not to lack of antigenic moieties in the antigen preparation.

Abstract 15: THE ROLE OF LYMPHOCYTES IN PULMONARY RESISTANCE TO COCCIDIOIDOMYCOSIS

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The ability of splenic lymphocytes to transfer resistance to an intranasal infection with Coccidioides immitis was determined in DBA/2 mice. The donors of immune spleen cells had been immunized with killed spherules. In three different experiments recipient mice were irradiated with 500 RADS and given 5 x 107 spleen cells from immune or normal mice intravenously. Some of the immune spleen cells had been incubated with rabbit antimouse theta serum and complement. The mice were subsequently infected with 50, 275 or 500 arthrospores intranasal1y and the deaths recorded for 40 days. The recipients of the immune spleen cells could survive an infection with 10 times the number of arthrospores which killed the recipients of normal spleen cells. Incubation of immune spleen cells with anti-theta serum and complement abrogated the ability of the cells to transfer resistance to infection with 50 or 500 arthrospores. When spleen cells from immune mice were cultured with arthrospores in vitro there was no significant killing of the-arthrospores observed in three hours. However, when a mixture of lymphocytes and peritoneal macrophages from immune mice were cultured with arthrospores 35% of the arthrospores were killed within 3 h. This indicates splenic lymphocytes stimulate macrophage mediated killing of arthrospores. (Supported by NIH Grant IROl AI-1506l)

Abstract 16: DETECTION OF ANTIBODIES IN COCCIDIOIDOMYCOSIS BY SOLID-PHASE RADIOIMMUNOASS13 (RIA)

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A solid-phase radioimmunoassay (RIA) was developed in an attempt to measure antibody in coccidioidomycosis (cocci) with improved quantitation over existing methods. Sera tested from 18 patients with active cocci (Group I) had a mean value of .85 mg equivalents/ml of anti-coccidioidin immunoglobulin $\pm$ .48 (ISD). 12 healthy controls (Group II) and 23 patients with non-coccidioidal diseases (Group III) had a mean level of .06 - .12. The difference between the active cases and the controls was significant (p (.0001). A correlation was evident between the CF titers and the RIA values derived from another set of 50 samples (r + .64). The CF test and the RIA are also compared with the clinical course in 2 serially studied cases with active cocci. In the examples cited, the RIA appeared to reflect the clinical situation more precisely.

These preliminary results suggest that the solid-phase RIA may prove to be a useful technique for cocci serology.

Abstract 17: 40 Year Follow-Up of Coccidioidin Skin Testing In Kern County

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Coccidioidin skin testing in students here had shown a dramatic drop since 1938, as previously presented. The attack rate had ranged from about 10% in the earlier years to less than 1% in the 1978 study. Because this did not match with our clinical experience, skin testing was done in adults in November 1979 and of the 450 who returned for reading, we found an annual attack rate of approximately 4%. Those exposed in earlier years would have had a higher attack rate and the figure may be skewed so the reliable figure may be closer to 3%, unreported at the time, but tests done since, have showed an incidence a bit lower so a 3% figure may be about correct. Details were given and further analysis will be presented later.

This confirms the impression that you can live here a long time and not be exposed but that, also, there is a considerable amount of coccy around.

Abstract 18: FOLLOWUP ON COCCIDIOIDOMYCOSIS RESULTING FROMDUST STORM OF DECEMBER 1977; AND THE LARGE NUMBER OF CASES IN 1979

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The number of new cases of coccidioidomycosis reported to the State Dept. of Health Services (CSDHS) following a severe and infectious dust storm of December 1977 for 1978 was 1095, whereas our department detected 1115 cases, virtually all from outside Kern County. We could ascribe clearly to the dust storm 427 clinically apparent cases. Sixty (15%) underwent extrapulmonary dissemination. Ten (16%) of the disseminated cases are known dead. The fate of 9 others of the disseminated cases is unknown to us. At least 22 cases (30% of the disseminated cases, 5% of the total clinically apparent cases) developed meningitis. The rate of dissemination in individuals infected during the dust storm in endemic areas was 8%, in non endemic areas 20%. Could this difference be due to a prior, immunizing infection in those from the endemic areas?

One of the heaviest seasons for coccidioidomycosis in our experience occurred in the summer and fall of 1979, 92, 77, 97 and 80 new cases being detected by us for the months of August, September, October, and November, respectively. This led to our recognition of 714 new cases compared with 620 reported to the CSDHS. It is suggested that this was a result of heavy winter rains of 1978-1979

Abstract 19: COCCIDIOIDOMYCOSIS SURVEILLANCE OF U. S. ARMY PERSONNEL TRAINING AT FORT IRWIN, CALIFORNIA

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Medical surveillance for coccidioidomycosis of selected units training at Fort Irwin in 1979 and 1980 was conducted through skin testing and monitoring of illnesses during and after training. Pre-and post-deployment skin testing using Spherulin (1:100) was conducted on a representative sample of units from Fort Carson that trained at the installation during a four week period in November 1979. Skin test positivity of 4.3% was noted prior to deployment, and a conversion rate of 1.3% was observed. No clinically apparent disease was documented.

In March 1980, over 1200 soldiers from the 7th Infantry Division Artillery were skin tested prior to deployment to Fort Irwin and Camp Roberts in April. A prevalence of positive skin tests of 4.6% was observed. Surveillance of this unit is in progress, and demographic data are being analyzed.

Abstract 20: Vasculitic Complications associated with Coccidioidal Meningitis

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Seven cases (C) of coccidioidal meningitis (cm) who's clinical course was complicated by proven or highly suspect vasculitis (V) associated CNS dysfunction are presented. 6 of the 7 C of cm were ≤ 40 years old. 6 were white and 1 was Hispanic. Immunological risk features were identified in 2 (diabetes 1, >70 years old, 1) high intensity dust exposure was identified in 4, other sites of involvement were seen in 4 C. duration of illness prior to diagnosis ranged from 3 to 5 weeks. Focal abnormalities (hemiplegia, aphasia) and/or global signs of CNS dysfunction (disorientation, hallucinations, psychosis, and seizures) were present in 5 C. One patient suffered bilateral internal capsule and basal ganglia infarcts and lapsed into a vegetative state (locked-in syndrome). Death attributable to cm occurred in 5 C. in 6 of 6 C studied; CT/MRI brain scans demonstrated focal abnormalities consistent with v process (infarcts/hemorrhages). Histopathological correlation was undertaken in 3 C and demonstrated V in 2. Gross findings were those of encephalomalacia. We describe previous studies reporting V-associated complications both in patients with cm and non-cm. These studies are consistent with the concept that V is part of the natural history of cm and are supported by the results of this study. The exact frequency of V complications, however, cannot be determined. The potential benefits of dexamethasone therapy as ell as its potential risks are discussed.