

# The Early History of Coccidioidomycosis: 1892–1945

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**Coccidioidomycosis was first discovered by a medical student in Argentina in 1892, and knowledge about the infection mostly arose from observations of clinicians and scientists in California, primarily at Stanford University Medical Center. Some discoveries came by chance. Many others arose from careful epidemiologic and clinical investigations in the San Joaquin Valley during the 1930s, when people migrated there from the "Dust Bowl" of the Midwest, and during the 1940s, when the events of World War II brought military recruits, prisoners of war, and persons of Japanese descent to camps and other areas of endemicity. Especially impressive were the contributions of Charles E. Smith, who tirelessly studied this disease throughout his professional career.**

In 1892, Alejandro Posadas, an intern in Buenos Aires, described a 36-year-old Argentine soldier who had experienced a dermatologic problem since 1889, beginning with a lesion on his right cheek [1]. Later, more red, itchy spots appeared and evolved into papules that ulcerated and discharged pus. In 1891, Posadas, then a medical student, first saw the patient, who had a large purple, fungal-like mass covering much of his right cheek, several ulcerative vegetations on his nose, one on his arm resembling a cauliflower, and many papules on his extremities and trunk. Posadas thought that the patient had the malignant skin disease, mycosis fungoides, but examination of skin biopsy specimens revealed organisms resembling the protozoan *Coccidia*. The patient eventually died in 1898 after 7 years of recurrent fever and progressive cutaneous lesions [2]. In the meantime, Posadas had successfully transmitted the infection to several mammals, including a dog, a cat, and a monkey, by inoculating them with material from his patient [3].

A year after Posadas' initial report, a 40-year-old native of the Azores entered a San Francisco hospital with

skin lesions similar to those of Posadas' patient [4]. In 1886, shortly after emigrating to California, where the patient was a manual laborer in the San Joaquin Valley, he had developed a slowly enlarging sore on his neck. New lesions appeared nearby and on his eyebrows, causing fungating masses that extended to cause swelling of both eyelids. The painful skin lesions progressed, becoming hideously disfiguring and horribly destructive; he lost both eyes, his nose, much of his upper lip, and half of one ear. Some of the mutilation presumably resulted from his treatment, which included not only topical methyl violet, iodine, bromine, oil of turpentine, carbolic acid, and potassium permanganate, but also excision of individual lesions and extensive curettage under chloroform anesthesia, followed by scrubbing of the raw surface with a brush soaked in bichloride solution. Nothing helped, and the patient finally died in early 1895. At autopsy, numerous nodules occupied the lungs, adrenals, lymph nodes, liver, peritoneum, prostate, spleen, and testes. On microscopy, they were granulomas, often with caseous necrosis similar to that from miliary tuberculosis, but containing abundant protozoa-like organisms. Specimens sent to 2 microbiologists yielded no organisms for one, and the other grew a mold that he discarded as a contaminant [5]. While the patient was alive, Emmet Rixford, a surgeon at San Francisco's Cooper Medical College (which became Stanford University Medical School in 1908), studied whether the skin disease might have spread by inadvertent self-inoculation. Apparently not, because no new lesions developed after Rixford rubbed some ma-

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terial containing the organism on the patient's abraded skin.

Rixford experimentally created a chronic ulcer by suturing infected tissue from the patient into a rabbit's subcutaneous tissue, and the pus that formed revealed the organism. He also inoculated some of the patient's tissue containing the microbes into a dog's leg. A lesion appeared, expanded, and ulcerated, and organisms consistently appeared in the pus exuding from the wound.

T. Caspar Gilchrist, Rixford's coauthor on this report [4] in 1896 and a pathologist at Johns Hopkins Medical School, examined the material, confidently concluding that the microbe was not a fungus. Instead, it was a protozoan resembling *Coccidia*, and helped by an eminent parasitologist, C.W. Stiles, Gilchrist and Rixford named the organism after both its morphologic and clinical features: *Coccidioides* ("resembling *Coccidia*") *immitis* ("not mild").

Gilchrist's self-assured conclusion that the organisms were protozoa had short-lived authority, because just 4 years later, William Ophüls and Herbert C. Moffitt cultured material from another patient with a fatal case in California and grew a mold that Ophüls initially considered to be a contaminant [6]. They inoculated tissue and pus from the case patient into the peritoneum of male guinea pigs, however, causing infection, including prominent orchitis, and they isolated the organism from the affected organs. They injected mycelia from the cultured mold into a rabbit, which developed typical nodules containing the visible organisms in various tissues. These findings proved that *C. immitis* was not a protozoan but was a fungus that existed in 2 forms: mycelia when in culture and spherical protozoan-like bodies (later called "spherules") in tissue where they reproduce—not by budding, but by developing numerous spores within them. In the life cycle of this tissue phase, the parent organism's capsule bursts, releasing the endospores, which themselves then develop into spherules. After Ophüls observed spherules in pus from a guinea pig, he incubated the slide and, on reexamination the next day, mycelia had developed. In a later experiment, he injected mold into a rabbit's ear, producing an abscess, and over the next 3 days, he observed that the organisms in the pus changed from mycelia to spherules [7]. In these studies, Ophüls conclusively demonstrated the transitions between the 2 fungal forms and the conditions under which they occur.

In 1905, Ophüls summarized the available information about the infection, which he called "coccidioidal granuloma" [8]. He delineated the diversity of the anatomic areas affected, including the skin, lungs, pleura, bones, adrenal glands, genital tract, lymph nodes, and meninges. He described a few patients in whom cutaneous involvement was absent but pulmonary lesions occurred, and he suggested that some cases develop from inhalation of the organism, rather than from inoculation

through the skin. In fact, subcutaneous injection of organisms into animals did not readily produce infection [7].

During the next 2 decades [9], important articles described additional cases, emphasized the lung as the major portal of entry for the organism, presented the radiologic features of the disease, and distinguished it from infections caused by other fungi—especially blastomycosis, which Gilchrist had first reported in 1894 [10]. As with *C. immitis*, he had originally misidentified the causative organism as a protozoan, a mistake that he later corrected himself [11, 12]. In 1905, after an autopsy of a patient in the Panama Canal Zone, Samuel Darling made the same error when he detected what he felt was a protozoan, which he called *Histoplasma capsulatum* [13]. In fact, it too was a fungus. Thus, the 3 major endemic fungi in the United States were all initially misidentified as protozoa.

In 1914, studies on the immunology of the disease began when Cooke [14] used an extract of dried culture specimens of the organisms as an antigen for skin testing and for serologic studies of precipitin and complement fixation reactions in a case of disseminated disease. Only the results of the precipitin test were positive. In 1924, intradermal injection of a suspension of the fungus produced a positive skin test result in a patient with disseminated infection [15], and in 1927, a filtrate of culture specimens obtained from another patient with disseminated disease provoked positive reactions when injected into the skin of the patient herself, but not into a human control subject [16]. Infected guinea pigs also reacted to the material, but uninfected animals did not react. Such filtrates, later called "coccidioidin," became widely used in skin testing to delineate the epidemiology of infection.

In 1929, a major insight to coccidioidomycosis inadvertently developed from the experience of a 26-year-old, second-year medical student, Harold Chope, who was studying *C. immitis* in the laboratory of Ernest Dickson at Stanford University Medical School (San Francisco) [17–20]. On his first day, Chope opened an old, desiccated culture to examine it more closely, and as he breathed on the plate, a cloud of spores arose, some of which he inhaled. Nine days later, he developed severe pleuritic chest pain, followed by a painful cough and purulent sputum, sometimes streaked with blood. A chest radiograph showed right upper lobe pneumonia. His chances of surviving coccidioidal infection seemed remote, and authorities at Stanford University, no doubt distraught about their student's impending demise, provided him a private hospital room and the impressive perquisite then of a radio. Newspapers and *American Weekly* [17], a national magazine, featured him as a young investigator facing imminent death, soon to become a martyr to science. One month after his exposure, he developed erythema nodosum, and sputum specimens demonstrated spherules on microscopy, yielded the organism on cultures, and caused infection when inoculated into the testes of a guinea

pig—the confirmatory test then used to identify the fungus. Over the next few months, Chope gradually improved.

The significance of Chope's illness became apparent when Dickson visited Kern County, California, in 1936 to solicit cooperation with the local health authorities to pursue studies of coccidioidal infections [21]. In 1934, Myrnie Gifford, a former student of Dickson's, had joined the Health Department there, which was interested in a disease called "San Joaquin fever," "Desert fever," or "Valley fever," a common disorder consisting of acute cough, chest pain, fever, pneumonia, and, later, erythema nodosum. In 1936, while reviewing case histories of *C. immitis* infection in preparation for Dickson's visit, Gifford noticed that 3 of 15 patients had developed erythema nodosum with the disease [21]. When she mentioned this fact to Dickson, he immediately recalled Chope's case, and they hypothesized that San Joaquin fever represented *C. immitis* infection.

After Dickson's visit, the Kern County Health Department began obtaining epidemiologic histories and performing skin testing with coccidioidin for all cases of San Joaquin fever. This investigation resulted in several important discoveries: most patients described a history of dust exposure; all had positive skin test results, compared with 25% in a random sample of persons in the county; and among 104 patients with San Joaquin fever, 94% were white, whereas 60% of cases of disseminated disease occurred in those who were not white [21]. These observations indicated that coccidioidomycosis was common in the area; racial differences, in part, determined the host's response to the fungus; and infection presumably occurred by inhaling dust containing the organism. The domain in which *C. immitis* ordinarily resides had, in fact, been discovered in Kern County in 1932, with isolation of the fungus from soil specimens collected from around the barracks of a ranch near Delano, which was chosen as a site to investigate, because 4 cases of infection with *C. immitis* had occurred among the Filipino crew working there [22].

After Chope left Stanford Medical School, Dickson recruited a classmate, Charles E. Smith, to replace him in studying the organism [17]. During his early investigations, Smith developed pleuritic chest pain that he thought might be tuberculosis, but he was relieved when his sputum acid-fast smear results were negative. In fact, as he later recognized, he had failed to diagnose his own case of coccidioidomycosis, which he, like many others working with this organism, had acquired in the laboratory [17].

In 1937, Smith began a 17-month study of coccidioidomycosis in Kern and Tulare counties in the southern end of the San Joaquin Valley [17, 23]. By contacting health departments, labor camps, and physicians in the area, he obtained the names and addresses of patients with Valley fever, defined in his study as erythema nodosum or erythema multiforme caused by *C. immitis*, as evidenced by positive coccidioidin skin test results

or isolation of the organism from sputum culture specimens. He visited 432 victims, half of whom were migratory farm laborers who had come to California in the 1930s after escaping from the "Dust Bowl" of the Midwest, especially Texas and Oklahoma. There, poor agricultural practices and harsh drought had severely dried the topsoil, which winds blew, along with the farm crops, creating dust storms that darkened the skies, making breathing difficult and cleanliness impossible.

From his collected information, Smith made several fundamental conclusions about coccidioidal infection. Knowing the interval between exposure and disease in Chope's case and a few others with clearly defined times of acquisition, he determined that the incubation period for the disease was between 1 and 3 weeks (usually ~2 weeks). By repetitive skin testing in several patients, he discovered that response to coccidioidin developed 2–17 days after symptoms began. Furthermore, cutaneous reactivity seemed long-lived. To help confirm this impression, Smith persuaded Chope, who had experienced Valley fever 9 years earlier and who had no exposure to *C. immitis* for 6 years, to undergo his first coccidioidin skin test. It produced a large area of erythema and induration that blistered and necrosed, leaving a permanent scar. Chope decided that his first coccidioidin skin test would also be his last [17].

Smith realized that the immunologic response to an attack, as reflected by skin reactivity to coccidioidin, seemed to protect people from further infection with *C. immitis*; only 2 of the 432 patients in his study may have had Valley fever twice (although both cases were dubious), and doctors in the area rarely diagnosed 2 episodes in the same patient. Moreover, among the workers in Smith's laboratory, no cases of infection occurred in those with a positive skin test result [23].

Smith also concluded that transmission of disease from one person to another did not occur, but instead, infection arose by inhalation of fungal spores. Most of the patients who he studied had shared their bed with at least one other person, and only rarely did their partners develop disease within the established incubation period. Furthermore, 18 people working in his department developed laboratory-acquired infections that could only have occurred by inhaling the organism [23].

Smith found that infection was much more common during the summer and fall, in part because the other months were wetter, but also possibly because agricultural workers did less field work during the winter and spring. Fortunately, the disease was usually self-limited, healing without clinical sequelae, but Smith noticed that persons of dark-skinned races rarely developed Valley fever. They were not exempt from *C. immitis* infection but, instead, had disseminated disease much more frequently than did white persons. Indeed, Gifford had earlier estimated that, compared with white persons, the risk of death from dissemination in Kern County was 23 times greater for black persons and 170 times greater for Filipinos [21].

In Smith's study, most of the persons with Valley fever were newcomers to the region, two-thirds having arrived within the previous 2 years. He figured, however, that these cases represented only a small percentage of all coccidioidal infections occurring during his investigation. Coccidioidin skin testing that Gifford had performed on 2718 schoolchildren showed that reactivity increased according to length of residence in the area—~80% of children had positive results after  $\geq 10$  years—but only ~5% of them had had Valley fever. Using this information, Smith calculated that his 432 patients reflected about 8000 new infections in the region [23].

In 1938, Farness and Mills [24] reported a case of a primary coccidioidal lung infection that produced an upper lobe cavity that healed spontaneously. This finding further supported the idea that *C. immitis* infection occurred through a respiratory route and could be self-limited. The following year, Smith and a Stanford pathologist, Alvin Cox, undermined the concept of coccidioidal infection as a usually lethal disease even more when they published an account of 4 cases of arrested coccidioidal pulmonary infection discovered during routine autopsies [25]. The specimens included nodules, scars, and lymph nodes that contained caseous, sometimes calcified, material harboring spherules. In the one case in which they could culture the tissue, *C. immitis* grew.

Additional evidence of this process came from a radiographic study of calcified pulmonary nodules among 3024 Native Americans of the United States and Alaska who had negative tuberculin skin test results [26]. Such findings were markedly more common among Pima Indians residing near Phoenix, Arizona, than among tribes in other areas, such as Wyoming and South Dakota. The authors demonstrated that this difference almost certainly occurred because of *C. immitis* infection among the Pima Indians, nearly all of whom had positive coccidioidin skin test results before the age of 20 years, whereas test results among Native Americans in the other locales were rarely positive.

In 1939, Smith stumbled onto an alternative to skin tests for diagnosis of coccidioidomycosis—serologic testing [17, 27]. He had tried to determine whether serum samples from infected guinea pigs could inactivate coccidioidin *in vitro*—with no success—but his delay in cleaning the laboratory glassware led to an important discovery. When he eventually examined the test tubes a week later, he saw a discrete “button” of precipitate on the bottom. This finding became the basis for the serum precipitin test. Smith's particular preparation of coccidioidin employed for the precipitin test became an effective antigen for complement fixation as well, and in 1940, he started performing both tests simultaneously to diagnose coccidioidal infections [27]. He found that the precipitin test was helpful for detecting acute infections, and the complement fixation serologic test was especially useful for diagnosis of disseminated disease.

Smith gained additional insight into the acquisition of *C. immitis* by investigating the first reported epidemic of coccidioidomycosis [28]. In April 1940, 10 Stanford University students and 4 faculty members participated in a biology field trip to San Benito County, near the San Joaquin Valley. Ten to 16 days later, 7 of the 14 participants, all students, became ill with symptoms that included headache, backache, chest pain, fever, and night sweats. All had abnormal chest film results and positive serologic test results for coccidioidomycosis, and 4 grew *C. immitis* from sputum specimens. The only time that an exposure could have occurred to infect the 7 victims, and not the others, was when a student vigorously dug into a ground squirrel hole into which he had seen a rattlesnake crawl, dispersing considerable dust in the process. Four months later, Smith accompanied the student back to the hole and recovered *C. immitis* from the soil.

At approximately this time, contemporary political conditions provided Smith with other newcomers to study besides migrant agricultural workers. During 1940–1941, with war appearing imminent, military commanders decided to train Army Air Forces pilots year-round at airfields in the San Joaquin Valley because of the many days of good weather and the unlimited space for emergency landings [17, 29, 30]. Smith and others warned them of the risk of coccidioidal infection, but he and the military concluded that the training advantages of the area outweighed the medical hazards. They recommended, however, that ground forces not practice maneuvers there. Moreover, they decided to conduct a systematic investigation of coccidioidal infection by skin testing all recruits on arrival at Minter Field in Bakersfield and Gardner Field in Taft, both in the southern San Joaquin Valley, and then semiannually for those whose test results remained negative. These studies confirmed that those with previous skin reactivity to coccidioidin did not develop disease and that the incidence of infection was greater during the summer than the during the winter. In fact, cases were especially common when dry months followed heavy rain during the winter and spring, presumably because the extra moisture allowed more robust growth of the fungi, and the winds dispersed the spores when the hot weather converted the soil to dust [31]. Smith's studies also revealed that 60% of infections were asymptomatic, and erythema nodosum occurred in ~5% of white men [32]. In 1943, arrival of members of the Women's Army Corps provided a comparison of sex differences, revealing that erythema nodosum occurred in 25% of white women with coccidioidal infection. Racial differences were even more impressive: erythema nodosum rarely occurred in black persons, who also had a rate of dissemination >10 times greater than white persons, even though they had the same food, housing, and medical care. Another important discovery was that dissemination of infection almost always developed during the course of the initial illness—during the

weeks to months afterwards—rather than years later, as occurs in many cases of military tuberculosis [32].

An additional significant insight emerged during World War II from other Army Air Forces camps: recognition of the areas where *C. immitis* is endemic. Earlier, the organism was thought to be nearly confined to the San Joaquin Valley, but diagnoses of active disease and skin testing demonstrated that it was also present in southern Nevada and Utah, western Texas, and, especially, Arizona, whose southern and central areas seemed to impose the highest risk of infection in the United States. In fact, at Minter Field in the San Joaquin Valley, about one-fourth of the susceptible recruits became infected during the first year, but at Florence and Williams Field in southern Arizona, the infection rate was ~50% during the first 6 months alone [32].

Among susceptible recruits at 2 camps in Kern County, the annual incidence of infection was 20%–25% during 1941–1942 [32]. In the summer and fall of 1941, during construction of the airfields, dust was ankle-deep and billowed in clouds over the area, and in the single month of August, >5% of all susceptible recruits became infected at one of the camps. Controlling dust by planting lawns, paving roads, and surfacing the airfields reduced the infection rate by half. In addition, construction of swimming pools encouraged aquatics as a substitute for field sports, further diminishing the recruits' dust exposure. At one camp, spraying highly-refined oil on the athletic areas used for calisthenics, volleyball, baseball, and other physical activities seemed to decrease the infection rate even more.

In 1942, another group of newcomers arrived in areas where *C. immitis* was endemic. In February, President Roosevelt signed an executive order authorizing the Secretary of War and any designated military commanders to prescribe “military areas” from which any or all people could be excluded. In May, Lieutenant General John DeWitt directed all people of Japanese descent living in “Military Area Number 1” (the Pacific Coast) to report to assembly areas from which they would be sent to “Relocation Centers.” More than 110,000 people, about two-thirds of them US citizens, resided for the remainder of the war at 12 of these internment camps, one of which was on the Gila River Indian Reservation that was ~50 miles southeast of Phoenix. There, outbreaks of coccidioidomycosis occurred among the ~13,000 residents [29].

Nearby, still another group of involuntary newcomers resided—prisoners of war, initially primarily from North Africa after the surrender of General Erwin Rommel's Afrika Korps in April 1943. By the end of World War II, >425,000 enemy prisoners, mostly Germans, but also ~50,000 Italians and 5000 Japanese, were incarcerated in the United States [33]. Approximately 13,000 of these prisoners lived on what had been a military reservation in Florence, Arizona, including all prisoners with active tuberculosis who were assigned there because of its supposedly salubrious climate. Unfortunately, the climate was

salubrious for *C. immitis* as well. Smith visited Florence in early 1944 and discovered that acute coccidioidomycosis was rampant among the prisoners. He speculated that two-thirds to three-quarters of new arrivals would become infected in 1 year [29]. Two had died of coccidioidomycosis, and of 89 patients with tuberculosis, 10 had become infected with *C. immitis*, acquiring the organism either while outdoors or by inhaling spores carried by breezes into the living quarters. Although the patients did not seem especially harmed by the superimposed coccidioidomycosis, the military decided to send them to other hospitals to protect them from any health hazard that *C. immitis* might impose and to avoid any criticism about violating the Geneva Conventions of 1929 governing the treatment of prisoners of war.

## CONCLUSIONS

Similar to many scientific enterprises, the discoveries and insights about coccidioidomycosis came from a slow accretion of information derived from numerous sources, including the contributions of 2 medical students (one unwittingly) and many gifted investigators. In the early history of coccidioidomycosis, however, 2 sources of discovery are especially impressive. First is the enormous contribution of the apparently indefatigable Charles E. Smith in his diverse investigations of *C. immitis* and the infection that it causes. He devoted his professional life to this focus of study, and even after he became Dean of the School of Public Health at the University of California at Berkeley in 1951, he continued to investigate coccidioidomycosis until his death in 1967. The other striking element in the early history of coccidioidomycosis is how certain kinds of social disruption provided crucial clinical and epidemiologic information. The migration of people from the “Dust Bowl” of the 1930s and the movement of military personnel, Japanese internees, and Axis prisoners of war to the San Joaquin Valley and other areas of endemicity in the Southwest during the early and mid-1940s as a consequence of World War II furnished the opportunity for Smith and others to study the disease. In that way, they added substantially to the fundamental discoveries of microbiology, epidemiology, clinical findings, and diagnosis that had emerged since Posadas' initial case report in 1892.

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