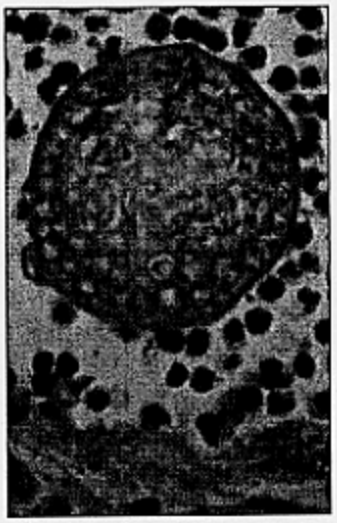
Questioning CDC's "Select Agent" Criteria

THE NEW ANTITERRORISM LEGISLATION THAT D. Malakoff and M. Enserink discuss in their News of the Week article "New law may force labs to screen workers" (2 Nov., p. 971) could result in the imposition of onerous security measures in laboratories doing research with any of the organisms on the Centers for Disease Control and Prevention's list of "select agents." We do not challenge the wisdom of such legislation in general, but we question the composition of the "watch list" of organisms. We cannot speak to the appropriateness of every organism on that list, but as investigators who have carried out clinical and laboratory research on *Coccidioides immitis* for more than 15 years, we can attest to the absurdity of including this particular one on the list.



The tissue form of *C. immitis* is the spherule (50 μM in diameter) shown here in lung tissue (hemotoxylin and eosin stain). Mature spherules contain hundreds of endospores, which then develop into spherules.

First, controlling and monitoring the few research laboratories that work on this pathogen will not limit access to the fungus because it is freely available to anyone who wants to take the trouble to obtain it. The fungus grows in desert soil and is endemic in the southwestern United States from mid-Texas to the Pacific Coast. It would take little effort to grow this mold. Furthermore, it is routinely grown from patients' specimens in microbiology laboratories all over the endemic area, where the annual infection rate reaches several thousand. These laboratories are not required to screen anyone who has access to those facilities; therefore, it seems unreasonable to expect that restrictions could be effectively implemented.

Second, the mild consequences of infection with *C. immitis* make it an unlikely choice as a biological weapon. Only ~30% of people who are naturally infected develop symptoms, which in most cases is self-limited pneumonia. In fact, should even 1000 people be exposed to *C. immitis* by means of a spray (although we know of no research on preparing the fungal spores for such a dispersal), the resulting "epidemic" would hardly be noticed if it occurred in the endemic area. A high incidence of illness outside the endemic area would naturally raise suspicions, but would hardly cause panic, given the nature of the illness. Moreover, unlike smallpox, *C. immitis* is not contagious, and unlike the rapid, fatal effects of anthrax and plague, the severe, progressive form of coccidioidomycosis is generally a prolonged illness. Even in rare cases of fatal outcome from *C. immitis* infection, patients do not die rapidly. Therefore, coccidioidomycosis is not likely to create the public panic that terrorists seek to engender.

Third, *C. immitis* is even less likely to be used against a military force because its infection rate is too low and its incubation period too long to disable a military unit, nor is there a vaccine to protect invading troops from their own weapon.

Other agents on the watch list are also unlikely candidates for biological weapons. We in the scientific community have the responsibility to take a closer look at this list to avoid imposing costly restraints that could impede legitimate research.

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Handout 10
B10329

Letters to the Editor

Letters (~300 words) discuss material published in *Science* in the previous 6 months or issues of general interest. They can be submitted by e-mail (science_letters@aaas.org), the Web (www.letter2science.org), or regular mail (1200 New York Ave., NW, Washington, DC 20005, USA). Letters are not acknowledged upon receipt, nor are authors generally consulted before publication. Whether published in full or in part, letters are subject to editing for clarity and space.

CREDIT: (LEFT) THEO KIRKLAND; (RIGHT) JON CHASE/HARVARD UNIVERSITY NEWS OFFICE

Handout 10
Bio 329

Fungus trail indicates ancient Texans' travels

Study of fungus helps chart movements of ancient people

By Robert Cooke
Newsday

In an effort to track down who moved where and when, scientists are charting the migrations of ancient people through the Americas — by following a fungus. And that fungus indicates that South America was originally populated by prehistoric Texans.

The fungus, Coccidioides immitis, causes an infectious disease in humans and other animals, and its presence in remote areas is taken as a sign that people had lived there. As a disease organism, it causes Valley Fever, a disabling and sometimes fatal lung disorder.

Now it's being used to sort out the migration patterns of prehistoric populations in the Western Hemisphere, scientists said.

Caution is required in such research, of course, because Valley Fever is dangerous enough that research on C. immitis is regulated under the U.S. Anti-Terrorism and Effective Death Penalty Act. The soil-borne fungus causes disease in many people annually in the Pacific Southwest, especially in California.

Though the symptoms are usually so mild that victims often don't know they're sick, in about 10 percent of cases the patients get quite ill, and in about 1 percent of cases the patient dies.

Using careful analysis of the genes found inside the fungal cells, microbial biologist John Taylor and his co-workers say they can follow human migratory patterns. They can tell from which part of North America a fungus sample came. And the patterns of where the fungus is now found strongly suggest that South America was populated rather quickly by people who migrated south, apparently from what is now Texas.

There is also a small chance, Taylor said, that the fungus was carried into South America by domestic animals the people had with them, or even by wild animals such as kangaroo rats. Nonetheless, the research team, working from the University of California-Berkeley, thinks it's far more likely that the fungus traveled rapidly with infected people. Its traces can still be found around places where prehistoric people settled, such as Monte Verde in Chile.

The new findings that fungi can serve as a tracer of human migrations were announced recently in the Proceedings of the National Academy of Sciences by Taylor, by Matthew Fisher at Roche Molecular Systems in Alameda, Calif., and by their co-workers in Venezuela, Brazil, Mexico and Argentina.

There are two main species of C. immitis. One is commonly found in central California and even down into Mexico; the other species is found most often in Arizona, Texas and Mexico, and to some degree in southern California. And within those two main species, the researchers have identified eight distinct populations. All of the fungi in South America are the Texas version.

The data suggest that the people from the Texas area probably spread rapidly throughout the southern continent, perhaps in a period of just 800 years. This is evident because the genes found in the fungi are so similar across all of South America.

Taylor and his colleagues said all the fungus samples collected in North America showed a correlation between geographic distance and genetic distance, meaning fungi that live far apart are also genetically distinct. But in South America, Taylor said, "that difference falls apart. There is no relationship between geographic distance and genetic distance." All of the fungi, in other words, are genetically similar, although spread over wide distances. That is what suggests that the people who traveled south spread throughout the continent in short order.

Spurs will honor Moore's shortened career

By Mark Rosner
American-Statesman Staff

Johnny Moore still assesses with ambivalence a basketball life cut short by a rare disease.

Moore, the career assists leader for the University of Texas and the San Antonio Spurs before retiring in 1990, said, "I guess there's a little resentment. But I have to be happy that I fulfilled a lifetime dream to play in the NBA. It should have been longer, but I had a good career."

Proof of that will be on display Friday night when the Spurs retire Moore's number, 00, during halftime of their game against Charlotte.

Moore, a point guard, passed for 3,865 assists, an average of 7.4 a game, during his nine seasons in the NBA that began in 1980-81. He averaged 8.6 assists before a contracting a form of meningitis commonly called "desert fever," in 1985. He also produced 1,017 NBA steals. Only Alvin Robertson made more for the Spurs. Moore holds records at Texas for assists in a game (19), season (242) and career (714).

Moore, who turns 40 on March 31, is the third Spur to have his number retired, preceded by James Silas (13) in 1984 and George Gervin (44) in '87.

The announcement of Moore's honor was made on Jan. 26, between the first and second periods of a Spurs' game against Houston. Moore thought he was just being introduced as part of the team's season-long 25th anniversary celebration. He wasn't expecting anything more.

"I was very surprised," Moore said. "As a point guard, you don't always receive a lot of recognition, especially when you play with such flamboyant scorers as Ice (Gervin) and Artis Gilmore."

Even so, Gervin, inducted into the Naismith Memorial Basketball Hall of Fame in 1996, can thank Moore, in part, for that. For five seasons — 1980-81 to '84-85 — Gervin, the Spurs' career scoring leader, shared the back court with Moore, the passer.

'I guess there's a little resentment. But I have to be happy that I fulfilled a lifetime dream to play in the NBA.'

Johnny Moore

In 1982, Moore led the league with 9.6 assists a game and ranked third with 2.1 steals.

In 1985, he averaged 9.95 assists, finishing third in the NBA, and 2.8 steals, which ranked second.

Early in the 1985-86 season, Moore was averaging 13 points — nearly four better than his career average — nine assists and three steals. Then he woke up with a serious headache on Dec. 21, 1985. He played that night, scoring 22 points and grabbing 11 rebounds, but his life would soon change forever.

The headaches, which Moore once described as a migraine magnified about a hundred times, didn't subside. Neither did the dizziness. Moore entered a San Antonio hospital, where he was diagnosed with coccidioidomycosis, which occurs in the arid Southwestern United States. It is caused by a fungus that enters the body through the skin's pores.

Moore missed the rest of the season. A small plastic reservoir was inserted under his scalp to regulate the flow of the medicine necessary to control the disease. But Moore said the symptoms often returned.

Slowly, though, Moore began playing ball again, summer league in 1986, 55 games for the Spurs in 1986-87. But occasionally he had to stop himself from blacking out while driving. On the court, his eyes often could not focus. His medicine made him sluggish. He averaged 22 minutes, 4.5 assists and 8.6 points that season.

Four games into the next season, 1987-88, he was traded to New Jersey, which released him after one game.

Moore later had his suspicions confirmed, that the disease had returned. This time his internist, Dr. Richard Thorner, offered him a new drug, one that could be taken orally instead of with a needle in his head.

He played summer ball again, in 1989, began the fall with a CBA team, and soon found himself in a familiar place — the Spurs' back court.

Playing as a reserve, 10 minutes a game, Moore finished his career where it started, with the Spurs in 1989-90. He was released after the season.

Moore said he has too many memories to isolate highlights. But he does recall fondly the 1983 playoffs. He averaged 22.5 points and 14.6 assists in series against Denver and the Los Angeles Lakers. He scored 39 and 27 points in consecutive games against Denver.

"And just the thrill of watching Ice play was a highlight," Moore said. "He would do something different every night to put the crowd in awe."

These days Moore and Gervin work together in the Spurs' community relations department. Moore speaks to civic groups and kids. He plays a lot of golf, a passion Moore developed as a Texan transplanted from Pennsylvania, where he was raised.

Moore still takes medication.

"It's for maintenance," he said. "I basically enjoy good health. I don't think it will come back."

January 18, 1986
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'Win for Johnny'

Fire Photo

San Antonio Spurs guard Johnny Moore at his annual basketball camp held in Texas for kids.

Spurs praying for sick teammate

By Randy Riggs
American-Statesman Staff

SAN ANTONIO — Outwardly, it was business as usual at the San Antonio Spurs practice Friday morning. The Spurs slowly made their way to the HemisFair Arena court, laughing and exchanging greetings and handshakes with the departing New York Knicks, who they would be playing that night.

Under one basket, coaches Cotton Fitzsimmons of the Spurs and Hubie Brown of the Knicks visited. Sitting on a courtside table, New York rookie center Patrick Ewing held a quick press conference while the Spurs yawned and stretched.

Business as usual? On the surface, perhaps, but not really. "Double-O" was missing.

While the Spurs went through a typical game-day "shoot around" Friday, point guard Johnny Moore — the victim of a relatively rare form of meningitis known as "desert fever" — lay in a hospital bed several miles away at Humana Medical Center.

The 1985-86 National Basketball Association season is over for Moore, the popular University of Texas product whose jersey number is 00. But the Spurs aren't so much worried about Moore's career as they are about Moore, period. This isn't exactly just an ankle sprain he is dealing with.

"Every night I pray for him," said guard Wes Matthews, who has stepped into Moore's starting spot. "We all feel for him, but we've still got to take care of business. Life goes on, and we've got 'x' number of games left and we've got to win them. And when we do win, we're winning them for Johnny. He might not be here, but he's still a big, big part of this team."

caused by a

The technical name for Moore's ailment is coccidioidomycosis, a fungus that is indigenous to the arid southwestern United States. Estimates are that as much as 10 percent of the population is exposed to the fungus, which can be picked up while breathing, but only one exposed

See Moore, A14

person in 1,000 contracts meningitis as a result.

"It's a dust-transmitted fungus spore," said James Perdue, a public health technician in the bureau of epidemiology for the state Health Department. "There's not a whole lot you can do about it. You can't eliminate dust."

Perdue said the ailment was assigned a "reportable disease" designation in 1984 so that public health officials could determine how common it is. In 1985, Perdue said, 20 cases — two fatal — were reported in Texas. The disease seems to affect blacks, Filipinos and pregnant women most, Perdue said. "But don't ask me why that is," he said. "We don't know."

*

At a news conference Wednesday, Moore's doctor was optimistic that his 27-year-old patient will recover.

"The fact that we had a relatively quick diagnosis helps," said Dr. Richard Thorner, the Spurs' internist who specializes in infectious diseases. "Skin tests have proven positive, indicating there is some immunity to the disease in his system. And the fact that he is in excellent physical condition helps."

Nobody is certain when — or if — Moore will return to professional basketball. Spurs officials are hoping he will be back next season.

Moore's early symptom was a constant, painful headache that began Dec. 20. He entered the hospital for tests the day after Christmas and was discharged Jan. 10 under the condition that he might return when it was determined what kind of meningitis he had.

The exact diagnosis was made last weekend, when doctors found that the fungus had spread through the central nervous system and infected brain tissue. Moore returned to the hospital Tuesday.

He has undergone two operations in two days. The first, on Wednesday, was conducted to insert a hollow, quarter-size plastic disc under his scalp on the top right side of his forehead. A tube runs from the disc, known as an Ommaya Reservoir, through a hole in the skull to the infected area of the brain.

The second operation was performed Thursday afternoon to alter the position of the tube after doctors found that Moore experienced a slight swelling on his brain Wednesday night.

The reservoir and tube will serve as the conduit for the medicine once treatment begins. A medicine known as Amphotericin B will be injected into the disc three times a week for two or three months.

Moore spent Thursday night in intensive care. He was moved to a private room Friday and was listed in satisfactory condition. His wife, Natalie, was not available for comment.

Spurs players and officials were plainly worried about Moore's condition as they practiced Friday.

"It's frightening," said Coach Fitzsimmons. "We think of ourselves as the healthy ones. We're the ones who go to the hospitals to visit people who are less fortunate than us. Then it touches you, and it's a totally different feeling you get."

With Moore in the lineup, the supposedly weak Spurs had gotten off to a surprising 17-12 start this season. Without him, they were 4-7 going into Friday's game with the Knicks.

"Our concern isn't wins and losses anymore," Fitzsimmons said. "It's Johnny Moore's health."

Knick guard Darrell Walker noted that athletes, especially professional athletes, accept possibly career-threatening injuries as an occupational hazard. But when they are mysteriously struck down by a malady over which they have no control, it's different.

"Man, this ain't a knee or an ankle. This is life and death," said Walker, the former Arkansas All-America guard. "It makes you realize how human you are."

Dr. Frank Kasman, an Austin dentist who became friends with Moore when he played at Texas from 1976-79, agreed with Walker's assessment.

"A lot of athletes feel they're invincible and that nothing can hurt them," Kasman said. "Then this happens, and it's probably more devastating than an injury. It's the unknown, and it shows athletes how tough it can be to come to grips with their own vulnerability."

But Kasman and others who have known Moore for years express confidence that he can overcome the disease and return to the NBA.

"If anyone can, he can," said Leon Black, the former Texas basketball coach who recruited Moore out of Altoona, Pa. "All you've got to do is see what he made of himself. Anyone who saw his determination to succeed, who saw what he put himself through to get there, knows what he's made of."

A two-time All-Southwest Conference selection for the Longhorns, Moore started every game for four years, and helped lead Texas to the 1978 NIT Championship. He was picked by the Seattle Supersonics in the second round of the 1979 NBA draft, traded to San Antonio and promptly cut. He returned to UT to work as a volunteer coach and made the Spur team the next season.

Before his illness, Moore was averaging 13 points and 9 assists a game. He already is San Antonio's all-time assist leader with 3,522. Those who know him expect him to eventually add to that total.

"Don't ever count him out because Johnny Moore will never, ever back down," Black said.

Reactivated in 1987; "Retired" 1988.

Thursday, January 22, 1987 • Austin American-Statesman

1/22/87

Spurs put Johnny Moore on active list

By Randy Riggs
American-Statesman Staff

SAN ANTONIO — Guard Johnny Moore of the Spurs was activated Wednesday after missing 12 games on the injured list because of his recurring problems with Desert Fever.

To make room for Moore, San Antonio waived forward Tyrone Corbin.

Moore, the former University of Texas star, has gotten off to a slow start after missing most of last year with Desert Fever, a form of meningitis.

Starting 23 of San Antonio's first 25 games, Moore averaged only 7.8 points, hitting just 43 percent of his shots. "He's better than he was the last month he played, but he'd almost have to be," Spur Coach Bob Weiss said. "December was a disastrous month for him."

Moore is still taking treatments for Desert Fever, but they now are limited to one every six weeks. His next injection of medicine into the small reservoir implanted in his scalp is set for the first week of February. The side effects of the treatment — nauseau and headaches — usually keep him grounded for two days.

1990 playing again S.A.
1991 retired again
1995 see next page

TABLE 1

COCCIDIOIDOMYCOSIS: A CLINICAL CLASSIFICATION

Disseminating Coccidioidomycosis (Coccidioidal granuloma)	Primary Coccidioidomycosis	Residual Pulmonary disease
Metapulmonary involvement (single or multisystemic)	Pulmonary	Chiefly nodules, cavities, abscesses
Respiratory	Asymptomatic (the coccidioidin converter)	Persistent, unstabilized
Pulmonary	Mild subclinical infection, unrecognized	Open cavities or abscesses
Extrapulmonary, pleural, chest wall	No pathologic-anatomic pulmonary changes	Nodules (coccidioidoma)
Lymphatic	Symptomatic	Infiltrate
Cutaneous and subcutaneous tissue	Febrile respiratory illness	Progressive, locally extending disease
Skeletal, including joints and tendons	Tracheo-bronchitis, pneumonitis	Enlarging or multiplying cavities and nodules
Visceral	Infiltration, nodular densities, consolidation	Abscessing nodules
Spleen	Hilar and/or paratracheal lymphadenitis	Extending infiltrate, consolidation
Liver	Cavitation, transitory	Regressive, stabilizing, end-point disease
Central nervous system	Pleuritis, ± effusion	Localized fibrosis, hyalinized foci
Meninges, brain, cord	Allergic form (5% of symptomatic patients)	Bronchiectasis, calcification
Cardiac	Hypersensitivity phenomena	
Myocardial, pericardial	Erythema nodosum or multiforme	
Endocrine	Arthralgia, periarticular swelling	
Thyroid	Episcleritis, phlyctenular conjunctivitis, keratitis	
Adrenal	Any of the symptomatic pulmonary changes above may occur.	
Pancreas	Percutaneous (primary cutaneous) usually after trauma chancroid syndrome	
Ophthalmic		
Urogenital		
Kidney, ureter, bladder, urethra		
Gonads, epididymis, ovarian tubes		

Reproduced with permission from "A Working Classification of Coccidioidomycosis and its Application to Therapy," in *Coccidioidomycosis*, L. Ajello, ed., University of Arizona Press, Tucson, 1967, p. 3.

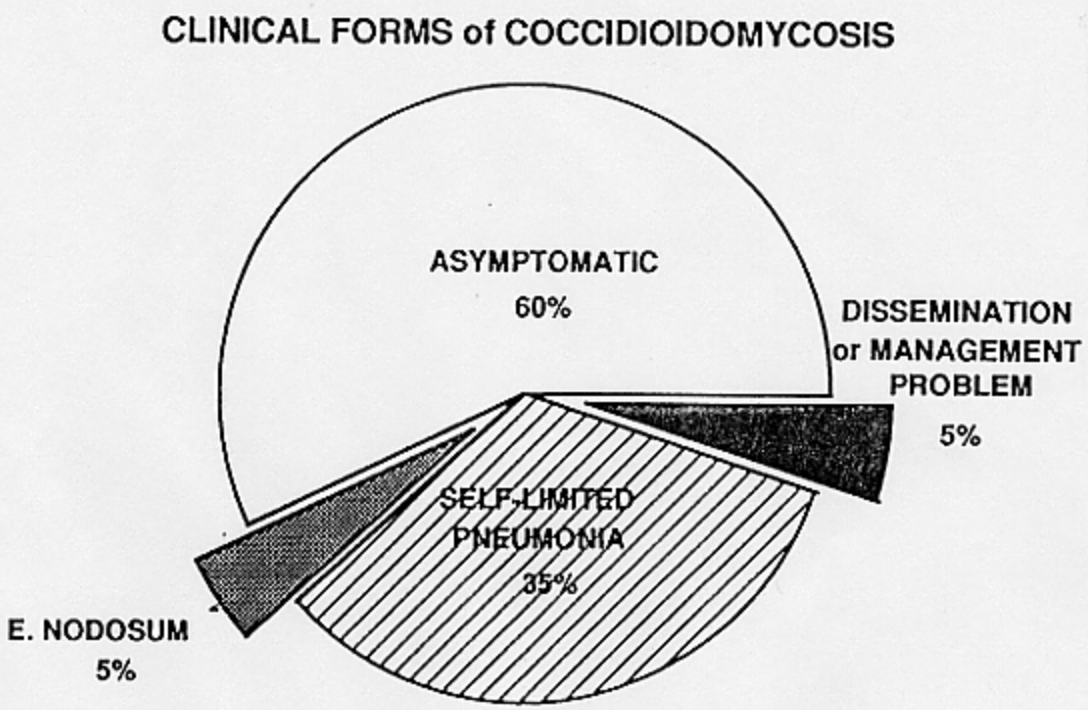


Figure 3. The most common clinical presentations of coccidioidomycosis in immunocompetent patients (16).

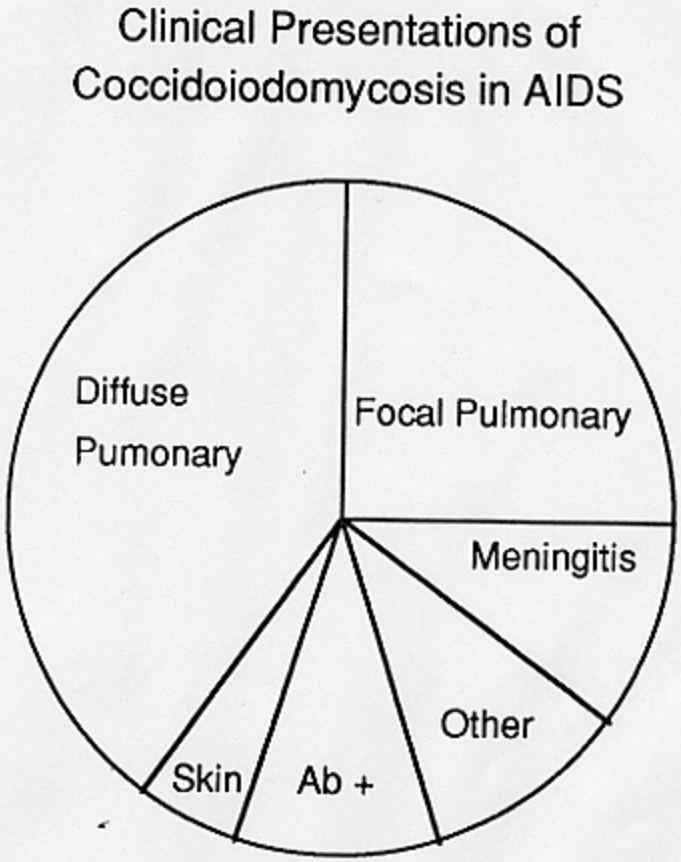


Figure 5. The most common clinical presentations of coccidioidomycosis in AIDS patients. The group "Others" includes dissemination to the lymph nodes, liver, spleen, and bone marrow. The antibody only group includes patients with serologic evidence of infection but no evident focus of infection. Since these were passively collected cases, a protocol to search for inapparent sites of infection had not been agreed upon (37).

Skin test conversion
83% 1st wk
93% 2nd wk } 60% w/o symp!
99% 3rd wk

if wanes after years reinfection can occur

1:100 dilution test = coccidioidomycosis
1:1000 past exposure

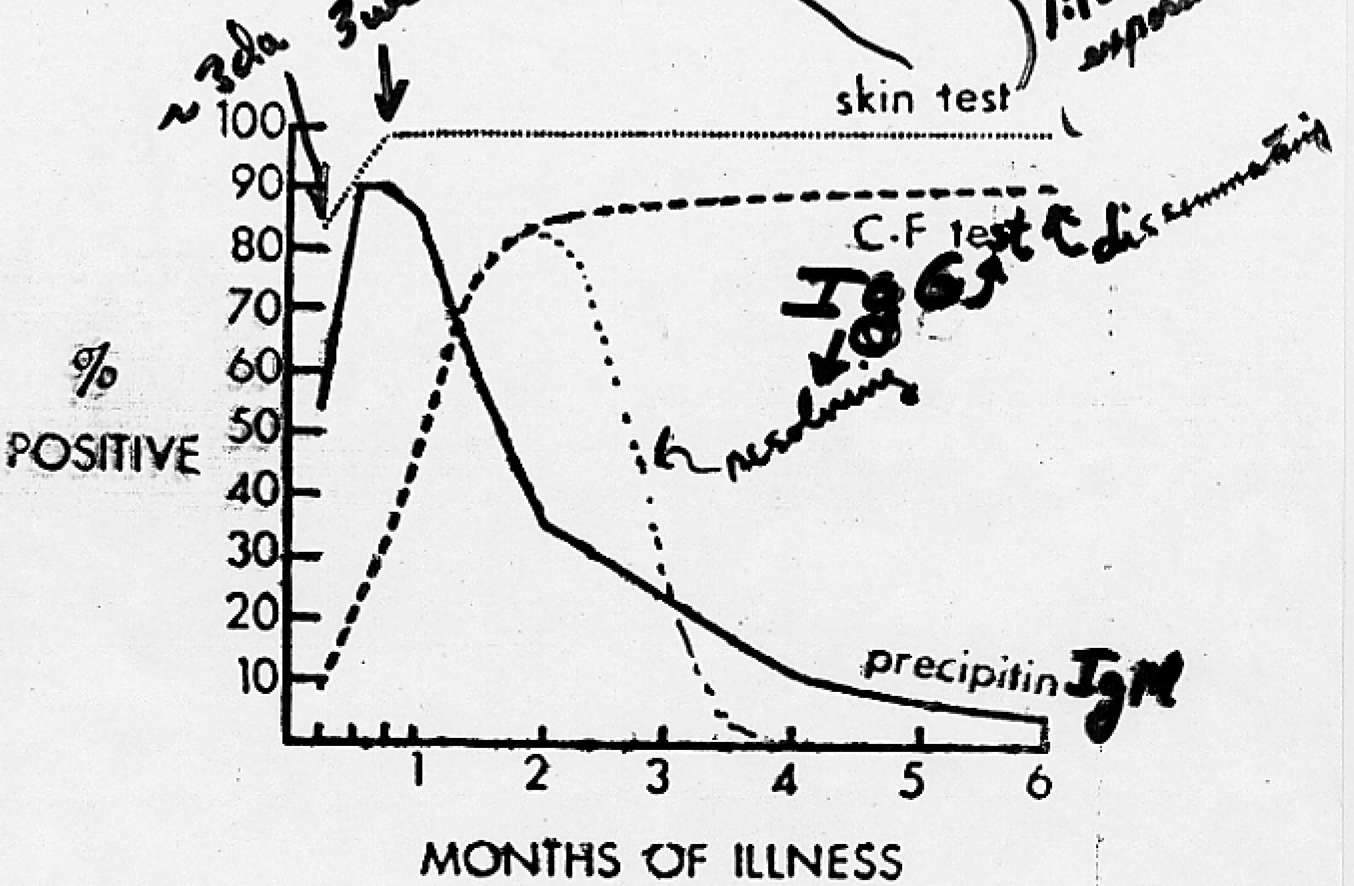


Fig. 3. Temporal relationship between coccidioidin skin-test reactivity and tube-precipitin and complement-fixing antibody titers. Reproduced from Huppert, M.: Serology of coccidioidomycosis, Mycopathol Mycol Appl, 1970, *41*, 108, by permission of the publisher, Dr. W. Junk, b.v.

skin test doesn't affect outcome of other serological tests.

VI. PREVENTION OF NATURALLY ACQUIRED INFECTION

A. Human Coccidioidomycosis

Vaccine?

1985 and counting

The possibility of preventing coccidioidomycosis by vaccination has been a specific goal for over two decades. If such a vaccine could prevent extrathoracic dissemination, it would be of value to all who might be exposed. Because the mechanisms underlying progressive disease are not understood, it is also possible that immunization would not prevent this sort of progression because in those individuals the vaccine would be no more likely to "take" than would a naturally acquired infection. However, a coccidioidal vaccine effective in preventing morbidity associated with the pulmonary infection would be of significant value, particularly to several special groups such as diabetics, those with severe pulmonary disease, and others in whom a severe pulmonary illness would be a particularly great hazard. Such a vaccine might be of value to groups at risk of high-inocula exposure, such as archeologists, laboratory technicians, and those working in earth-moving occupations in the endemic areas.

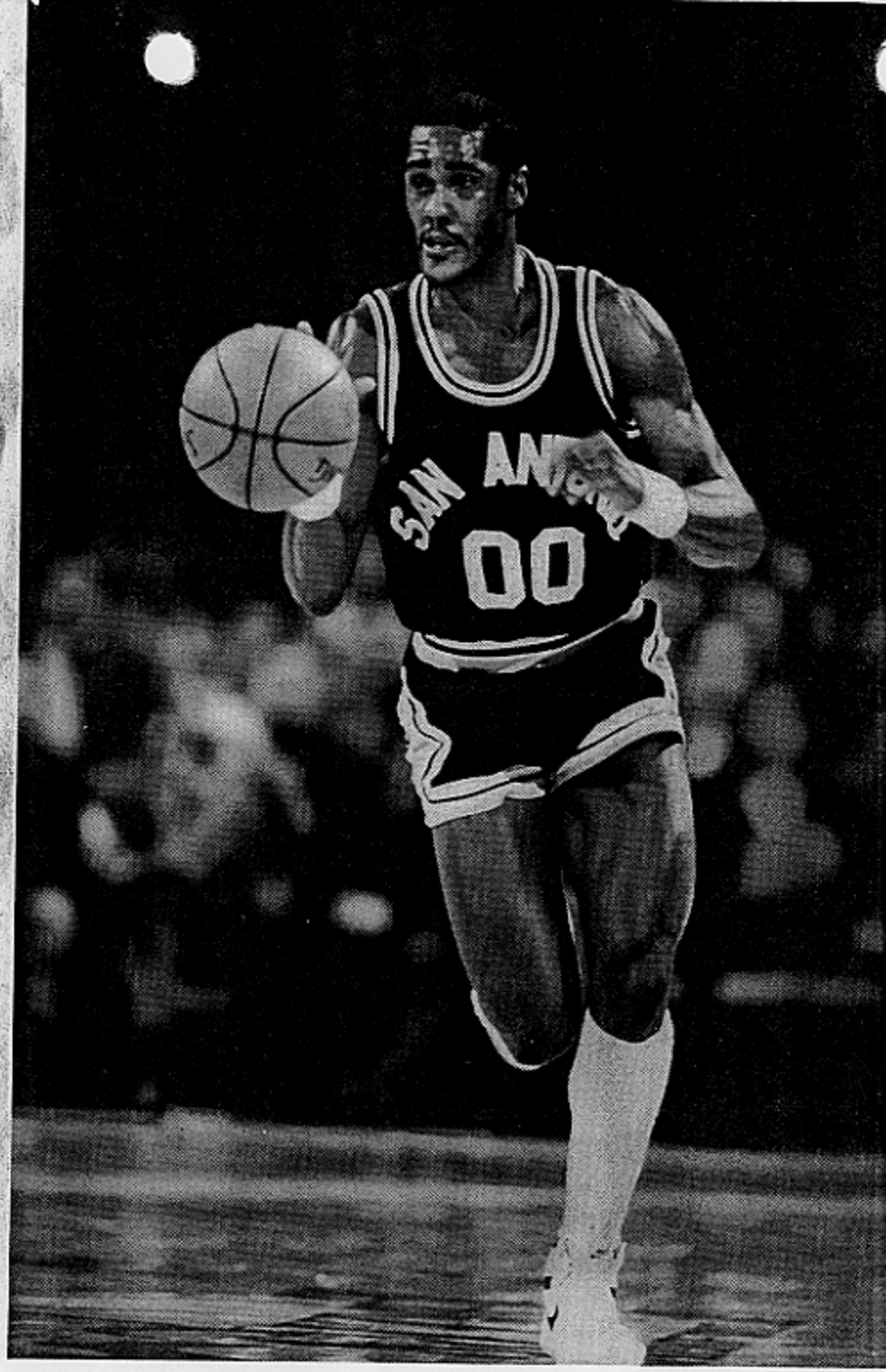
Recently, a collaborative effort has begun to determine the efficacy of a coccidioidal vaccine in humans. The vaccine consists of Formalin-killed spherules. Preliminary trials to assess acute toxicity of the vaccine have been conducted [74, 101]. In those studies, multiple intramuscular doses of 1.75 mg were found to give mild to moderate pain at the injection site but with no abnormalities in standard hematologic and chemistry surveillance. With higher doses, reactions at the injection site were found to be unacceptable. Skin-test conversion occurred in 55% after three doses of vaccine and 100% had boosting of their lymphocyte transformation to coccidioidal antigens.

Since the initial safety trials, a study was begun in 1981 to test vaccine efficacy. Participants are being enrolled at study sites in Bakersfield, Lemoore and Visalia, California, and Tucson, Arizona. Volunteers between the ages of 18 and 55 are eligible for randomization if negative results are obtained with all coccidioidal skin tests (coccidioidin and spherulin, each at the usual and high test strengths). Those randomized have a chest roentgenograph and are bled for serologic studies before receiving either vaccine or saline intramuscular injections administered in a blinded fashion on days 0, 7, and 49. Two weeks after the last injection, skin tests and phlebotomy are repeated. Participants are then surveyed for the duration of the study for episodes of illness compatible with acute coccidioidomycosis, at which time evaluations are performed to establish a diagnosis. For the purposes of this trial, a case is defined by recovery of *C. immitis* and/or a conversion of coccidioidal serologic tests. The data collected at all study sites is being collated for sequential analysis by a review team at Stanford University. Based on the assumption of a 1% per year detectable case rate, it is expected that 9000 participant-years will need to be accrued in order to test the primary hypothesis satisfactorily.

After 2 years of work, over 4000 volunteers have contributed to nearly 2000 randomized participants (the remainder were found to have at least one positive coccidioidal skin test) and approximately 3000 participant-years of surveillance. The trial is expected to finish enrollment (3000 randomized participants) in 1983 and then proceed for an additional 2 or 3 years.

Outcome: no difference was found in the number of cases of cocci or the severity of the disease in the vaccinated vs that of the placebo-receiving control group.

see Reserve Reading 52.12 for review of status of fungal vaccine development!



"I was thinking, if I can just get to the game, I'll be all right."

JOHNNY MOORE
SAN ANTONIO, TEXAS

The point guard for the Spurs never made it to that game against the Lakers back in 1985. Instead, he landed in the hospital, where after 10 days he was diagnosed with a serious fungal disease.

For months, Johnny was plagued by excruciating headaches and terrible nausea. His doctors told him he might go blind and lose the use of his limbs. They said he might even die.

Thanks to excellent care and a medication made possible by the research we do, none of these came to pass. And Johnny got another shot at life.

Health care legislation must ensure that this research continues, so companies like Pfizer can find new medications. And help more people like Johnny.

"They told me I'd probably never have kids," he says. "And now I've got my little girl. I'm so thankful."

1995

Pfizer

WE'RE PART OF THE CURE.

Medline ID:	96149381
Citation:	A Burt, Carter DA, Koenig GL, White TJ, Taylor JW, *Molecular markers reveal cryptic sex in the human pathogen* ***Coccidioides immitis***., Proc Natl Acad Sci U S A **93:** 2, 770-3, Jan 23, 1996.
Address:	Department of Plant Biology University of California Berkeley 94720 USA. #5926

Abstract

Coccidioides immitis, cause of a recent epidemic of "Valley fever" in California, is typical of many eukaryotic microbes in that mating and meiosis have yet to be reported, but it is not clear whether sex is truly absent or just cryptic. To find out, we have undertaken a population genetic study using PCR amplification, screening for single-strand conformation polymorphisms, and direct DNA sequencing to find molecular markers with nucleotide-level resolution. Both population genetic and phylogenetic analyses indicate that C. **immitis** is almost completely recombining. To our knowledge, this study is the first to find molecular evidence for recombination in a fungus for which no **sexual** stage has yet been described. These results motivate a directed search for mating and meiosis and illustrate the utility of single-strand conformation polymorphism and sequencing with arbitrary primer pairs in molecular population genetics.

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