INTRODUCTION

The sixth annual meeting reported in the following pages has been noteworthy in several respects. From the basic and experimental standpoint, there were important reports on epidemiologic and immunologic studies, the production of disease in rabbits, the current progress in the development of a vaccine, and on the pathogenetic aspects of human disease. From the clinical standpoint, there was demonstrated indirect inter-human transmission of the disease, and the various discussions revealed much crystallization of thought on the surgical aspects of pulmonary cavities and on the use of Amphotericin B.

A particularly significant development has been the change in the character of the program itself. Developed originally as a Cooperative Study to conduct controlled randomized investigation, it has changed to a Study Group without this function. However, it can return readily to its original Cooperative Study status when conditions become favorable.

This new VA-Armed Forces Study Group will continue to provide communication between physicians and scientists and bring together the individuals whose research relates to the problems of coccidioidomycosis.

For their continuous aid and encouragement, we are deeply grateful to many in our Central Office, and especially to Doctors William B. Tucker, Edward Dunner and James H. Matthews.

DAVID SALKIN, M.D.

Chairman

March, 1962.

Administrative Session
Thursday Morning, Nov. 30, 1961

Official Representatives Attending

David Salkin, M.D., San Fernando, Calif. (Chairman)
Lawrence G. Wayne, Ph.D., San Fernando, Calif. (Secretary)
Stephen H. Cheu, M.D., Fresno, Calif. (Executive Committee)
Leroy Hyde, M.D., Long Beach, Calif. (Executive Committee)
Robert Stonehill, M.D., Lackland AFB, Tex. (Executive Committee)
Milton Huppert, Ph.D., San Fernando, Calif. (Director, Coccidioidomycosis Central Laboratory)
James H. Matthews, M.D., VACO (Chief, Clinical Research in Pulmonary Diseases)
Arthur L. Ringle, M.D., San Francisco, Calif. (Area Director Professional Services)
Richard Behan, Ph.D., Santa Monica, Calif. (Statistical Consultant)
Wilfrid J. Dixon, Ph.D., Los Angeles, Calif (Statistical Consultant)
Roger O. Egeberg, M.D., Los Angeles, Calif. (Consultant)
Sydney Finegold, M.D. VA Center, Los Angeles, Calif.
Joseph A. Hawkins, M.D., Fitzsimons Army Hospital, Denver, Colo.
William Hentel, M.D., VA Hospital, Albuquerque, New Mex.
A. Gerson Hollander, M.D., VA Hospital, Oakland, Calif.
Donald C. Kent, M.D., US Naval Hospital, San Diego, Calif.
Howard E. Liston, M.D., VA Hospital, Phoenix, Ariz.
John A. McChesney, M.D., Travis AFB, Calif.
Peter R. Meis, M.D. Davis-Monthan AFB, Ariz.
Jean Newton, M.D., VA Hospital, Houston, Tex.
Hugh P. Reveley, M.D., VA Hospital, Kerrville, Tex.
J. C. Soderstrom, M.D., VA Center, Whipple, Ariz.

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Dr. Salkin opened the Administrative Session at 9:15 A.M. with a brief review of the status of the Study.

A total of 757 cases were reported for the years 1955 through 1958, and there are probably an additional 100 to 150 unreported cases. One of the probable reasons for incomplete reporting from some stations was staff transience. After 1958, the Study slowed down for two reasons. Statistical help was not available for evaluating the data already accumulated, and no really good therapeutic agent was available for study.

Last year statistical help became available, and the report forms were revised in the light of shortcomings detected in the analysis. The Executive Committee met at San Fernando VAH on October 16, 1961, and attempted to develop well defined protocols for the Cooperative Study. It soon became apparent that, in the absence of a dramatically effective drug with low toxicity, a chemotherapy protocol could not be adopted. With Amphotericin B as the only drug now available, most of the committee were not willing to use chemotherapy on a regular basis on any but meningeal and miliary cases. This study has averaged only 10 non-meningeal disseminated cases per year, and six meningitis cases per year. Similarly, a history of only 18 resections for cavities per year, and a marked diversity of opinions about indications for surgery made it impossible to develop a protocol for randomized study of surgery.

The Executive Committee concluded that continuation of the Cooperative Study was not appropriate and recommended that a Coccidioidomycosis Study Group be established in its place. Such a group could serve as a nucleus for reactivation of a Cooperative Study at such time as a therapeutic regimen suitable for a protocol study becomes available.

Dr. Matthews was asked to clarify the respective functions of a Cooperative Study and a Study Group. Both are supported by the Research Service. A Cooperative Study accumulates data, its members having accepted a protocol designed to answer specific questions. A Study Group is usually smaller, and brings together people with a particular knowledge in a field. They do not usually submit data on patients to a common pool. Meetings are held once or twice a year and papers may be presented. Only the actual Study Unit members are sent to the meeting with Research funds, but travel for other VA people who present papers may be supported from Cooperative Study money as for Unit VA details and other meetings. The Armed Forces people would be encouraged to belong to and participate in the Study Group; each service would have to arrange its own travel funding. One of the functions of the Study Group would be to evaluate the possibilities for reactivating a Cooperative Study.

The following motion was made by Dr. Stonehill and seconded by Dr. Hyde: "Because of the many sincere differences of opinion with regard to the use of symptomatic therapy, surgery, and intravenous Amphotericin B, the various proposed randomized protocols

for the VA-Armed Forces Coccidioidomycosis Cooperative Study would not be acceptable to enough units to make the small results valid. Therefore, be it moved that the VA-Armed Forces Coccidioidomycosis Cooperative Study be disbanded."

The motion was passed unanimously.

The following motion was then made by Dr. Hyde and seconded by Dr. Meis: "It is moved that this group recommend to the VA Research Service that a VA-Armed Forces Coccidioidomycosis Study Group be established to hold regular meetings of individuals interested in this disease, for the exchange of experiences and ideas. This Study Group could serve as a nucleus for reactivation of a Cooperative Study when a favorable drug appears. The Annual Meeting of the VA-Armed Forces Coocidioidomycosis Cooperative Study has been recognized on a national level as a useful and productive forum for investigators in the field. It is anticipated that the proposed regular meetings of a Coccidioidomycosis Study Group would continue this function. The Armed Forces are encouraged to continue their collaboration with the Veterans Administration in the study of this disease."

The motion was passed unanimously.

In order to complete the missing cases from the 1955-58 group, and to collect a series of selected types of cases, Dr. Salkin offered to review the charts and complete the forms for these missing cases. He requested that the charts be sent to him.

Dr. Huppert presented a summary of the services performed for the Study by the Coccidioidomycosis Central Laboratory. The Laboratory has had the following three major functions:

1. Distribution of a standard lot of skin test antigen.

2. Serological services, including the manufacture of antigens, performance of serological tests and distribution of antigens.

3. Culture bank, including maintenance of culture collection, and performance of special tests on cultures, such as drug sensitivities, and virulence assays.

Summaries of the results of these functions are indicated in the following tables:

Table I

Use and Distribution of Skin Test Coccidioidin
(Smith's Lot 64D4)

1. USE:	Dilution Used	Volume Used	Test Doses
	1:100	1790 ml	17,900
	1:10	315 ml	3,150

2. DISTRIBUTION:

A. VA Units: Albuquerque, Kerrville, Long Beach, Los Angeles, Oteen, Phoenix, San Fernando, Tucson, Whipple.

B. Others: Davis-Monthan AFB, Lackland AFB, Parks AFB, Ft. Detrick, San Diego Naval Base.

Table II

Use and Distribution of C. immitis Serological Antigens

1. Complement Fixation Antigen

a. Use: 16,218 ml.; approx. 8,000 tests.
b. Distribution: Fresno VAH, Kerrville VAH, Long Beach VAH, Los Angeles VAC, Memphis VAH, Minneapolis VAH, Oteen VAH, San Fernando VAH, Tucson VAH, Walter Reed A. I. R.

2. Precipitin Antigen

a. Use: 2,723 ml.; approx. 8,000 tests.
b. Distribution: Fresno VAH, Kerrville VAH, Long Beach VAH, Los Angeles VAC, San Fernando VAH, Tucson VAH.

Table III

Comparison of Serological Results

1. Central Laboratory with Los Angeles VA Center.

2. Central Laboratory with U.C. School of Public Health. (2 series).

	*LA VAC	*U.C.(1960-61)	*U.C.(1957)
Total Specimens	130	85	37
Equivalent Tests	121	77	37
Percent agreement	93	91	100
Central Lab +, other -.	3	7	0
Central Lab -, other +.	5	1	0
Both +, (different titer).	1	0	0

* 1957 series was a controlled study. 1960-61 series and LA VAC were not controlled.

Table IV

Serological Tests Performed by the Central Laboratory

1. Stations for which serology was performed: Kerrville VAH, Livermore VAH, San Fernando VAH, Whipple VAC.

2. Stations cooperating with split specimens: Fresno VAH, Los Angeles VAC, Phoenix VAH, Tucson VAH.

3. Total specimens tested			5679
a. For coccidioidomycosis only		1356	
b. For coccy, histo and blasto		4323	
4. Total number of cases			4556
a. Total negative		4202	
b. Total positive		354(8%)	
Coccy only +.	246(70%)		
Histo only +.	35(10%)		
Blasto only +.	18(5%)		
Coccy and histo +.	19(5%)		
Coccy and blasto +.	7(2%)		
Histo and blasto +.	18 (5%)		
Coccy, histo, and blasto +.	11 (3%)		

Table V

Culture Bank

1. Collection:

Species	Strains
C. immitis	291
H. capsulatum	24
B. dermatitidis	13
Crypto. neoformans	3
Others	
Dermatophytes	47
Candida Species	62
Nocardia Species	220
Miscellaneous Species	24

2. Special Tests Performed on C. immitis cultures.

a. Amphotericin B susceptibility:
For experimental purposes 253 tests
For patient therapy 33 tests

b. Virulence Assay 21 cultures
Range of results 17 days - no end point.
(days from infection to 50% mortality)

Following Dr. Huppert's report, a brief discussion centered around the significance of differences in virulence of various coccy strains for mice. The available evidence indicates that there is no correlation between relative virulence for mice and for man.

The future status of the Coccidioidomycosis Central Laboratory was next considered. Dr. Matthews felt that the Laboratory would probably revert to a local project within the framework of the San Fernando VAH research program. However, he pointed out that the lack of a formal cooperative study need not preclude collaborative studies to continue some phases which were in the Cooperative Study. Such collaborations would not be centrally directed. They might lead to pilot studies which, in turn, could lead to resumption of a new Cooperative Study.

The Administrative meeting was adjourned.

First Scientific Session
Thursday Morning, Nov. 30, 1961

R. Egeberg, Chairman

1. THE VA-AF COCCIDIOIDOMYCOSIS COOPERATIVE STUDY

D. Salkin
San Fernando, California

1. The 4-year retrospective study (1955-58) of proved coccy cases admitted to VA-AF hospitals yielded 757 patients. We are certain that this is not a complete figure; some Study Units failed to report a substantial number of their cases due to frequent staff changes and (we suspect) disinterest in some hospitals.

2. The study then slowed down for a number of reasons, but chiefly because of our inability to obtain adequate statistical help and the lack of a first class treatment for the disease.

3. In the past year, we were able to obtain adequate statistical aid, first from the Planning Research Corporation, and then from the System Development Corporation (Dr. Behan). In addition, Dr. Wilfrid Dixon consented to be our consultant in biostatistics. After many sessions, we finally developed 5 types of forms for any proposed controlled studies: (1) registration, (2) cavity cases, (3) dissemination cases, (4) chemotherapy, and (5) surgery.

4. With full armamentarium and full intention to start randomized studies, the Executive Committee met Oct. 16, 1961 and analyzed the number and type of cases to be expected as gauged by the retrospective study:

	Total cases	Disseminated Cases		Resections for cavities
		Meningeal	Other	
All VA-AF hospitals	757	61	30	111
Original 18 Study Units	645	44	26	87
Present 15 Study Units	562	41	26	72
Yield per Annum (Based on 15 Study Units)		10	6	18

5. After much discussion, no conclusion could be reached on any randomized type of study. In disseminated cases, the use of Amphotericin B ranged from treating all cases to treating none. In meningitis, everyone wanted to treat all cases. In surgery for cavitary disease, opinions ranged from one end of the spectrum to the other.

6. Because of the many irreconcilable differences of opinion, the various considered randomized studies would not yield enough cases to give statistically meaningful results and it was therefore agreed unanimously that the Cooperative Study should be disbanded.

7. It was agreed, however, that, in its place, there should be a VA-AF Coccy Study Group and that the Annual Meetings should be continued.

(Post Scriptum

(1) The entire Study Group upheld the decision of the Executive Committee by a unanimous vote.

(2) Central Office agreed to the establishment of such a Study Group and to the Annual meetings.)

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2. PITFALLS ENCOUNTERED AND LESSONS LEARNED IN THE COCCIDIOIDOMYCOSIS STUDY

R. A. Behan
Santa Monica, California

Pitfalls in a research program arise out of an attempt to deal with problems on an unfortunate level of generality. As such, pitfalls are symptomatic of inadequate planning on the part of the investigator.

The research program should be arranged to include a period for testing data collection procedures prior to the start of the program proper. Such a test period, if adequately planned, allows one to encounter certain pitfalls prior to entering upon the formal research program; thus pitfalls can be used to improve the research effort.

During the planning phase of the research project there are three procedural conventions, which, if followed, help eliminate many pitfalls. The first of these is to make a concrete statement of the problem, or problems, to be investigated. A concrete statement of the problem makes it possible to specify the data which must be collected and thus allow one to determine data collection techniques. Failure to state the problem adequately results in lack of comparability of data and frequent changes in research procedures.

A second convention is to define the terms used in the statement of the problem in relation to things people will do in the process of generating data. Such an operational definition specifies data generation procedures and facilitates communication among researchers, which is particularly important in cooperative studies. Failure to prepare operational definitions results in the collection of unreliable data and in the preparation of invalid conclusions.

A third convention is to specify the conditions under which the study will be run. Considerations here include rules for: (1) admission of a patient to the study; (2) specification of the treatment a patient will receive; (3) specifying conditions for a change in treatment regimen; (4) determining criteria to assess success of treatment, etc. Failure to specify the conditions under which a study will be run is often indicated by reliance upon large numbers of cases, in the hopes that differences will be randomized away. This is a false hope. Randomization is a procedure for eliminating the effects of differences among patients. Differences in procedure can only be confounded in the data. These operate to reduce the validity of conclusions drawn from the data.

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Discussion from the floor: In a cooperative study, a pilot run permits use of judgments in modifying a protocol, but once a protocol is established, it relegates participants to a role where judgment is minimized. In the long run, the final accumulation of data is tedious and nothing can prevent this. Although most important medical discoveries have been made, in the past, without benefit of the elaborate statistical controls discussed here, future progress will probably demand more and more of these statistical controls. As the more dramatic and straightforward answers are found, the problems that remain will require ever more subtle and sophisticated analyses to resolve them.

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3. EPIDEMIOLOGIC ASPECTS - 20 YEAR CHANGE IN COCCIDIOIDIN REACTIVITY

T. R. Larwood
Bakersfield, California

In 1938-9 Gifford, et al, skin tested over 3,000 Kern County students with coccidioidin, finding 68% positive reactors among 900 high school students and 55% reactors in the 2,200 elementary students tested. In 1959 we had the opportunity of testing 870 high school students and 2,960 elementary children. Twenty years after the original study the positive reactor rates had, surprisingly, fallen to 40% and 17%, respectively. This reveals a drop of 41% in the high school group and 69% in the elementary grades. Differences in testing methods (personnel and nature of coccidioidin) were mentioned but could by no means account for a change of this size. Other studies were referred to, but no such comparisons after a period of years have been made. This seems to show that Kern County has conceded to Southern Arizona the honor of highest incidence of coccidioidin reactivity (ergo infection rate).

Possible factors accounting for the change were discussed and it was concluded that they are probably the obvious ones: (1) Great increase in cultivation of the area; (2) Less students in the fields; (3) More living in towns.

It would be interesting to see the results of follow-up studies in some of the other areas where large surveys were done 10-20 years ago, perhaps where the above factors have not changed.

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Discussion from the floor: A number of participants questioned the comparability of the coccidioidin used in Gifford's original survey and the current survey. The need for more study of long term persistence of a positive skin reaction in people who are removed from an endemic coccy area, was also stressed.

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4. SOME STUDIES WITH DIFFERENT FRACTIONS OF THE CULTIVATED SPHERULE OF COCCIDIOIDES IMMITIS IN COMPLEMENT FIXATION, INDICATING ANTIGEN CONCENTRATION IN ONE FRACTION.

A. M. Breslau and E. T. Peterson
Los Angeles, California

This is a report on some complement fixation studies using spherules of C. immitis that have been under continuous culture for three years. In determining optimal dilution of antigen fractions, controls were utilized at each dilution to detect hemolytic and anti-complementary activity. Two units of complement were employed.

Whole spherules, washed free of medium, reacted optimally in dilution of 1:400 to 1:700. The pattern of reaction with a number of sera and spinal fluids was similar to that of Dr. Huppert's mycelial antigen diluted 1:8.

Both cytoplasm with its polysaccharide, and cell wall exposed by homogenization reacted optimally at 1:400 in one and 1:250 in the other set of tests. The exposed cytoplasm decreases complement fixation, perhaps by blocking wall antigen.

Electron microscopy of washed cell walls demonstrates mats of microfibrils enclosing amorphous matrix. The optimal dilution for complement fixation is 1:250 in the first set and 1:125 in the second. The pattern reaction is still very similar to Dr. Huppert's antigen utilized at 1:8 dilution. The loss in activity is probably due to washing.

Washed cell walls were sonicated and rewashed. Electron microscopy demonstrates the removal of amorphous material from the wall. Optimal dilution dropped to 1:50, and below this, marked anti-complementary activity is present. Centrifuging the supernate at 4500X gravity supplied a fraction composed of microfibrils and amorphous material which fixed complement optimally at 1:600 dilution, with a reactive pattern similar to that of Dr. Huppert's antigen. The supernatant, when reconcentrated, showed little activity.

Washing with distilled water instead of saline halved the complement fixation activity of the whole spherule and of the broken spherule, and removed all the activity from all the other fractions.

We may conclude tentatively that most, if not all, complement fixation activity of the cultivated spherules is in the wall, in the fraction that is removed by sonication and water from the fibrous meshwork.

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Discussion from the floor: In reply to a question about the identity of in vivo and in vitro spherules, Mr. Breslau indicated that the mode of spherule development was different and that the phospholipid layer appeared to occur only in spherules developed in vivo.

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Second Scientific Session
Thursday Afternoon, Nov. 30, 1961

A. Ringle, Chairman

5. INTERESTING ASPECTS OF A CASE OF DISSEMINATED COCCIDIOIDOMYCOSIS

W. E. Escovitz
Long Beach, California

This 38 year old white male dug for sharks' teeth for one hour, several miles from Bakersfield, California, on August 5, 1961. On August 23, he had his first symptoms of cough, wheezing, fever and chest pain. On August 30, the first sign of dissemination occurred: scattered, pruritic, erythematous papules. Chest x-ray and chills started on September 5. The coccidioidin skin test (1:100) was positive on September 13; it had been negative in 1960.

On hospitalization the temperature was 100.4°F. The liver and spleen were not palpable. The lesions were now papulo-vesicles up to 4 cm. in diameter, with central umbilication.

Skin scrapings on September 27 showed large endospores; skin biopsy on September 28 showed coccidioidal dermatitis. Sputum cultures of September 28 grew Coccidioides immitis.

The patient received 473 mg. Amphotericin B intravenously between September 26 and October 27; further treatment was precluded by the patient's refusal to continue with the medication. Vomiting continued almost daily even after Amphotericin B was stopped. After trial of many medications, vomiting stopped abruptly when thorazine, 50 mg. qid, was started; on discontinuance of thorazine 2 weeks later, vomiting did not recur. The patient, afebrile since October 8, began to ambulate with rapid clinical improvement thereafter.

The following serial observations were made just before treatment with Amphotericin B began, and extended to one month after completion of therapy. The coccidioidin skin test (1:100) gradually was reduced from 2 plus to just minimally positive. However,

skin test with 1:1
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A 34 year old
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he developed cou

test with 1:10 dilution was 4 plus. The precipitin test changed 1:40 to 1:10 and complement fixation titer rose steadily from 1:4 64, at which level it stabilized. The BUN rose from 8 mgs% to gh as 46 mgs% during treatment but returned to normal there-r. The hematocrit fell from 43% to 32%; eosinophiles from 27% %; the sedimentation rate rose from 35 mm. to 46 mm. (uncor-ed for anemia). The following tests were normal: serial alyses, liver function, and spinal fluid examinations (including ology for coccidioidomycosis). Because vomiting continued ts after Amphotericin B was discontinued, an EEG was taken showed convulsive disorder of centrocephalic origin. Skull ys were compatible with either thinning of the occipital bone or ns of the corpus callosum. Neither the x-ray nor EEG findings as yet been evaluated as to their relationship to coccidioido-sis.

The patient's two children, ages 9 and 13, who stood about 4 feet the patient while he was digging, have negative skin and are ptomatic.

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Discussion from the floor: No information was available on the cal EEG pattern or on the effect of Amphotericin B, itself, on EG. Several participants expressed a desire to hear a follow-up his case a year later, since the failure of the complement fixation r to drop suggests that the disease may recur. Dr. Hyde has seen nts remain well after therapy, even though the titer did not drop w 1:64. Dr. Stonehill pointed out that a high percentage of patients, out a significant drop in titer, break down later. Dr. Einstein that the type of disease described here usually has the best prog-s, among caucasians, of any disseminated types, even without photericin B.

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6. COCCIDIOIDAL MENINGITIS WITH EARLY NEGATIVE SEROLOGIC STUDIES

L. Hyde
Long Beach, California

A 34 year old white male, L.D.K., had a routine chest x-ray in e 1960, which was said to have been normal. On October 3, 1960 developed cough, fever, and right chest pain, and was

admitted to the VA Hospital at Tucson, Arizona. Chest x-rays revealed a bronchopneumonic density at the right base with a small pleural effusion. The impression was bronchopneumonia, probably coccidioidomycosis. His coccidioidin skin test (strength not noted) was positive at that time. He developed headaches at discharge 10 days later, and went to the VA Hospital, Amarillo, Texas, as the intensity of his headaches steadily increased. On 1/3/61, he was readmitted to VA Hospital, Tucson, with evidence of meningitis, and severe headaches, especially located in the occipital and temporal areas.

Spinal fluid examinations on numerous occasions were always abnormal with varying amounts of cells between 200 and 500 (mainly lymphocytes), and increased protein (between 100 and 125 milligrams percent). Direct examination of the fluid was negative for acid-fast bacilli, spherules, and Torula.

The chest x-ray was now entirely normal, and coccidioidin skin tests with 1:100 antigen were repeatedly negative; with the 1:10 antigen the reaction was negative on several occasions, but positive on one occasion. Serologic tests for coccidioidal infection were done on January 18, 1961, February 9, 1961, and February 23, 1961, andthese were reported as being entirely negative.

Subsequently, the patient required craniotomy because of rapidly increasing intracranial pressure, and he was transferred to Long Beach VAH. No tumor was found, but biopsy of the meninges revealed coccidioidal spherules. The fourth coccidioidal complement fixation study done on August 16, 1961, was positive on both blood serum at 1:8 (4+) and spinal fluid at 1:4 (4+). The early negative serologic studies are unusual and emphasize that negative coccidioidal serologic studies cannot always rule out coccidioidal meningitis.

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Discussion from the floor: A number of participants had also had experience with coccidioidal meningitis with negative CSF complement fixation test. Up to 25% of meningitis cases may show this. Dr. Einstein mentioned a case of meningitis with falling titer; autopsy showed a coccidioidal lesion around the pituitary gland.

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7. PALLIATIVE VENTRICULOATRIOSTOMY IN COCCIDIOIDAL MENINGITIS

J. A. Hawkins
Denver, Colorado

This is a report of a case of coccidioidal meningitis treated by ventriculoatriostomy with sustained relief of symptoms of increased intracranial pressure.

This patient is a negro female who was 23 years old and living at Edwards AFB, California in January 1959, when she developed symptoms of headache, nausea, vomiting and double vision and was found to have papilledema. Study showed her to have a positive coccidioidin skin test, positive precipitin test and positive low titer coccidioidal serologic complement fixation test. She had increased CSF pressure, lymphocytosis, increased protein and lowered sugar. Cultures of cerebrospinal fluid were negative and remained so throughout her course, as have all other attempts to recover the organism. Chest x-ray was negative and remained so. Initial CSF complement fixation titers were negative. On January 24 she was started on intravenous Amphotericin B. No intrathecal drug was given. By mid-March 1959 she had lost her meningeal symptoms and a short time later her papilledema disappeared. Her precipitin test became negative quite shortly. Complement fixation studies of serum increased to a maximum of 3+ at 1:32 dilution in May and June and then continued positive at a lower titer. Complement fixation test of cerebrospinal fluid became positive in March and remained so, also in low titer. In November 1959 intrathecal Amphotericin B was recommended to the patient. She was reluctant to accept this and was lost to follow-up for almost one year. In November 1960 she was readmitted with recurrence of her symptoms of headache, nausea and diplopia. She was again found to have papilledema, increased CSF pressure and abnormal spinal fluid cells, protein and sugar. It was decided that intrathecal therapy should be given. An initial dose of .025 mgm was given without incident and over a period of days this was increased to 0.1 mg. On the evening of the day of this dose the patient became acutely ill with severe headache, severe vomiting and blindness. These symptoms were transient but we were dissuaded from pursuing this form of treatment. Over the next few months she developed difficulty with memory, drowsiness, rather marked ataxia and later, bilateral temporal field defects. In early April 1961

ventriculography was performed. Marked ventricular enlargement was demonstrated involving all ventricles including the fourth ventricle and no cisternal air was seen.

On April 11, 1961, a ventriculoatriostomy, using a Holter valve, was performed. Her CSF pressure has returned to normal. Her vision has not returned but she has good mentation and is now ambulant at home. Her valve is functioning very satisfactorily. Spinal fluid CF titer in November 1961 was 1:512 and her serologic titer was 1:64.

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Discussion from the floor: Dr. Winn presented a similar case and noted marked palliation of the disease.

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8. SUBARACHNOID BLOCK DUE TO COCCIDIOIDAL MENINGITIS, TREATED BY VENTRICULOATRIOSTOMY

M. O. Locks
Long Beach, California

In chronic coccidioidal meningitis, the strategic location of the inflammatory exudate in the posterior cranial fossa results in mechanically blocking the egress of the cerebrospinal fluid from within the ventricular system of the brain to the site of absorption in the subarachnoid space external to the brain and spinal cord. This blockade produces a progressive internal hydrocephalus with increasing compression of the brain substance, and eventually contributes to the patient's demise.

Numerous procedures have been devised to shunt cerebrospinal fluid from within the ventricular system to absorptive areas external to the brain. Many had to be discarded because of ineffectiveness of the mechanical device employed for the shunt, or because the procedure employed resulted in a serious neurological deficit. A device is now available consisting of a unidirectional plastic valve and tubing which permits the flow of cerebrospinal fluid from the brain to the right atrium of the heart. This procedure, termed ventriculoatriostomy, is technically simple and does not cause any significant neurological deficit. By this means, increased intracranial pressure, with its attendant symptoms, may be relieved

promptly, and the institution or continuation of appropriate antibiotic therapy directed against the causative organism responsible for the subarachnoid block is made possible.

Two patients ill with chronic coccidioidal meningitis and severe subarachnoid block manifested by increased intracranial pressure were submitted to ventriculoatriostomy. Both achieved relief from the symptoms and signs of increased intracranial pressure, and this was confirmed by manometric measurements within the subarachnoid space. As a result of this procedure it was possible to institute appropriate antibiotic therapy to one patient, and to repeat additional courses of antibiotic therapy in the second patient. Had not the elevated intracranial tension been relieved, both patients would have rapidly succumbed to their disease.

Problems related to maintenance of a patent shunt have occurred, and these are primarily related to the proper placement of the distal portion of the shunt tube within the right atrium. The danger of colonization of these shunting devices with bacteria, particularly Staphylococcus aureus, with consequent bacteremia is of significant concern, and demands review of methods and techniques utilized for this procedure.

For the present, however, when confronted with an adhesive arachnoiditis resulting from the mycotic infection which prevents the proper circulation of cerebrospinal fluid, we have available a procedure that affords the patient a chance for useful survival without inducing any serious neurological deficit. At the same time it provides the clinician with a further chance of administering appropriate therapy to combat the underlying disease.

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Discussion from the floor: The question was raised of the hazard of hematogenous spread of infective units introduced by this technique, from the spinal fluid. Dr. Hawkins felt that it added no significant increase in such units; he has seen no new disease foci in his patient.

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9. SCALENE LYMPH NODE INVOLVEMENT IN PRIMARY AND DISSEMINATED COCCIDIOIDOMYCOSIS - EVIDENCE OF EXTRAPULMONARY SPREAD IN THE PRIMARY INFECTION

J. W. Coburn
Los Angeles, California

In only two previous instances has a positive scalene node biopsy been reported in coccidioidomycosis, and in neither report was clinical information about the extent of the disease given. Six cases are reported in which a diagnosis of coccidioidomycosis was made by scalene node biopsy. Only two patients suffered disseminated disease. A third had a pulmonary residual which remained stable during a follow-up period of two years. In the other three patients, although there was fear of dissemination, the clinical course and multiple serological studies provided no evidence of dissemination; it is concluded that these patients had benign primary coccidioidomycosis without dissemination.

These data, as well as a review of clinical and pathologic evidence in the literature, indicate that involvement of the scalene node with coccidioidomycosis occurs in both primary benign infections and as part of disseminated disease. It is concluded that the scalene node biopsy may be a useful method of obtaining an early diagnosis of coccidioidomycosis; however, other clinical and serologic observations are more important with respect to prognosis.

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Discussion from the floor: Dr. Salkin mentioned 7 cases in the Cooperative Study in which definitive diagnosis was made by scalene node biopsy. There is a need for a study of all acute primary cases to see how high up the lymphatics coccy can go without causing disseminated disease, as suggested in the Cooperative Study Newsletter of July 1, 1959.

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PANEL

SURGERY IN COCCIDIOIDOMYCOSIS

Moderator: J. D. Steele, San Fernando, California

Panelists: B. Evans, Fresno, California
G. A. Paulsen, Bakersfield, California
J. M. Salyer, Santa Ana, California
R. B. Stonehill, Lackland AFB, Texas

Moderator: What are your indications for surgery?

Salyer: 1. Peripheral cavitary lesion - i.e., if considered near pleural surface - appropriate localizing roentgenographic studies having been accomplished.
2. An enlarging cavitary lesion regardless of pulmonary location.
3. Cavitation considered to be the site responsible for repeated and troublesome hemoptyses.
4. Recurrent cavitary disease(following previous resection) - if such is considered etiologic in production of significant pleuritic symptoms and/or bronchopleural fistula.
5. The rare secondarily infected and symptomatic coccy cavity.
6. Suspected coccidioidoma (granuloma) for purposes of definite pathologic identification or for reasons related to furtherance of military occupation.

Evans: Agrees with Salyer. Used mainly against residual disease.

Paulsen: Urgent indications are enlarging or tension cavities, and ruptured cavities. Elective procedures are resection of residual cavities, coccidioidomas, and bronchiectasis and decortications.

Stonehill: The Air Force has an extra indication; personnel can't fly with a cavity. Therefore they routinely resect air containing spaces. In a test series, x-rays showed only one patient's cavity to enlarge at 40,000 feet, but cavities of others might block later and expand at altitude.

Moderator: Any disagreement from the floor?

None was expressed.

Question: (Hollander): How much bleeding is an indication for surgery?

Evans: Recurrent hemoptysis, even though small. Frank hemorrhage is infrequent.

Moderator: What is your experience with complications?

Salyer: Wedges or segmental resection for cavities give most frequent complications, about four times as frequently as seen with lobectomies.

Evans: The most dangerous complication is an infected pleural space. Four of a series of 100 resected patients had recurrent cavities; 3 were lobectomies, with one recurrent cavity on the opposite side, and the other two elsewhere in the same lung; the fourth recurrent cavity occurred adjacent to a wedge resection.

Paulsen: Had similar experiences.

Steele: The surgeon should note what residual disease he leaves in the lung in order to be able to evaluate whether a "recurrent cavity" is actually a surgical complication.

Question: (Cotton): How many recurrent cavities are actually caused by surgery?

Salyer: Some.

Evans: Has had one, due to incomplete prior surgery. The old sutures were in the "new" cavity.

Paulsen: Has had two, due to incomplete removal of cavities.

Salkin and Birsner: Pre-operative planigrams and other x-ray studies are needed to tell if the "new" cavities actually existed before surgery.

Salyer: Feels that complications occur more frequently in coccy surgery than in surgery for comparable TB.

Paulsen: In comparing 100 TB and 100 coccy surgeries, he feels the TB's looked worse. Is no more afraid of coccy than any other pulmonary surgery, e.g., Staph abscess, TB.

Stonehill: Agrees with Paulsen. Is against prophylactic Amphotericin B.

Question: (Winn): How many resections have you backed away from?

Salyer: None of large cavities; has questioned need of resecting some small ones and withdrawn.

Evans: Two, both 12-14 cm cavities, to avoid pneumonectomy.

Paulsen: One case with prior surgery which had led to new lesions.

Steele: One, in which he substituted thoracoplasty.

Stonehill: Has seen few complications; some air spaces, very few bronchopleural fistulas. The young age group and excellent physical condition of his patients minimizes the problems.

Paulsen: Four of seven of his complications have been in diabetics.

Salkin: Presented the following figures on complications from 200 resections in the Cooperative Study: Total complication rate was about 13%. Specific coccy complications occurred in about 4.5%. This is comparable to TB surgery figures.

Moderator: What kinds of surgery do you do? In cavities, satellites are scattered through the lobe and lobectomy can avoid recurrent cavities. In nodular disease, satellites are closer in and segmentals are safer.

Question: (Sachs): What is the incidence of multiple cavities in non-operated cases?

Salkin: In 167 with cavities, reported in the Cooperative Study, 29, or 17%, had multiple cavities; 6 patients had bilateral cavities.

Winn: Of 250 cavities he has followed, about 5% are multiple.

Evans: Worries most about residual space, since long persistence is likely to lead to coccy infection of the space. Lymph nodes are probably always involved and surgery just attacks a local mechanical problem, i.e., it is not eradicative. He is conservative with cavitary disease.

Question: (Hollander): What percent of resected cavitary patients in the Air Force return to flying duty?

Stonehill: Practically all. Ventilatory function tests are performed pre- and postoperatively and are very rarely seen to drop below normal. The exceptions are cases with borderline function preoperatively. What is the surgeon's experience with coccy empyema?

Paulsen: Treats like any other empyema.

Evans: Has success with decortication.

Salyer: Of four treated, good results were obtained with decortication, drainage and tailoring thoracoplasty.

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Third Scientific Session
Friday Morning, Dec. 1, 1961

J. Matthews, Chairman

10. EXPERIMENTAL COCCIDIOIDOMYCOSIS IN THE DUTCH RABBIT

E.A. Brosbe, J. Kietzman and N.B. Kurnick
Long Beach, California

Previous work carried out in our laboratory indicated that the rabbit may be a good animal to employ for evaluation of drugs in the treatment of disseminated coccidioidomycosis, since the course of the disease could be followed by complement fixation (CF) studies. However, the new Zealand albino rabbit was somewhat variable in its response to an intravenous inoculation of Coccidioides immitis, and it appeared worthwhile to determine whether a more reproducible disease could be induced in another breed of rabbit.

Young, male, Dutch rabbits were inoculated intravenously with Silveira strain of C. immitis. An infective dose of 6,000 viable units resulted in 4 of 6 deaths occurring from the 13th to the 32nd week following inoculation. The maximum CF titer ranged from 1:4096 to 1:16,384 and was attained at the 6th to the 24th week. Six of 8 rabbits inoculated with 12,000 viable units died from the 11th to the 28th week after infection. Accidental deaths of the 2 remaining animals occurred at the 12th and 30th week. The maximum CF in this group of 8 animals ranged also from 1:4096 to 1:16,384, and was reached at the 8th to the 20th week. In both series the titers generally dropped slightly from the maximum before death, but good correlation was found with the extent of the disease observed at autopsy.

These findings indicate that the Dutch rabbit is highly susceptible to experimental coccidioidomycosis induced by intravenous inoculation of the Silveira strain of C. immitis and that the course of the disease can be followed by complement fixation studies.

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Discussion from the floor: Precipitin tests were rarely performed in this study, and were unsuccessful. Urine cultures were not performed, but cultures of kidneys were positive.

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11. A VIABLE PROPHYLACTIC VACCINE AGAINST COCCIDIOIDOMYCOSIS IN MONKEYS

J. L. Converse, M. W. Castleberry, and E. M. Snyder
Fort Detrick, Maryland

Monkeys (Macaca mulatta) received either a single injection of a viable vaccine (10,000 or 1,000 Coccidioides immitis, strain Silveira, arthrospores, 4 animals per dose level) or 3 injections of formalin-killed arthrospores (an additional 4 animals), in the medial surface of the right forearm. Six months after vaccination these animals, together with a group of nonvaccinated control monkeys, were challenged by the respiratory route with a calculated inhaled dose of approximately 7,000 viable strain Silveira arthrospores. An additional group of monkeys receiving the viable vaccine (10 to 10^8 spores in 10 fold increments) but not challenged by the respiratory route, was maintained as "dissemination controls".

The effects of subcutaneous inoculation of the viable vaccine were determined by clinical observation, coccidioidin skin test, precipitin and complement fixation tests, and x-rays. These observations were continued after respiratory exposure. Histopathological and cultural examinations were performed at death, or upon sacrifice at 5 months postrespiratory challenge.

Vaccination with live arthrospores resulted in subcutaneous lesions 1 to 3 cm in diameter. Enlargement of the right axillary lymph nodes and draining arm lesions were noted in approximately 50 percent of the animals. The open lesions healed, and the majority of the axillary lymph nodes had returned to normal size 6 months following vaccination. At this time, all monkeys receiving the viable vaccine exhibited skin hypersensitivity to coccidioidin; the reactions of those vaccinated with the killed product remaining doubtful (some erythema, but no induration). With one exception, the precipitin and complement fixation titers of all vaccinated animals had either returned to normal or were at a low level (1:4 to 1:64).

Following respiratory exposure, the nonvaccinated control monkeys, and those vaccinated with the formalin-killed product, exhibited extreme debilitation, suffering from loss of appetite, emaciation, and pronounced accelerated respiration accompanied by coughing. Widespread, wispy, infiltration throughout all lobes of the lungs and visible consolidation in some areas were noted in x-rays of these animals 15 days after respiratory exposure. The complement

fixation and precipitin titers of the majority of the nonimmunized controls rose to 1:256, (with extremes of 1:64 and 1:1024) during the 5 months holding period. More than half of the control group and of the formalin-killed vaccine group died from pulmonary coccidioidomycosis within 4 months after respiratory exposure.

In contrast, monkeys vaccinated with the viable preparations exhibited no visible clinical symptoms of the disease, following respiratory challenge. The x-rays were negative throughout the 5 month holding period, and the majority of serological titers remained at a low level (1:4 to 1:64). No deaths occurred in this group.

Upon autopsy, the lungs of the nonimmunized control group and formalin-killed vaccine group were bosselated in appearance, and were covered with surface lesions. Large palpable consolidated areas present throughout all lobes of the lungs were caseous and necrotic upon section. There was extensive adhesion of the lungs to the pleura and diaphragm. Histopathological examination revealed granulomas with spherules in the lungs of every animal in these two groups, and extrapulmonary dissemination in more than half of them. All lung cultures were positive for C. immitis.

In 5 animals of the viable vaccine group, histological lung sections revealed several self-contained, focal lesions containing spherules. This minimal involvement, because of the character of the lesions and the time intervals involved, was attributed to the vaccine injection rather than the respiratory challenge. This was further indicated by the increase in the number of animals showing this condition with increases in the viable vaccine dose. Moreover, the only positive lung cultures in this group occurred in animals receiving the highest vaccine dose.

Eighty percent of the "dissemination controls" (vaccinated but not challenged by the respiratory route) exhibited this same minimal systemic dissemination of the organism from the cutaneous infection to the lung, but with no physical signs of illness.

It was concluded that the administration of a viable vaccine (strain Silveira) protected monkeys against pulmonary infection from a later respiratory challenge with C. immitis. This protection was not strain specific, since similar use of strains Cash or M-11 as a viable vaccine resulted in equal protection. It was further concluded that, although minimal, self-contained, systemic dissemination resulted

from injection of higher doses of viable vaccines, none resulted from a 10 spore dose. No protection resulted from the use of a nonviable vaccine.

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Discussion from the floor was deferred until after presentation of the next paper.

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12. INFLUENCE OF A KILLED SPHERULE VACCINE IN CYNOMOLGOUS MONKEYS INFECTED WITH AIRBORNE COCCIDIOIDAL ARTHROSPORES

H. B. Levine, R. L. Miller and C. E. Smith
Oakland, California

Immunity to coccidioidomycosis, induced by killed vaccines, has been examined primarily in the mouse; however, recently the susceptibility of Cynomolgous monkeys to the disease has been documented. It was found in the present study that 5 of 10 untreated Macaca irus died and 2 were moribund within 9 months after respiratory infection with 200 coccidioidal arthrospores. None of 7 animals previously vaccinated with formalin-killed spherule-endospore elements of the fungus succumbed to the above dose but one vaccinated animal, challenged with approximately 400 arthrospores, died within a seven-week period. It was demonstrated roentgenographically that both early and late pathologic changes in the lungs were less extensive in the vaccinated group than in the control group and these observations were in accord with findings at necropsy. The etiologic agent was recovered from the lungs of all surviving animals but histopathologic studies demonstrated that the parasite was contained more effectively within the pulmonary lesions of the vaccinated monkeys.

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Discussion from the floor: In answer to questions on future plans for the vaccination studies, Dr. Levine intends to continue working with Cynomolgous monkeys, using lower infecting doses, fewer boosters and a longer holding period. Although interested in comparison of species of monkeys, he believes that Cynomolgous monkeys show greater pulmonary involvement than do Rhesus monkeys and

will confine his work to the former. The low inoculum studies will employ challenge doses of 20 viable units, and he expects discrete lung lesions and a few deaths.

Mr. Converse will concentrate, in the immediate future, on the problem of dissemination of the viable vaccine beyond the site of inoculation. He is not sure whether the pulmonary lesions that followed vaccination were a result of true dissemination, or of transfer of fungi from the skin to the mouth and thence to the lung. Mr. Breslau inoculated a small series of mice subcutaneously in the back, with a viable spherule vaccine, and saw no dissemination. Dr. Levine encountered less than 10% dissemination in mice with the Silveira strain.

Dr. Winn has seen about 6 human cases of primary cutaneous infection in man, and has seen no dissemination beyond the regional lymph nodes; he has heard a rumor of a case with fatal dissemination. Dr. Meis has seen 2 human cases of primary infection in the foot and knows of 4 more, and none disseminated beyond the regional nodes.

Dr. Stonehill asked whether low virulence strains are available for vaccine study, since there did not appear to be strain specificity in the vaccines studied. Mr. Converse replied that there is no correlation between severity of disease in man and mice, mice and dogs, or mice and hamsters. He knows of no strains which are avirulent for all animals. Dr. Huppert has a couple of strains which do not kill mice but produce lesions. Dr. Levine stressed the importance of route of inoculation in such studies. He has experience with a riboflavineless mutant of the Silveira strain produced by x-irradiation. It was non-lethal on intranasal inoculation of a million viable units to mice, but later reverted to virulence. If a stable, non-virulent strain were found, that could be eradicated from the host, it could be used.

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13. INTERHUMAN TRANSMISSION OF COCCIDIOIDOMYCOSIS

B.H. Eckmann, M. Huppert, and G. Schaeffer
Riverside and San Fernando, California

Interhuman transmission of coccidioidomycosis has not been definitely demonstrated to have occurred in the past. Direct transmission of the disease is still subject to considerable doubt, although

this is theoretically possible. Indirect transmission via fomites has been previously described on numerous occations, but is a relatively uncommon occurrence. Evidence is presented here to show that indirect transmission has occurred in nature, in a hospital situation. This method has been by interhuman transmission via growth on a bedside fomite. Six cases of primary coccidioidomycosis developed almost simultaneously. Evidence of this infection in these individuals varied from frank clinical findings with recovery of the organism, to conversion of the coccidioidin skin test, to x-ray and serologic findings consistent with this diagnosis. The method of transmission in this case was apparently a plaster cast in proximity to a draining coccidioidal sinus from a knee and ankle. Organisms were cultured from this cast.

A new hazard in the handling of draining or open lesions of coccidioidomycosis has therefore been described. Recommendations are made to avoid such a situation, if possible, and to control it if it is suspected.

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Discussion from the floor: A follow-up study is being made of other hospital personnel who didn't become ill. Included in the study will be contacts and non-contacts of the original source at that hospital, as well as personnel of other hospitals in the area. Dr. Huberty described a similar episode that occurred at U.C.L.A.

Dr. Eckmann said he believed two of the cases received compensation for the infections.

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14. PATHOGENETIC CLASSIFICATION OF COCCIDIOIDOMYCOSIS

D. Salkin
San Fernando, California

Despite the fact that coccy and tuberculosis are caused by two very different organisms, the reactions they produce in the human host have so many similarities that it is advisable to compare their pathogenetic patterns. This will include a discussion of the primary

phase, the production of immunity, the existence of a reinfection phase and the occurrence of late dissemination. There will then be proposed a pathogenetic classification of coccy.

Pathogenetic Classification of Tuberculosis (current concepts).

1. Primary disease (infection phase) - This first infection may heal or progress and may disseminate to extrapulmonary foci.
2. Reinfection disease (secondary or post-primary).
   A. Endogenous (post-primary progression) - extension or reactivation of the disease may occur even years after it has been considered quiescent or healed. It is the common form of reinfection tuberculosis.
   B. Exogenous
      (1) Reinfection - a new exogenous infection in the case of a previously existing healing or healed lesion.
      (2) Superinfection - a new exogenous infection occurring in a patient with an active lesion.

Current Classification of Coccy

In 1938, Dickson and Gifford announced that the common benign San Joaquin Valley Fever and the highly fatal coccidioidal granuloma were different manifestations of the same disease caused by Coccidioides immitis. They suggested the name coccidioidomycosis for the disease and the pathogenetic classification of:

PRIMARY - for the first infection (Valley Fever).

SECONDARY - for the progressive granulomatous phase.

Just exactly what the term "secondary" meant is difficult to say, for at that time "secondary" tuberculosis was still commonly used in textbooks to mean the reinfection phase and, at the same time, the term was used to denote extrapulmonary dissemination.

It is our impression that "secondary" coccy meant progressive primary disseminated disease and not the reinfection phase which was considered practically non-existent.

I would suggest the following terminological changes in coccy:

(1) To drop the term "secondary".
(2) To use the term "reinfection" (exogenous and endogenous) for post-primary infection.
(3) To use the term disseminated in its broad aspects to include pulmonary dissemination from an older pulmonary focus (bronchogenic, miliary) and extrapulmonary dissemination (lymph nodes, skin, bones, meninges).

Immunity in Tuberculosis

In tuberculosis, the primary disease confers a considerable degree of immunity, otherwise everyone with a positive tuberculin test would show active disease and die. However, the immunity is quite imperfect for reinfections are fairly common and breakdowns may occur under various conditions affecting the immune processes, such as malnutrition, adrenal cortico-steroids, diabetes, alcoholism, and emotional stresses. The reinfection syndrome occurs in the sensitized host and may be endogenous or exogenous, and this lesion shows a number of differences from the primary one. The commoner endogenous reinfection develops in four main ways: Breakdown of the primary focus, rupture of a lymph node into a bronchus, new pulmonary foci from a lymph node focus, and exacerbation of these foci even after years of quiescence.

In coccy it is stated that "immunity conferred by the primary disease is life-long and complete". This statement will be re-examined in the light of additional experience in the past decade.

Is There a Reinfection Phase in Coccidioidomycosis?

(1) Smith reported a case of an immune laboratory worker who developed mild symptoms and recurring precipitins after a laboratory exposure to C. immitis (exogenous reinfection).
(2) Tiggert reported a case of an immune laboratory worker who accidentally inoculated into a wrist bone and developed a coccy osteomyelitis which persisted until the lesion was resected (exogenous reinfection).
(3) It is not uncommon to see "residual primary nodules" become rarefied and cavernous (abscessing coccidioma) even years after the primary infection (endogenous reinfection).
(4) Coccy nodules have been known to be arrested for years and then start to grow. Small described one such case where growth of the nodule occurred over 5 years after its discovery. In San Fernando VA Hospital we have had 4 such cases. In the VA-AF Solitary Nodule Study, Steele has collected 9 such cases out of 55 coccy nodules; the original nodules were from 1 cm to 2 cm in size and had increased to 2 to 4 cm when resected; the increase occurred after a period ranging from 3 months to 4 years (endogenous reinfection).
(5) The classical benign residual cavity may be quiescent for months or years and then show such changes as hemorrhage, enlargement, blocking or even rupturing (endogenous reinfection).

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(6) Following pulmonary resectional surgery for coccy, complications may occur which are examples of endogenous reinfection:
(A) Recavitation - either old cavities become more apparent, which may be largely a mechanical process, or nodules break down and become cavernous.
(B) Exacerbation or spread of the disease (bronchogenic).
(C) Development of empyema.
The delicate immune processes can be disturbed by surgical trauma.

In tuberculosis, all primary residuals which break down, are considered as reinfections. The same concept should apply to coccy and should include all cavities (changing or static), all changing nodules and all cases of chronic fibrocaseous disease. For by that time, there have occurred such great changes in the allergy and immune factors that they can no longer be regarded as manifestations of the first meeting of organism and host.

There is undoubtedly a reinfection phase in coccy and the immunity conferred by the primary disease is far from being life-long or complete. Endogenous reinfection in coccy is not rare and further studies may show it to be common. Exogenous reinfection is quite rare; we should be more alert to discover cases similar to those of Smith and Tiggert, but occurring outside the laboratory. I know of no cases representing superinfection.

Late Dissemination in Coccy

In tuberculosis, both pulmonary and extrapulmonary dissemination can occur during the primary and reinfection phase. In coccy, its occurrence in the primary phase is well known but its development during the reinfection state is overlooked.

Examples of pulmonary dissemination in "reinfection" coccy are:
(1) The occurrence of recavitation and spreads following pulmonary surgery.
(2) We have seen at least 4 cases of bronchogenic spreads from coccy spreads, simulating the picture seen commonly in tuberculosis.
(3) Small reported two cases of coccy cavities showing bronchogenic spreads.

In the case of extrapulmonary dissemination, it is assumed that all cases occur during the primary phase. There are, however, a number of examples which suggest its occurrence also as a manifestation of reinfection coccy.

(1) In a series of 41 patients, there were two instances where the first evidence of dissemination occurred 2 years and 6 years after the known primary disease. Such examples are common to all students of the disease. Is there any reason to believe that they are "primary" manifestations?

(2) In 61 disseminated cases, fully 20 (or 31%) had no symptomatic primary and the first discovered illness was extrapulmonary. Such an event is common in tuberculosis where it may be of either primary or reinfection origin. Could it not occur similarly in coccy?

(3) We have had a patient who developed a coccy bone lesion following a pulmonary resection years after his known primary disease. Should one assume that the bone lesion was present for years and then became apparent after the lung surgery or is it more logical to suppose that the surgical trauma caused an extrapulmonary spread?

More observation is needed to document more accurately the problems associated with extrapulmonary dissemination, but the evidence, at this time, suggests that, although it occurs commonly in primary coccy, it can also occur in reinfection coccy.

Summary

1. The pathogenetic classification used in tuberculosis can be applied to advantage in coccidioidomycosis:
   PRIMARY - May be symptomatic or asymptomatic; produces a high degree of immunity.
   REINFECTION - Occurs fairly commonly.
   Endogenous reactivation - The common form of reinfection.
   Exogenous reactivation - Rare but the exact incidence is unknown.
   DISSEMINATION - Can occur in both the primary and reinfection phases and may be pulmonary or extrapulmonary.
2. This classification best explains our present-day knowledge of the disease and opens up new avenues of clinical observation and experimental studies.

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Fourth Scientific Session
Friday Afternoon, Dec. 1, 1961

J. Matthews, Chairman

15. THE USE OF AMPHOTERICIN B IN THE TREATMENT OF DISSEMINATED COCCIDIOIDOMYCOSIS WITH SPECIAL REFERENCE TO THE NEPHROTOXICITY

W. G. Sanford, J. R. Rasch and R. B. Stonehill
Lackland AFB, Texas

Six patients with disseminated coccidioidomycosis were treated with intravenous Amphotericin B. The minimum total dose was 1.56 grams and the maximum total dose was 28.5 grams.

During the long term treatment of these six patients it became apparent that they had sustained renal dysfunction as well as microscopic renal pathology. Four renal biopsies were successfully performed on three patients during their treatment. The biopsy specimens all showed varying degrees of tubular damage, and most striking was the uniform presence of a marked degree of nephrocalcinosis. The glomerular filtration rate was uniformly reduced in all patients. The effective renal plasma flow was significantly reduced on four patients. Blood gas and pH studies were performed on three patients. These patients all had the findings of a compensated metabolic acidosis. One patient, who incidentally was in the 8th month of pregnancy, had marked hypokalemic paralysis thought to be on the basis of tubular loss of potassium. All patients studied had a low fixed urine specific gravity which persisted for varying periods of time following the cessation of therapy with Amphotericin B.

On the basis of our findings we feel that prolonged administration of Amphotericin B regularly produces a form of renal tubular acidosis. We also believe that permanent renal damage may be produced in some patients. Our data indicates that the presence of significant renal damage does not depend on the total dose administered. A relatively small dose of Amphotericin B is accompaned by a high relapse rate of the disease. However, our experience would indicate that the incidence of permanent morphologic and physiologic renal alteration is not insignificant when adequate dosage is used. We would suggest that close attention be paid to frequency of treatment based on renal function studies.

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Discussion from the floor was deferred until completion of the next two papers.

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16. STUDIES ON THE TOXICOLOGY OF AMPHOTERICIN B

C. W. Holeman and H. E. Einstein
Bakersfield, California

This report summarizes our observations on the toxic effects of intravenous Amphotericin B on potassium balance, the kidney, and the red cell in man. Twenty-five adults received 3 gms. or more in a three month period; sixteen received 1.5 - 2.5 gms. in four to eight weeks. Six children received 2 - 2.5 gms. in three months.

Hypokalemia was first observed in an adult who developed profound muscular weakness after receiving 2 gms. of Amphotericin B. The serum potassium was 2.2 mEq/L. There was marked clinical improvement 24 hours after intensive oral replacement was instituted, and the serum potassium returned to normal levels four days later. Subsequently a child became moribund after receiving 0.5 gms. of Amphotericin B, and the serum potassium was found to be 2.4 mEq/L. He improved dramatically after intensive replacement. Ninety percent of the patients complained of generalized muscular cramps and some weakness. We suspect that these symptoms were due to potassium loss, but since 50% of the total body potassium must be depleted before hypokalemia develops we have been unable to document this hypothesis. Twenty-four hour urinary potassium excretion was determined in one patient on a controlled diet and rose sharply from an average of 35.5 mEq/L prior to treatment to 82 mEq/L the second day of treatment.

Kidney tissue obtained from autopsy in six cases, and by biopsy in two patients, revealed thickening of the walls of the renal arterioles, and extensive necrosis of the distal tubular epithelium in all cases and calcinosis in two. Elevation of the BUN occurred in all cases usually returning to normal one month after cessation of therapy. Therapy was temporarily discontinued whenever the BUN reached 50 mgm%. There was complete loss of ability to concentrate urine after two months of therapy in all cases. There was return of concentrating ability one month after treatment, but in no instance did

The urine specific gravity approach pre-treatment levels. The 15 minute PSP excretion revealed marked impairment after two months of treatment, and had not returned to pre-treatment levels two months after cessation of therapy.

Anemia developed in virtually all cases. Red cell indices, reticulocyte counts, and bone marrow examination before and during therapy in twenty cases were not revealing. Red cell survival studies in six cases revealed a significant decrease in survival time after therapy was initiated.

We have been led to speculate as to any causal relationship between the potassium depletion noted by ourselves and others, and the observed renal tubular necrosis although we must agree that the damage to the renal vessels might be the sole explanation.

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17. LOW DOSAGE AMPHOTERICIN B THERAPY IN PROGRESSIVE PRIMARY PULMONARY COCCIDIOIDOMYCOSIS

H.E. Einstein and C.W. Holeman
Bakersfield, California

The paper concerns the detailed case reports of four juvenile patients with progressive primary coccidioidomycosis, accompanied by high serological titres and marked clinical severity of illness. In all of these cases small amounts of Amphotericin B, not exceeding 600 mgs. was able to arrest the disease process rapidly, clear the pulmonary lesions, and reduce the titre.

All of these patients are well with follow-up, up to 2 1/2 years. Particularly remarkable in this series is a case now followed for almost 3 years, of a Japanese infant, 4 months old at the time of admission, who was admitted in a terminal condition with a massive right lung pneumonitis. This child is now well and developing normally. Another Japanese youngster, age 11, with massive pulmonary effusion and high fevers, is included in this series, as is an 11 year old boy with massive enlargement of tracheal nodes, causing severe strangulation and requiring extreme measures, including tracheotomy, for survival.

The point of the paper is to show in selected cases the very early and bold use of a drug allowing remarkable results in a rather short period of time, with only small amounts of the drug. An additional point brought out in the paper was the adjunctive use of corticosteroids, which was employed in the two cases mentioned in detail above.

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Discussion from the floor: Dr. Kent asked whether forced feeding of potassium were tried during Amphotericin B therapy. Dr. Rasch had not, but Dr. Winn has used intravenous potassium as well as forced feeding. Fishberg and PSP tests indicated impaired concentrating abilities. Dr. Einstein said it looked like kaliopenic nephropathy, and suggested this may be the cause rather than result of Amphotericin B toxicity. Dr. Cheu asked whether Dr. Holeman's patients were on steroids; they were not. Dr. Stonehill pointed out that serum potassium doesn't correlate well with tissue levels. According to Dr. Holeman, a reduction in total body potassium of about 50% is required before the loss is reflected in serum or urinary potassium.

Dr. Winn mentioned that purity of Amphotericin B was a problem during the early days of its use, but the quality has improved recently. Traces of Amphotericin A in the drug have been reduced to 2%, and some toxic reactions seem to be related to residues of this substance. Dr. Kent has done two liver biopsies on Amphotericin B patients after six weeks of therapy, and found both normal. There were no new animal toxicology studies.

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PANEL

AMPHOTERICIN B IN COCCIDIOIDOMYCOSIS

Moderator: D. Salkin, San Fernando, California

Panelists: S. Cheu, Fresno, California
H. E. Einstein, Bakersfield, California
H. Gierson, Los Angeles, California
W. A. Winn, Springville, California

Moderator: What are your indications for use of Amphotericin B?

Winn: Presented the following indications:

1. Persistent fever, prostration, elevated blood sedimentation rate, persistent or extending pulmonary involvement and hilar adenopathy.
2. Evidence of spread from the primary pulmonary focus: C. immitis invading other systems (lymphatic, cutaneous, skeletal, cardiac, genitourinary, meningeal, pleuroperitoneal, etc.)
3. Weak or negative skin reaction to coccidioidin in the presence of active disease.
4. Racial susceptibility, i.e., Negro, Filipino.
5. Unstabilized serology:
   1) Rising titer of complement fixation (1:64 dilution or above).
   2) Persistent precipitins, incomplete complement fixation.
6. As surgical coverage (to be given for three weeks prior to operation) for:
   1) Removal of pulmonary cavities and abscesses.
   2) Excisional or drainage procedures of infected bone, *gonads, lymph nodes, soft tissue abscesses, sinus* tracts, and fusion of joints.
   3) Drainage of empyema and decortication.
   4) In conjunction with high-frequency electrical coagulation, drainage, or excision of granulomatous skin lesions and superficial abscesses and ulcers.
7. Prevention of dissemination of primary coccidioidomycosis during pregnancy.

Einstein: Agreed with most of Winn's indications but would also add "infants under one year." He feels that race alone is not an indication, hasn't found the drug necessary as surgical coverage per se, and, although he watches primary coccy in pregnancy very closely, he considers renal toxicity too much of a hazard for use in pregnancy.

Winn: Reiterated that the table lists factors to be considered; no single item alone is absolute indication for use of Amphotericin B.

Cheu: Treats acute primaries in pigmented races. Also treats severe primaries who show no improvement without the drug, or show rising complement fixation titers and/or reversion to a negative skin test.

Gierson: Individualizes treatment rather than following a general policy. A reversion of skin test and rise of complement fixation titer to 1:64 would be indication if the patient is sufficiently ill.

Question: (Stonehill): How soon can you get an effect of Amphotericin B on coccy organisms in vivo? Can three weeks of therapy for surgical coverage be expected to do anything?

Winn: Tries to maintain serum levels of 0.5 micrograms per ml. In surgery, with accidental release of a few organisms to new tissue, the suppressive effect of the drug is of value, and may shift a delicate balance in a favorable direction.

Cheu: Described a case of direct instillation of 2 mg. of Amphotericin B into a bone lesion twice in 3 days, and a 4 month course of intravenous Amphotericin B, resulting, on subsequent curettage, in the demonstration of non-viable spores in the tissue. Recommends prophylactic injection before bone surgery.

Question: (Stonehill): When can we move in with Amphotericin B in rapidly progressive disease?

Einstein: Small dosages, as described in his paper, can help most in the rapid acute fulminating reproductive phase of infectious disease. If the cases resemble those described in his paper, he would treat. Fever usually drops very fast after start of the drug.

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Winn: Believes in moving in fast, when indicated, sometimes not waiting for laboratory results.

Moderator: Do you use Amphotericin B for a small, thin walled asymptomatic cavity?

Chorus: No.

Einstein: If it persists over six months, consider surgical intervention.

Winn: Distinguished between a coccy abscess and a thin walled cavity. The abscess is a result of excavation of a solid lesion and has satellites; the thin walled cavity has little satellitism.

Moderator: Do you treat all disseminated cases with Amphotericin B?

Einstein: Not if only evidence of dissemination is a high CF titer. Most patients with extrapulmonary foci demonstrated, are treated. Exceptions are some bone lesions and some draining sinuses which may do well without the drug.

Cheu: Treats all definitely disseminated cases, but he also doesn't treat on basis of a high CF titer alone.

Gierson: Treats sick patients with high titer, even if extrapulmonary lesions not proven.

Winn: Agreed with Gierson, i.e. treats "impending dissemination". Also a titer of 1:64 or higher alone is not enough; there must be clinical evidence of progressive primary disease as well.

Moderator: What is your experience with Amphotericin B intracisternally in coccy meningitis?

Einstein: This is local use of the drug, comparable to bone lesion instillation, etc. Uses 1 mg., once a week. Has had no serious complications yet. Patients work, attend school, etc., and come in once a week for therapy.

Winn: Same experience, but used 0.5 mg. Also gives an intravenous course every few months.

Moderator: What are your experiences with local use of Amphotericin B?

Cheu: Has used a 1% lotion locally against Candida infection and one or two applications stops developing thrush in Hodgkins disease patients. In treatment of a coccy neck abscess, intravenous therapy combined with twice a week local application of Amphotericin B powder to an open lesion was effective in another patient.

Gierson: Has had similar experience. Prepares 20 mg. of drug in 20 ml. of diluent; aspirates abscess and replaces removed fluid with a slightly smaller volume of the drug.

Salkin: Application of Ampho soaked gauze packs in an open empyema case treated previously with decortication gave good results. Has also saved a finger by local injections of Amphotericin B.

Winn: Has had good results by using only a 3% solution locally on an open ulcer.

Einstein: Has used in similar manner, but with concomitant intravenous therapy. However, his intracisternal experience, without concomitant intravenous therapy, suggests good local effects.

Steele: In one case of isolated limb perfusion, the results were not good.

Moderator: What aspect of Amphotericin B toxicity disturbs you most and how do you cope with it?

Einstein: Toxicity is the chief limiting factor in the use of the drug. Permanent renal damage occurs. Must balance danger of the disease versus hazards of the therapy in each case.

Cheu: Agrees the main problem is kidney damage. Anemia is also significant. Feels that in very severe disease, the toxic effects are prices he must pay.

Winn: About half of the drug, as supplied, is sodium desoxycholate vehicle. Recent improvements have been made in the purity of the Amphotericin B itself. However, the drug, as used is a suspension, not a true solution, which contributes to the problem. Consideration should be given to more use of steroids to reduce toxic reactions.

Salkin: Advises caution in use of steroids; some spreads have been attributed to them. The physician must know the danger.

Winn: Steroids must be covered with Amphotericin B.

Einstein: Had good results with steroids, before the days of Amphotericin B, in non-disseminated coccy, and had no serious sequelae. Now, however, when steroids are used they should be accompanied by Amphotericin B. In the progressive primary pulmonary cases presented earlier, steroids were necessary. Has used them in meningitis too. ACTH was useful in combating intrathecal Amphotericin B induced arachnoiditis, but isn't needed with intracisternal therapy.

Gierson: Tries to avoid steroids. Prefers morphine and aspirin to control symptoms of Amphotericin B therapy. Has used steroids, but conservatively.

Cheu: Uses steroids when starting Amphotericin B therapy.

Question: (Hollander): What frequency and duration of Amphotericin B therapy is used in a case of non-meningeal dissemination with rising CF titer?

Einstein: Has used 1 mg/kg daily until 1.5 to 2 grams, total, have been administered. May change to a planned interval program.

Winn: Full therapy consists of using 1 mg/kg until there is evidence of healing with clinical improvement and stable or falling CF titers. Has seen no deaths due to Amphotericin B.

Gierson: Uses it every other day. Doesn't consider total amount of drug given. Gradually tapers to twice a week, then once a week for a year or two.

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