MILTON HUPPERT, Ph.D.
Chief, Mycology
Research Laboratory

TO: Committee Members, Study Units, and other Parties Interested in the VA-Armed Forces Coccidioidomycosis Cooperative Study.

SUBJ: Minutes of the Second Annual Meeting

1. There is a certain feeling of permanence in being able to write of the Second Annual Meeting of the VA-Armed Forces Coccidioidomycosis Cooperative Study. The meeting was held at the Los Angeles Regional Office of the Veterans Administration on December 5 and 6, 1957, the transcripts of the meeting have been edited and the following pertinent materials are enclosed:

a. List of Study Units

b. List of Participants in the Meetings

c. A Summary of Recommendations of the Committee on Plans and of the Laboratory Committee

d. Minutes of the Meeting of the Committee on Plans

e. Minutes of the Meeting of the Laboratory Committee

f. Revised Laboratory Standards for Laboratory Diagnosis of Coccidioidomycosis.

2. Among the achievements at the meeting were the decisions to establish a protocol for treatment of disseminated coccidioidomycosis with Amphotericin B, and to extend certain phases of the retrospective study. The tentative drafts of the necessary protocols and report forms are in preparation and will be distributed for comment as soon as possible.

3. We wish to express our thanks to Dr. Turner Camp for arranging facilities for the meetings; to Mmes. Meryle Acosta and Bessie Z. Rubin for invaluable stenographic help in preparing the minutes; and to all the participants who kept the meetings stimulating and productive, yet informal and enjoyable.

Lawrence G. Wayne

LAWRENCE G. WAYNE, Ph.D.
Recording Secretary,
Coccidioidomycosis Cooperative Study

Encl.

VA-ARMED FORCES COCCIDIOIDOMYCOSIS COOPERATIVE STUDY UNITS

Veterans Administration Hospital:
Albuquerque, New Mexico
Dallas, Texas
Fresno, California
Houston, Texas
Kerrville, Texas
Long Beach, California
Los Angeles Center, California
Phoenix, Arizona
San Fernando, California
Tucson, Arizona
Whipple, Arizona

U.S. Air Force
Parks Air Force Base, California

U.S. Army, Fitzsimmons Army Hospital
Denver, Colorado

U.S. Naval Hospital
San Diego, California.

PARTICIPANTS IN SECOND ANNUAL MEETING

** Dr. R.S. Armstrong, VAH, Tucson
Dr. C.A. Bachrach, VACO
Dr. E. Bogen, Olive View, Calif.
** Dr. E.A. Brosbe, VAH, Long Beach
Dr. G.R. Callender, VACO
Dr. T. Camp, LARO
** Miss C.C. Campbell, Walter Reed Army Med. Center, Wash. D.C.
Dr. S. Cheu, VAH, Fresno
* Dr. R. Egeberg, L.A. County General Hospital
Dr. S. Finegold, VAC, Los Angeles
Dr. C. Halde, UCLA
** Dr. W.H. Hall, VAH, Minneapolis
Dr. R. Hampson, Kern County Health Dept.
* Maj. N.M. Hensler, Parks Air Force Base
Dr. G. Hildick-Smith, Squibb Institute for Medical Research
Dr. D.H. Howard, UCLA
** Dr. M. Huppert, VAH, San Fernando

* Dr. L. Hyde, VAH, Long Beach
Mrs. Keetsman, VAH, Long Beach
Dr. N.B. Kurnick, VAH, Long Beach
Dr. K.T. Maddy, USPHS, Phoenix
Dr. E. McNall, UCLA
Dr. P.I. Melnick, VAH, San Fernando
Dr. W.E. Myers, VAH, San Fernando
* Dr. S. Netzer, VAH, Tucson
Dr. V.D. Newcomer, UCLA
* Capt. E. Ricen, U.S. Naval Hospital San Diego
Dr. A.L. Ringle, VA Area Office, San Francisco
* Dr. D. Salkin, VAH, San Fernando
* Dr. C.E. Smith, U. of Calif.
Dr. J.D. Steele, VAH, San Fernando
Mrs. L.J. Walker, VAH, San Fernando
Dr. L.G. Wayne, VAH, San Fernando
* Col. J.A. Wier, Fitzsimons Army Hospital, Denver

* Member, Committee on Plans

** Member, Laboratory Committee

A rather high incidence of skin lesions was reported in the disseminated cases. However these may include ulcerated subcutaneous abscesses along with the classical coccidioidal verrucous lesions. Dr. Egeberg expressed the opinion that Filipinos are particularly prone to skin lesions.

Laboratory Data. Direct microscopic examination of sputum gave poor yields. Dr. Huppert felt that it was hardly worth doing and recommended that cultures be done on sputum and spinal fluid (see minimum Laboratory Standards). In biopsy material and pus, on the other hand, direct microscopic examination for C. immitis is useful.

Mice appeared about twice as sensitive to inoculation of C. immitis as did guinea pigs, according to the tables. These figures may be biased, however for several reasons. First, a laboratory with more experience with C. immitis is more likely to use mice, and secondly, it is possible that some of the inoculations were made from subcultures from the specimen recorded, particularly in the case of the mice. A study of the relative effectiveness of inoculation of mice and guinea pigs with the actual specimen is needed. The strain of mice and route of inoculation are probably important factors.

B: CONCLUSIONS FROM RETROSPECTIVE STUDY

Prognosis of cavitary disease has not been clarified in the retrospective study. In order to determine the need for surgery, a longer follow-up is needed. Dr. Wier suggested that all of the cases in the 1956 and 1957 retrospective groups be followed up for another 5 or 6 years. The films could be evaluated by a central group. An alternative to this would be a retrospective study extending back 5 or 6 years.

Data were acquired on incidence and outcome of disseminated coccidioidomycosis, upon which a program of chemotherapy could be based.

The data accumulated to date is too limited to permit publication at this time. It was the consensus that findings may be published at a later date after adequate analysis has been made and upon agreement of the committee.

Some further minor modifications in the report form, to be used in subsequent studies were proposed.

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Upon completion of discussion of the retrospective study, Dr. Egeberg's film on "Coccidioidomycosis: Its Epidemiological and Clinical Aspects" was shown. (N.B. Dr. Egeberg's presence was particularly welcome as he was unable to attend the previous year's Study meeting due to some personal research he was conducting on Clinical Aspects of Coccidioidomycosis).

SECOND ANNUAL MEETING OF THE VA-ARMED FORCES COCCIDIOIDOMYCOSIS COOPERATIVE STUDY COMMITTEES

A. SUMMARY OF SPECIFIC RECOMMENDATIONS BY THE COMMITTEE ON PLANS

1. Each study unit should have at least one representative on the committee, even though all will not be able to attend meetings.

2. Recommendations regarding the retrospective study:

   a. Since many Latin Americans are included in the "white" category of race, the report forms should have a note added to Item 11 to "specify national origin; e.g. Mexico, etc."

   b. Duration of stay in endemic area should be broken down into 6-month intervals.

   c. For the sake of uniformity, the X-ray findings will be used to decide if a cavity exists.

   d. A gas containing coccidioidal cavity will be defined as "open", regardless of presence or absence of a bronchial block; all others will be classed as "filled".

   e. If a patient has ever had cavitary disease, this fact should be recorded.

   f. Films from the cases included in the 1956-1957 retrospective study should be sent to a central unit for uniform classification; these cases to be followed for another 5 or 6 years.

   g. In all future cases studied, films should be made in duplicate and one of each sent to a central unit for uniform classification; e.g. one of a stereo pair.

   h. Findings may be published at a later date after adequate analysis has been made and upon agreement of the committee.

3. The results of his studies on the in vitro and in vivo effect of various antibiotics and chemicals on Coccidioides immitis may be published independently by Dr. Ruppert.

4. Protocol studies on Amphotericin B (Fungizone):

   a. A protocol study on intravenous Amphotericin B will be adopted by the Coccidioidomycosis Cooperative Study.

   b. Only disseminated coccidioidomycosis will be included in the protocol at the present time.

c. The protocol study on disseminated cases will not be randomized, but results will be compared to data already available.

d. All disseminated cases except meningitis are to be treated only after a baseline is established by criteria to be defined.

e. All meningitis cases are to go on protocol as soon as diagnosed.

5. Consideration of surgical protocols should be deferred until more information on cavitary disease is available.

6. Chemotherapy protocol report forms based on those adopted by the VA-Armed Forces Histoplasmosis Cooperative Study are to be used after specific modifications to be approved at a later date.

B. SUMMARY OF SPECIFIC RECOMMENDATIONS BY THE LABORATORY COMMITTEE

1. Amphotericin B sensitivity testing is to be performed on cultures from protocol cases. This can be done within the Culture Bank Program provided additional help is made available.

2. All study units will use coccidioidin skin test antigen from a single batch prepared by Dr. C. E. Smith and distributed by Dr. M. Huppert.

3. Individual laboratories will perform their own serology if facilities and antigen are available.

4. Spot checks are to be performed on split specimens sent to reference laboratories.

5. Since uniform antigen is essential for meaningful serological studies in this program:

a. A central antigen preparation laboratory should be established;

b. VA Central office shall be requested to make funds available for such a central antigen preparation laboratory.

6. The committee is to inquire about the U.S. Post Office regulations regarding the mailing of infectious materials.

7. The committee is to write to the Armed Forces Institute of Pathology about setting up a program of maintaining a museum of coccidioidomycosis tissues.

8. No screening program on skin test or on serology surveys will be set up by this study group at this time.

9. The Laboratory Standards are to be revised and redistributed.

MINUTES OF THE SECOND ANNUAL MEETING OF THE VA-ARMED FORCES
COCCIDIOIDOMYCOSIS COOPERATIVE STUDY COMMITTEES

COMMITTEE ON PLANS

The committee on plans met on Thursday, December 5, and part of Friday, December 6, 1957. Dr. David Salkin served as chairman.

I. Introductory Business

Participants in the meeting, including committee members and visitors, were introduced. Mention was made of meetings of some of the committee members at St. Louis and at Pleasanton. Certain problems relative to the retrospective study and the need for a protocol study were discussed at those meetings and these topics were placed on the agenda for the current meeting.

The question of committee representation of all study units was raised. It was the consensus that it was necessary to have some form of representation from every unit in order to maintain active interest in the study; it was further recognized, however, that fund limitations would not permit all representatives to attend the meetings.

The committee resolved, by unanimous vote, that each study unit should have at least one representative on the committee, even though all will not be able to attend meetings.

II. Retrospective Study

A. REPORTS

Dr. Salkin reviewed some of the highlights of the retrospective study, which covered the calendar years 1955 and 1956 and thanked Dr. Hyde for handling report forms from 130 cases outside of the endemic area. There was considerable discussion of certain features which needed further clarification.

Race. Although, as Dr. Bachrach pointed out, it was not the intent of the study to determine epidemiology of the disease, it was agreed that analysis of dissemination rates in different racial groups was important. It was noted that the number of Latin Americans appeared low for the areas under study. Inasmuch as Americans of Mexican descent have a high dissemination rate, it was felt that some measures should be taken to identify them on future report forms. Regular VA records include all Latin Americans as whites. For the purpose of prospective studies, however, it was agreed that the report forms should include a category for Mexicans e.g. on the retrospective report form, item 11, have a note added to "specify national origin e.g. Mexico." The high dissemination rate among Negroes and Filipinos was confirmed in this study.

Age. Approximately 32% of the coccidioidomycosis cases in the series involved patients over 40 years of age. The problem of distinguishing the disease from pulmonary carcinoma is therefore significant. Age does not appear to be a factor in dissemination.

Duration of Stay in Endemic Area. The analysis of relationship of time spent in an endemic area to incidence of coccidioidomycosis was inadequate, since the smallest time interval recorded was "under five years." Months or even weeks of exposure are significant. It was agreed that this category be broken down into 6 month intervals.

Cavitary Disease. As might be expected from previous experience in tuberculosis studies, definition of cavitary disease in coccidioidomycosis received a lion's share of the discussion of the group. Two main aspects of this problem were discussed: 1) What standardized definition of a cavity should be adopted in future studies? and 2) In cases where the lesion changes or fluctuates between open and closed, which classification should be applied?

1. Although there are discrepancies between X-ray and pathologic determination of cavitation, not many of the patients are resected to permit evaluation by the pathologist. Therefore, for the sake of uniformity, the X-ray findings will be used to decide if a cavity exists. A gas containing coccidioidal cavity will be defined as "open", regardless of absence or presence of a bronchial block; all others will be classed as "filled". Dr. Smith pointed out that there is a different prognostic significance to different types of cavities. Thus, although the classical smooth walled coccidioidal cavity rarely if ever disseminates, the chewed out liquefied lesions may frequently accompany dissemination. Therefore the type of cavity should be reported. Dr. Wier suggested that films from the cases included in the 1956-1957 retrospective study be pulled and sent to a central committee for uniform classification, and that these patients be followed up in future years. Dr. Steele recommended that, in all future cases studied, films be made in duplicate, and one of each be sent to a central unit for uniform classification (e.g. one of a stereo-pair).

2. Since coccidioidal pulmonary lesions may fluctuate between "open" and "filled", the question arose as to when a cavity must have been open to be so classed. Dr. Hyde reported that about half of the cavities he has seen closed spontaneously by two years i.e. disappeared or left nodules. They may fluctuate. Dr. Bogen felt that we should try to distinguish cavities that fill, from pneumonic lesions that become nodules without evidence of a cavitary transition phase. It was the consensus that if a patient has ever had cavitary disease, this fact should be recorded.

Coexisting Pulmonary Tuberculosis. About 10% of the coccidioidomycosis cases in the retrospective study had tuberculosis also. Which came first? It was suggested that the TB occurs in eastern U.S. cases after admission for the coccidioidomycosis, whereas, in the Arizona area, the TB patient picks up his coccidioidomycosis after coming west for his TB.

Dissemination. Among the disseminated cases of coccidioidomycosis, over 60% had disseminated within the first two months of the primary infection and 84% within the first six months. Dr. Smith felt that we must examine "late dissemination" very critically. Dr. Wier raised a question as to the prognosis of those cases that survived six or eight years of disseminated disease.

Of 61 disseminated cases reported in the study, 20 had no X-ray evidence of pulmonary involvement. As mentioned above, certain types of cavities may be associated with dissemination, and the total picture of pathogenesis, X-ray findings and serology must be known before the relationship can be clarified.

Dr. Halde had observed protection of mice using the insoluble form of the drug on mice that were almost moribund from massive infection with C. immitis. Dr. Halde also presented some very interesting data on the depressing effect of C. immitis cells (and cell wall polysaccharide) on properdin levels in mice and correlated this with depressed properdin levels in patients with disseminated coccidioidomycosis.

Dr. Huppert presented figures on his study of in vitro and in vivo activity of amphotericin B. Of particular interest were the different in vitro susceptibilities of different strains of C. immitis from the Culture Bank, to this drug. The total population of a given strain also exhibited varying degrees of resistance.

Employing both the soluble and insoluble forms of amphotericin B, introduced intraperitoneally into infected mice, Dr. Huppert observed significant protection against the disease, on administration immediately after infection, and after a 7 day delay.

B. Nitrogen Mustard

Dr. Kurnick has treated some cases of disseminated coccidioidomycosis with nitrogen mustard with some encouraging results. He suggested that it might be producing its effect by reducing hyperplastic reactions, which he has found more pronounced in Negroes.

V. Protocol Studies

A. AMPHOTERICIN B

It was generally agreed that the old, insoluble oral form of amphotericin B is not readily absorbed and is not effective for treatment of coccidioidomycosis. It was furthermore decided to defer any protocol for oral use of the soluble i.v. preparation. It was agreed by unanimous vote, that an intravenous amphotericin B protocol will be adopted by the Coccidioidomycosis Cooperative Study. Dr. Hildick-Smith indicated that more of this drug will be available to us than had originally been planned.

Due to the toxicity of the drug, objections were voiced to a protocol for treatment of acute primary and cavitary or nodular pulmonary disease. Later, if an effective, non-toxic oral form of amphotericin B looks promising, a protocol for the pulmonary form will be considered. The committee voted that only disseminated coccidioidomycosis will presently be treated in a protocol.

The group then engaged in intensive discussion of the problems of case selection. Opinions were expressed for and against randomization. Dr. Hyde pointed out that old disseminated cases usually have a history of recurrent spontaneous remissions, and was in favor of studying fresh disseminated cases in the protocol program.

With the limited number of cases which will be available for study, randomization was not considered practical. Furthermore, toxicity will eliminate some patients from the study, upsetting the randomization even further. In view of the data already available on prognosis of disseminated coccidioidomycosis, it was the consensus that the protocol study not be randomized, but that all disseminated cases be treated. The criteria for success, then, would be a dramatic shift in survival statistics. If no such dramatic change is observed, then a

Dr. Egeberg expressed the opinion that a period of stabilization was necessary before treatment of disseminated coccidioidomycosis, since spontaneous remissions do occur. Dr. Maddy presented his experience with chemotherapeutic treatment of dogs with disseminated coccidioidomycosis wherein delayed treatment was unsuccessful due to failure of drug to penetrate the older granulomatous lesions. Early treatment, before extensive granuloma formation, was successful. (This also suggested that nitrogen mustard, affecting hyperplastic-reaction, might be used in parallel with amphotericin B in old cases). The consensus was that some baseline information was necessary, but that too long a delay in treatment was undesirable. Dr. Egeberg clarified his concept of stabilization: it does not mean the patient is on a plateau, but rather that the course and direction of disease are known. Because of the uniformly bad prognosis for meningitis, no need was recognized for stabilization in these cases. The committee therefore voted that all disseminated cases except meningitis are to be treated after a baseline is established by criteria to be determined; and that all meningitis cases are to go on protocol as soon as diagnosed.

The committee felt that drug sensitivities of the C. immitis isolated from protocol cases should be determined as is done in the tuberculosis cooperative study.

B. SURGICAL

Inasmuch as the retrospective study provided only limited information on course of cavitary disease, it was decided to defer consideration of a surgical protocol until more information was available e.g. through a follow-up of our retrospective study or through a 5 or 6 year retrospective group.

VI. Report Forms for Cases Under Study

Case registry will continue, using the retrospective report forms, with modifications adopted at this meeting.

For the chemotherapy protocol, it was voted to employ report forms based on those in use by the VA-Armed Forces Histoplasmosis Cooperative Study, but with specific modifications to be approved at a later date. Specific recommendations for modifications were to be sent to the Chairman of the Plans Committee by January 1, 1958.

VII. Exhibit

No funds will be available for a coccidioidomycosis exhibit in 1958, but we will plan one for 1959.

VIII. New business

The problem of representation of all study units had been disposed of earlier. Lack of funds precludes special cross representation with the Histoplasmosis group, but some exchange will undoubtedly occur at the Tuberculosis Cooperative Study Conferences.

MINUTES OF THE SECOND ANNUAL MEETING OF THE VA-ARMED FORCES COCCIDIOIDOMYCOSIS COOPERATIVE STUDY COMMITTEES

LABORATORY COMMITTEE

The laboratory committee met on Friday, December 6, 1957. Dr. Milton Huppert served as Chairman.

I. Review of Laboratory Phases of the Retrospective Study

This review was carried out as part of the retrospective study analysis during the plans committee meeting and was reported there. Briefly, it was reported that culture was superior to microscopic examination of sputum or spinal fluid for C. immitis, and that mice appeared superior to guinea pigs for infectivity studies.

II. Decisions of Committee on Plans Affecting Laboratory Committee

Antibiotic Sensitivity testing. It was voted that antibiotic sensitivity testing be performed on cultures from protocol cases. Some representatives wished to have hospitals do their own testing. Many hospitals are not equipped to do this. A standardized test is essential, as is an occasional check on hospitals doing their own work, by a central reference laboratory. The staff of the Coccidioides Culture Bank at San Fernando can do some of this extra work, but will require extra personnel in order to run the sensitivity tests for the whole program. Dr. Huppert, in the meantime, will prepare and distribute a sensitivity test protocol.

Serology. As with sensitivity testing, some study units will wish to perform their own serological studies, whereas others will be unable to do so. Two problems were discussed at length: 1) Uniformity of antigen and 2) uniformity of technique.

1) Although skin test antigen is available commercially, all study units will use coccidioidin from a single batch prepared by Dr. Smith and being distributed by Dr. Huppert at San Fernando VAH. No precipitin or complement-fixation antigens are available commercially. Dr. Smith will not be able to supply all of the antigen needs of the protocol study, and suggested that it would be economically most practical to pay a serologist to prepare and standardize a uniform antigen for the whole program. Uniform antigen is essential for meaningful serological studies in this program. The committee voted that

a) the Committee recommend to VACO that a central antigen preparation laboratory be established and that
b) the Committee recommend that VACO make funds available for such a central antigen preparation laboratory.

2) Dr. Smith pointed out that, although he encourages initiative in attempting modifications in serologic procedures, the cooperative study would require uniformity of technique. He further invited laboratory personnel who would be performing Coccidioides serology to visit his laboratory to

observe the techniques. Unfortunately, limitations in funds would probably preclude any but local personnel from taking advantage of this opportunity. There is always variation in technique from hospital to hospital; therefore it was agreed that spot checks in one or more reference laboratories would be necessary. Miss Campbell, Dr. Smith and Dr. Huppert are all able to do some serology for other study units but would not be able to take on the whole program without extra personnel. Another advantage to a central reference laboratory would be the saving of antigen, since certain controls may be set up for one test or fifty tests with the same amount of antigen.

The consensus was that individual laboratories will perform their own serology if facilities and antigen are available, and that spot checks are to be performed on split specimens by control laboratories.

III. Role of Laboratory Diagnosis

Mycology. Dr. Huppert has seen a number of cultures which do not look like the textbook pictures of C. immitis but which were proven to be that organism. He concludes that there is no truly typical C. immitis colonial type. Similarly, he has received certain other cultures which grossly and microscopically (cultures) resemble C. immitis but which appear to be saprophytic contaminants. The criteria used by the culture bank for confirmation of identity of suspected C. immitis cultures are endosporulating spherule production in vivo and Actidione(R) resistance. A yeast agar culture is used for preparing inoculum for the mouse. The culture needn't kill mice to be identified as C. immitis but on sacrifice at 2 or 3 weeks the mice must be shown to be harboring endosporulating spherules. Data were presented indicating that the non-pathogenic "Coccidioides-like" cultures are inhibited by 400 ug/cc concentrations of cycloheximide (Actidione(R)), whereas true C. immitis is not.

Dr. Huppert has developed a technique for antibiotic sensitivity testing of C. immitis, which he will try to simplify for inclusion in the Study's Laboratory Standards. There is as yet no spectrochemical analysis for Amphotericin B in body fluids. The Squibb company is working on this problem and will notify the laboratory committee when one becomes available. This will be necessary for evaluation of toxicity and therapy.

The need for extreme caution in handling C. immitis cultures was also restressed. Dr. Egeberg mentioned particularly the infectious hazard of older dry cultures. Dr. Hall suggested that the committee prepare a movie on safety aspects and laboratory methods in coccidioidomycosis. It was generally agreed that the CDC movie did not present safe methods for working with cultures.

The committee is to inquire of the post office regarding infectious material shipment regulations.

Histopathology. Several of the study units wish to keep portions of pathologic specimens for their own museums. On the other hand, it was felt that an arrangement with the AFIP would also be desirable. Dr. Callender recommended that we keep what we wish for the museums, and send the remainder to AFIP. He pointed out that 30% of undiagnosed granulomas are diagnosed by specific histochemical examination at the AFIP. The committee will write to the Armed Forces Institute of Pathology about setting up a tissue program.

There is a gap in our knowledge of the pathology of acute primary coccidioidomycosis and Dr. Wayne suggested that the Armed Forces are particularly well situated to make a study of pathogenesis of the disease. Such a program would entail autopsies of accidental death victims known to have converted to coccidioidin a short period prior to death.

Immunology. As mentioned above, study units should get their supplies of coccidioidin by writing to Dr. Huppert at San Fernando VAH.

Problems of setting up routine precipitin and complement fixation testing are discussed above.

A discussion of cross reactions between histoplasmosis and coccidioidomycosis followed, particularly with respect to skin tests. Miss Campbell pointed out that many primary histoplasmosis cases may have a negative skin test, and Dr. Wier observed that about 20% of coccidioidomycosis cases may be negative to 1:10 coccidioidin, using the commercial antigen. Further complications are introduced by the facts that a group component in histoplasmin cross reacts with coccidioidomycosis patients, but the reverse is less likely to occur, and that many patients may be truly positive to both antigens. In some cases, a"cross titration" of skin tests may be necessary to rule out the cross reaction.

It was concluded that no screening program be set up by this Study group at this time. Some studies of cross reactions are already being run elsewhere so no such program was adopted by the committee.

Culture Bank

Dr. Huppert reported on the status and activities of the Coccidioides Culture Bank. At the time, there were 106 strains in the Bank and all were being checked for Actidione(R) resistance and mouse pathogenicity.

The use of Millipore Filter technique for isolation of C. immitis from spinal fluid was discussed. Among the advantages cited were total recovery of very sparse spinal fluid organisms and the practicability of washing residual drugs out of the specimen. Also mentioned was the lack of adsorption of sugar and chloride by the filters so that filtrates can still be used for analyses. Some protein is lost on filtration.

Among other activities of the culture bank are studies of the biology of C. immitis, banking storage techniques, and screening of potential chemotherapeutic agents.

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Dr. Ringle made a brief closing address and suggested we continue the retrospective analyses into 1957.

VETERANS ADMINISTRATION
HOSPITAL
San Fernando, California

October 3, 1957

TO: Committee Members, VA-Armed Forces Coccidioidomycosis Cooperative Study

SUBJ: Agenda for next meeting

1. The proposed agenda for the next meeting is enclosed. Committee members are urged to send any desired additions to the proposed agenda to the undersigned as soon as possible.

2. Also enclosed is an outline of the suggested chemotherapy protocols. Committee members are requested to study these protocols and to be prepared to discuss and modify them at the meeting in Los Angeles.

3. The meeting will be held at the Veterans Administration Regional Office, 1031 South Broadway, Los Angeles, California, on December 5 and 6, 1957. A list of hotels in the area will be sent out at a later date.

4. Information concerning travel funds and other such matters should be obtained from Dr. Dunner, at VACO.

Lawrence G. Wayne

LAWRENCE G. WAYNE, Ph.D.
Recording Secretary,
Coccidioidomycosis Cooperative Study

Encl.

PROPOSED AGENDA OF THE COMMITTEE ON PLANS THURSDAY, DECEMBER 5, 1957

I. Introductory business
   A. Introductions
   B. Comments on meetings at St. Louis and Pleasanton
   C. List of study units and structure of committees
   D. Shall all study units have representatives on the committees?

II. Retrospective study
   A. Reports
      1. Statistical - Mrs. Livings
      2. Clinical -
      3. Laboratory -
   B. Conclusions from retrospective study
      1. Extension of this study?
      2. Publication of results?

III. Reports on new drugs under laboratory investigations - M. Huppert, Ph.D.
   A. Parabens
   B. Waksman drug 40-14
   C. Waksman drug Antimycoin (C-381?)
   D. Miscellaneous
      1. Candidin, Candicidin
      2. Aspirin and INH
      3. Nepera #1968
      4. Ciba #SU 3068

IV. Drugs under consideration for protocol chemotherapy studies
   A. Fungizone (amphotericin B)
      1. Reports and comments
         C. E. Smith, M.D.
         G. Hildick-Smith, M.D.
         C. Campbell, B.S.
         M. Huppert, Ph.D.

V. Protocol Studies
   A. Chemotherapeutic: Discussion of proposed protocol
   B. Surgical

VI. Report forms for cases under study
   A. Initial
   B. Follow-up

VII. A coccidioidomycosis exhibit for
      NTA - Philadelphia
      Amer. College of Chest Phys. - San Francisco
      AMA - San Francisco

VIII. New business
   A. Representation of all study units?
   B. Cross representation with Histoplasmosis Cooperative Study?