February 1965

No. 2

Progress Report

of the

Veterans Administration - Armed Forces

COCCIDIOIDOMYCOSIS

Study Group

Veterans Administration Hospital
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San Fernando, California
91342

INDEX

A. Foreword

The first Progress Report was issued as a memorandum in July 1959, to maintain some degree of communication between the Study Units during the period between the annual meetings. Even a modest publication prevents a total vacuum between the Study Units and keeps everyone informed of various administrative activities, medical matters, research on the half-shell, and serves as an exchange medium for ideas.

It was our original intention to call these publications Newsletters, but we were advised that the term has an official connotation of a formal publication, and we are not permitted in that field. So we toyed with words like Minutes and Memorandum, and came up with Progress Report. The selection was prompted by the venerable and enviable reputation and structure of the Quarterly Progress Report on the Chemotherapy of Tuberculosis.

In fact, we cannot do better than emulate those Reports. If you are not acquainted with them, borrow one from your TB friends. Since we have no plans to publish it with time-table regularity, we will call it simply Progress Report. So, if you have any comments, suggestions, advice, ideas, gimmicks or just plain gripes, write to us and they will be presented in succeeding Reports (unless you object), which will be published at irregular intervals. We hope that each Study Unit may be able to contribute at one time or another.

This issue will be a combination of the Minutes of the 1964 Annual meeting and various notes. Upon reviewing the 1959 Memorandum, we were reminded of several pleasant features in it and we will reprint a few of them since the Study Group has changed considerably since that time.

The lapse of 5 years between the two issues is easily explained. In 1960, our annual meetings became 2-day events and it took most of the year (in our spare time) to prepare the Transactions. Since we are now back to our closed one-day meetings and the general meeting is managed by others, we can revert to the original plan of increased intra-Study Group communication.

B. Minutes of

The 9th VA-AF Coccidioidomycosis Meeting

1. Back to the Old Corral

Among the hopes of our first meeting, held in 1956, were the initiation of clinical cooperative studies, stimulation of basic research, and greater clarification of the clinical picture of the disease. After several years' attempts, we were unable to develop cooperative studies because of the great divergence of opinions on the two major issues; the use of Amphotericin B and the indications for pulmonary resection. The title was therefore changed from a Cooperative Study to a Study Group with the chief emphasis on research, both basic and clinical.

In the meantime, our meetings must have filled a vacuum and fulfilled a need for they grew to great proportions and attracted students of the disease, not only in the endemic area but from several distant states as well. The meetings became two-day events and featured basic research and clinical topics, and fully 2/3 of the 133 attending last year's affair were guests.

Since we could not legally use research monies for such public educational meetings which evolved, we divided the meeting into two parts: Our own VA-AF closed one-day session, and a general two-day meeting sponsored by the California Thoracic Society, the TB and Health Association of California and the TB and Health Association of Los Angeles.

Next year, we will hold our own one-day closed session on Tuesday, December 7, 1965, in Phoenix Arizona. The large meeting will be a three-day affair held December 8, 9, and 10, and will be sponsored by 5 bodies: Arizona Thoracic Society, Arizona TB and Health Association, Arizona State Health Department, Maricopa County Health Department, and the U. S. Public Health Service. It should be a gala event. After that, we will probably resume our meetings as usual at Los Angeles.

2. The Agenda

The Study Group met at the Wadsworth Hospital of the Los Angeles VA Center complex. The room, the members and the chairman were cheerful, the doughnuts and coffee were free and all

facilities were available--blackboard, projectors and pleasant service. Discussion was lively and even the old jokes were accepted as new friends. Our consultant Egeberg reflected the spirit of the meeting with his story on why a Dean is like a fire hydrant.

The meeting began at 10 A. M. and ended at 5 P. M. The business meeting was somewhat long (2 hours) but seemed necessary because of our return to togetherness. It should be shorter on future occasions.

The agenda was a simple one and followed along the two main lines of administrative matters and research reports from the various Study Units.

For their kindness in making the meeting room available to us, and for their aid in transportation and other gracious acts, we are indebted to Doctor H. M. Engle, Doctor W. Davis, Mr. J. McKinley and Mrs. Rossi. I've already warned them that their hospitality earned them a return engagement in 1966.

3. Structure of the Study and the 1964 Representatives

STUDY GROUP

Chairman - David Salkin, M. D.
Secretary - Milton Huppert, Ph. D.
Consultants - Roger O. Egeberg, M. D.
Charles E. Smith, M. D. (absent)
Central Office - James H. Matthews, M. D.
Area Office - Harold H. Birnbaum, M. D.
Western Research Support Center, VAH, Sepulveda - H. Jorgensen

STUDY UNITS		REPRESENTATIVES
(1) VA	Fresno	Cheu, Sorensen
(2)	Long Beach	Brosbe, Hyde
(3)	Los Angeles	Finegold, Warren
(4)	San Fernando	Huppert, Salkin
(5)	Tucson	Wallraff
(6) Army	Fitzsimons	Spotnitz
(7) Air Force	Lackland	Rasch
(8)	Davis-Monthan	Meis
(9) Navy	San Diego	Spence

OFFICIAL GUESTS

(1) U.S. Army Biological Laboratory, Ft. Detrick, Md. - Converse, Sinski
(2) U.S. Navy Biological Laboratory, Oakland, Calif. - Levine, Kong
(who failed to read their correspondence and came a day late)
(3) Comm. Disease Center (CDC), Atlanta, Ga. - Ajello, Kaplan, Kaufman
(4) Nat'l. Inst. Health (NIH), Bethesda, Md. - Lones
(5) Univ. Calif. Berkeley, (UCB) - Pappagianis

OTHER WELCOME GUESTS - Sam Salvin, Matt Noon, Jewel Kietzmann, Dan Omieczynski, Dwayne Savage.

AND OUR RIGHT ARMS - Mesdames Cleo McCubbin, Olga Stacy, Johnsie Bailey, Jackie Briggs.

WE MISSED AGAIN THIS YEAR - OUR GRAND DADDY: "Chuck" Smith.

4. Invitation to other units

You may have noticed that our "official guests" are almost as numerous as we are and that many are permanently official. It was therefore voted unanimously by the Study Group, to formalize the marriage, and the 5 official guests were invited to become official Study Units. We will initiate the proper correspondence through the proper channels to affect this resolution.

Dr. Matthews stated that the Study Group need not be limited solely to federal units and that other study groups may join if they are interested and acceptable to the Study Group.

It was also felt that, regardless of additional memberships, we should retain the name "VA-AF Coccidioidomycosis Study Group."

NOTE: At the time of this writing, the Army Biological Lab, the Navy Biological Lab, the Comm. Dis. Center and NIH have accepted our invitation and are now full fledged members of the Study Group.

PS. UCB has just accepted! All our official guests are now full fledged members.

5. The Annual Transactions.

1956, 1957, 1958, 1959	- Mimeographed
1960	- Printed by L. A. County TB & Health Ass'n.
1961, 1962, 1963	- Printed by Calif. TB & Health Ass'n.

Those printed by the TB Associations had a circulation of over 800 copies, - 400 to members of the California Thoracic Society and 400 to other requesters from all over the country.

This year, our own meeting deliberations (administrative and research) will be included in this Progress Report. The papers of the general meeting will be printed again by the California TB Association. We will make sure each one attending our meeting receives a copy.

6. Coccidioidomycosis Exhibit.

The exhibit was developed in 1958 by the Exhibit Committee (Netzer, Cheu, Brosbe), and modified in 1962 by Salkin. It is really a beautiful, artistic display made by Central Office. It has been shown at the following meetings:

1959	A. M. A.	Atlantic City
	National Tub. Ass'n.	Chicago
	Am. Pub. Hlth. Ass'n.	Atlantic City
1960	Coccy Coop. Meeting	Los Angeles
	Arizona Med. Ass'n.	Phoenix
	VAH Fresno	Fresno
	VAH Long Beach	Long Beach
	Am. Coll. Phys.	San Francisco
1961	Antelope Valley Fair	Lancaster
	A. M. A.	Los Angeles
1962	A. M. A.	Chicago
1963	Am. Indust. Hlth, Conf.	Washington, D. C.

NOTE: The two repeat performances at the A. M. A. were at the specific request of that organization.

The exhibit is located at San Fernando. It is folded and crated. When unfolded it measures about 15 to 18 feet in length and above 4 feet in width.

If you desire to display it, let us know and we will arrange with Central Office to ship it to you free of charge.

We are attaching a picture of the exhibit.

P.S. The exhibit needs one or two more modifications. We'll try to correct them. If we don't, you, the displayer, will sound real learned as you add your own ideas on the Lower Sonoran Life Zone, Amphotericin B, surgery, etc.

7. Publications

OFFICIAL BIBLIOGRAPHER

Dr. Stephen H. Cheu is the Official Bibliographer of the Study Group. Two years ago, he distributed to each member a volume containing a bibliography of all papers written on Coccy from 1892 to the present. And each year he will add another year's collection. I have converted my own volume to a loose-leaf book in a 3-ring hard cover protector and expect to add additional pages easily. If you do not have a copy, write directly to Dr. Cheu at VAH, Fresno, California.

In addition, he would like to compile a set of reprints of all papers on the subject, so please send a reprint of your publications to him (and one to me.)

PUBLICATIONS

As gleaned from Steve Cheu's bibliography, the journal publications on Coccy in the literature and those from this Study and associates (CDC, Naval and Army Biol. Labs.) follow. (Our own Transactions are omitted.)

YEAR	TOTAL PUBLICATIONS	STUDY GROUP PLUS
1960	33	2
1961	34	6
1962	23	6
1963	43	7

ADVERTISEMENT

The monograph entitled "The Treatment of Mycotic and Parasitic Diseases of the Chest", edited by John D. Steele, published 1964 by C. C. Thomas, selling for $14.75, has a 65 page section on Coccy by Salkin and Evans and a 52 page section on Laboratory Aspects by Huppert. The reviews have ranged from excellent (by the authors) to poor (by competing authors).

8. The General 2-day Conference

The California Thoracic Society sponsored the 2-day meeting which followed our own closed session. It was held at the International Hotel, a very fortunate selection especially for those from out-of-town. It is a new hotel, located at the airport and near the San Diego Freeway and the accommodations were excellent.

Out of a total of 28 papers presented, 9 were from the Study Group and 8 more from our associates. Three clinical panels also had good representation from the Study Group.

A report of the proceedings of the Study Group was given to the General Conference by ye chairman.

Huppert was the chairman of the program committee and deserves praise and commendation for an excellent series of papers, discussions and panels.

C. Research reports presented at the meeting.

The research reports will be listed briefly by the Study Unit involved; a number of them were presented at the General Coccy Conference.

FRESNO VAH

(1) Survival characteristics of C. immitis.
(2) Official bibliographers to the Study Group. Continuous bibliography of the world literature on Coccidioidomycosis. (A reprint to Dr. S. H. Cheu).

LONG BEACH VAH

(1) Epidemiological survey of soil samples from California and Mexico. Thus far, 58 out of 274 soils sampled yielded 3 strains of C. immitis and 8 strains of Cryptococcus neoformans.
(2) Drug screening project for anti-coccy agents. Over 2500 drugs have been tested to date and 256 (10%) showed some anti-fungal activity. One drug, fungimycin, showed good activity in vivo but somewhat less than that of Amphotericin B.
(3) Time lapse cinematography of C. immitis. At this session, there was a striking demonstration of the sudden rupturing of spherules releasing endospores and the cytoplasmic activity of mycelial forms.
(4) Continuing coccidioidin skin test surveys of hospitalized patients.
(5) Continuing clinical studies of pulmonary cavities.

SAN FERNANDO VAH

(1) Continuing studies on the immunodiffusion test and its correlation with the classical complement fixation test (CFT).
(2) The factors underlying the immunodiffusion tests. To date, the antigen corresponding to the complement fixation test has been separated. The antigen corresponding to the precipitin test has also just been separated and it appears that this test may be more sensitive than the classical tube precipitation test.
(3) Identification of some of the specific antibodies in immuno-electrophoresis.
(4) Attempts to demonstrate a sexual phase by mating individual strains of C. immitis against each of the 350 strains in their collection.

(5) Continuing study and follow up of the Control group of over 700 coccy patients hospitalized during the 1955-58 reporting period.
(6) Continuing study of the pathogenetic classification of coccy.
(7) Continuing studies on the clinical and activity classifications of coccy.

LOS ANGELES VAC

(1) Study of C. immitis in the blood stream in humans with coccy.

TUCSON VAH

(1) Factors involved leading to skin reactions in coccy sensitive individuals.
(2) Use of micro-serological techniques in performing coccy serological tests.

SAN DIEGO (USN)

(1) Clinical study of 221 coccy patients in a 6 year period. In 165 thoracotomies on 155 patients, there were 11 complications (6.7%) and included 1 death, 1 decortication, 1 wound infection, 2 recurrent cavitations, and 6 air leaks.

DAVIS-MONTHAN AFB

(1) Early precipitin formation in humans and the underlying factors.

ARMY BIOLOGICAL LABORATORY, FT. DETRICK

(1) Vaccination developments against C. immitis.
(2) Retest skin reactions in a coccy sensitive human.
(3) Immunological reactions in infected and immunized animals.

NAVAL BIOLOGICAL LABORATORY, OAKLAND

(1) Effect of physical exertion on the mortality of coccy infected mice.
(2) Development of an anti-coccy vaccine for humans. Recent results have been highly encouraging.

COMMUNICABLE DISEASE CENTER (CDC)

(1) Continuing studies on the development and usage of the Fluorescent Antibody Inhibition Test. Studies show a 90% correlation with the Complement Fixation Test.
(2) Study of C. immitis distribution in various soils, climates, and atmospheres.

UNIVERSITY OF CALIFORNIA, BERKELEY

(1) Effect of steroids on coccidioidal infections.
(2) Use of immunosuppressive agents.
(3) Vaccine studies.
(4) Immuno-electrophoresis studies.

NATIONAL INSTITUTES OF HEALTH

(1) Studies on the growth and metabolism of C. immitis.

Cooperative Study under development: Immuno-electrophoresis studies on human patients from the first sign of a primary infection and followed for some months.

In general we are highly gratified at the number and quality of research projects under investigation. We are particularly hopeful that next year we may be able to report upon further developments in vaccine efficacy and diagnostic immunological studies.

D. Medical TID - BITS

1. When to call a case disseminated?

1959 Report: It has been accepted that the primary pulmonary complex consists of a parenchymal lesion plus one in the mediastinal lymph nodes. And it is easy to accept the concept that paratracheal lymphadenopathy should be considered as mediastinal. How about scalene and other low cervical nodes (palpable or otherwise) which are so easily removed surgically, and how about the superior mediastinal nodes amenable to cervical mediastinotomy? It is hard to know just where to draw the line! Until proved otherwise, we are considering cervical nodes showing coccy as making the case disseminated because meager evidence to date shows that they behave like disseminated cases.
NEEDED: A series of routine cervical node biopsies in cases of acute coccy to establish the degree of lymph node spread in the average case.

1965: Has anyone added anything new since then?

2. What is a critical complement fixation titer (CFT)?

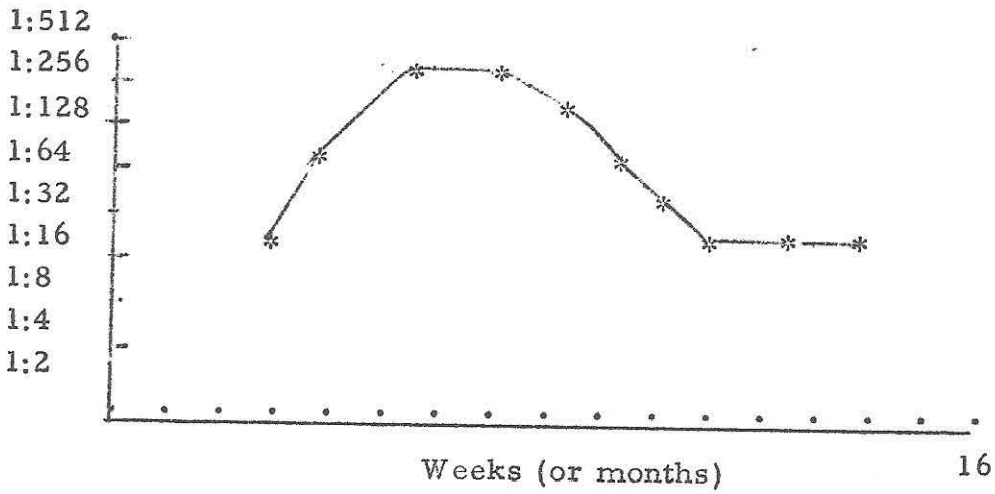
1959 Report: We all know that severe and even fatal disease can occur with low serum titers such as 1:2 or 1:4. Of course, high titers are to be regarded with some danger at all times, such as 1:64 or higher. However, a problem arises in interpreting a 1:16 or a 1:32 titer after "successful" treatment of a patient with Ampho B or surgery, and disappearance, and healing of lesions. We have been in the habit of regarding a persistent titer of 1:16 or 1:32 with serious regard and are classifying our good results into 2 groups: (1) Good clinical result with low CFT (under 1:16), and, (2) good clinical result with high CFT (1:16 and over).

Huppert stresses the fact that the titers above refer only to Dr. C. E. Smith's technique. Other methods may have either higher or lower critical titers.

1965: Since the above was written, we have classified good clinical results with high CFT as Quiescent and are observing them closely.

3. How to graph the CFT.

1959 Report: Have you also been overwhelmed by a large series of CFT tests when you tried to analyze them in orderly fashion? Here is the way we are solving the problem partially. We merely chart the highest dilutions with a 3 or 4 plus result against the time.



4. Classification of coccy

1959 Report: Every student of the disease likes to use his own classification, and since I am a newcomer I have one also to offer. As in tuberculosis, the classifications (all good) may be designed to portray pathogenesis, pathology, clinical picture, focalization, and dissemination, and so on. To the clinician, the clinical picture is most important and it is with the clinical classifications that I will deal.

The standard textbook classification is - (1) primary infection (symptomatic and asymptomatic), (2) benign residuals, and, (3) dissemination.

My own reasons for not liking this classification are: - (1) the primary infection includes two different clinical pictures, a large asymptomatic group and a small symptomatic one, (2) the term residuals connotes a benign condition which is far from the actual state of affairs in many clinical cases and certainly far from it mycologically and pathologically, (3) we have had a number of cases which are neither acute nor benign residuals but are best described as SUBACUTE. So the clinical classification we offer, and which we presented at our last annual meeting follows:

(1) Asymptomatic infection.
(2) Acute coccy.
(3) Subacute coccy.
(4) Chronic coccy - includes so-called residual cavities, nodular foci, and fibrocavernous disease, and such complications as bronchiectasis and pleural pathology.
(5) Dissemination.

Several of my colleagues prefer a simpler classification and prefer putting the subacute cases into the chronic group, viz:
Asymptomatic - acute - chronic.

To date, I prefer the subacute term because it describes a distinct syndrome and stresses the protean nature of the disease.

1965 Report: Since then we proposed 3 classifications:
Pathogenetic - (1) Primary, (2) Reinfection.
Clinical - (1) Asymptomatic, (2) Acute, (3) Subacute, (4) Chronic, (5) Dissemination.
Activity - (1) Active, (2) Quiescent, (3) Inactive.

Of course, there are several other classifications possible, each stressing certain special phases but the above appear to be the more basic ones for all cases.
(ADV. See book edited by Steele on Mycotic and Parasitic Diseases of the Chest -- $4.50 for the book and $10.00 for the cover).

5. S.F.D. Fungizone (Squibb).

In addition to Amphotericin B, fungizone contains sodium desoxycholate, dibasic sodium phosphate, monobasic sodium phosphate, and sodium chloride. The Squibb company modified the formula by adding more sodium phosphate buffer and substituting phosphoric acid for HCL to produce sodium phosphate in one step. The new product - SFD Fungizone.

Several months ago, Dr. John T. Groel, the associate clinical research director at the Squibb Institute, distributed a number of the new vials for clinical trial. It was hoped that the new mixture would be tolerated better by the patient - less fever, nausea, etc.

We have used it ourselves on 12 patients and gave about 200 SFD injections and compared it with over 250 controls on the usual

commercial fungizone. The patient did not know which fungizone he was getting, but the doctor did know. Our score - 9 patients had significantly less reaction with SFD, 2 showed no difference, (1 showed no reaction to either), and 1 was worse with SFD.

In the large Conference, during the Amphotericin panel, Dr. Groel stated that of the 42 patients that had both the regular drug and SFD, 14 patients had significantly less reaction with SFD, 4 did better with the regular preparation, and in 24 cases there was no difference.

Our latest correspondence with Dr. Groel stated that they are now out of SFD and they have not finalized their plans whether they will produce it commercially. Although SFD is tolerated at least as well as the present Fungizone, they need to determine if it is sufficiently better to change present techniques.

Apparently, the findings of other investigators are not as overwhelmingly favorable as our own.

Suggestion: Next time, let us do a double-blind study with both patient and physician unaware which preparation is being used.

6. The Ommaya operation for coccy meningitis.

Until you receive the Transactions of the General Meeting, you may want to be reminded of the discussion on the Ommaya valve. His article is in Lancet, November 9, 1963, pages 983-4.

At the time of the Conference (Dec. 9, 1964), he personally had used it in 20 patients; 12 for cryptococcal meningitis and 8 for brain tumor. At Bethesda, the "pump" had been in use for 13 months, and he had done 400 punctures without a leak. It is estimated that each capsule should be good for 200 punctures, and if it leaks, it can be replaced.

This procedure may be a blessing to both patient (and doctor) who cannot stand intrathecal therapy for 5 years and longer. And it appears to be superior (on paper) to ventriculo-atriostomy shunts which have already produced their own dissemination. (See Steve Cheu.)

7. The Bakersfield Coccidioidal Study Group.

Since March 1963, our Bakersfield friends have formed their own Study Group and from a copy of their Minutes one surmises that they have very instructive and stimulating meetings. The group consists of such worthies as Larwood, Einstein, Huntington, Levan, Iger, Hampson, Cunningham, etc., all well known to all of us. It is a pity that the group is ill with coccy if I interpret the title correctly! Ordinarily I would never have noticed the adjective, but when you live with such a semanticist as John Steele, you become sensitized. You would not say 'Tuberculous Study Group', would you, Tom?

They discuss various phases of treatment, unusual cases (and they see plenty), researches, epidemiology, etc. I like one of their lists of unproven popular assumptions:

"You can only get the disease once. (We wish it were still so.)
Histo calcifies, coccy doesn't. (Not so).
Disseminated coccy is fatal. (We are glad that it is not always so).
You don't die of coccy pneumonia. (Not true)."

Any medical tid-bit from them is always welcome.

8. A suitable abbreviation for COCCIDIOIDOMYCOSIS.

The common ones in use are:

Cocc - Pronounced COX - used in Bakersfield.
Cocci - Pronounced COX-SEE.
Coccidio - Used at scattered places.
Coccy - Used at San Fernando and other places now.

Oatway noted the following: Hans Einstein told him that there appears to be a direct relationship between the length of the name used and the distance from "hot" endemic areas; e.g., coccidioidomycosis in the East, coccy at San Fernando, and Cocc in Bakersfield. Oatway proposes that this observation be referred to as "Einstein's theory of relativity."

I personally used to use COCCI, but Huppert, several years ago suggested COCCY. Some of his bacteriological conferees objected to COCCI because of its similarity to staph- and streptococci.

May I move the official adoption by the Study Group of the abbreviation COCCY? It is a sound complete in itself as opposed to the others which are sawed off versions of the long word and it is euphonic. COCCY.

E. NOTES

1. Of the 28 papers presented at the 2-day Conference, 17 were delivered by the Study Group which also had good representation on the 3 clinical panels. Ye editor gave a summary of our own proceedings at the meeting.

2. The Transactions of the 9th Annual Conference are being edited and should be in your hands in about 2 months. If you know of others who would be anxious to have a copy, let us know immediately.

3. The next Study Group meeting will be held at Phoenix, Arizona, on Dec. 7, 1965, and the Conference on Dec. 8, 9, 10. Both meetings will probably be held at the TOWNHOUSE. As soon as we learn the definite location we will notify you. Matt Noon is the arranger.

4. A coccy serology Reference Laboratory has been set up in the Clinical Laboratory at San Fernando VAH by the VA Central Office. This is not a research laboratory although Huppert will continue to serve as consultant and to provide the standardized antigen and control sera. The Reference Laboratory will perform complement fixation, precipitin, and immunodiffusion tests for all VA hospitals requiring such service.