

# JOINT AND BONE DISEASE DUE TO MYCOTIC INFECTION

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The importance of pathogenic fungi as a cause of bone and joint disease has taken on added significance as the result of several developments. First, the control of pathogenic bacteria with chemotherapeutic and antibiotic agents has increased the relative frequency. Second, increased travel incident to military service and other factors has resulted in a dissemination of fungus infections. Third, therapeutic agents of a more effective nature for several of the mycotic organisms have become available recently.

Twenty-five cases of fungus disease observed at the McGuire Veterans Hospital and the Hospital Division of the Medical College of Virginia in a five year period from 1949 through 1954 have been reviewed. This included 11 cases of blastomycosis, 4 of coccidioidomycosis, 4 of cryptococcosis, 3 of actinomycosis, 2 of histoplasmosis and 1 of nocardiosis. In eight cases there was involvement of bone or joint (Table 1).

The incidence of mycotic infection is much larger than is generally appreciated.<sup>1, 10</sup> The types of infection encountered here are about as anticipated for this area with the possible exception of the four cases of coccidioidomycosis. Each of these, however, gave a history of having traveled or maintained a residence in one of the endemic areas of California. The age range varied between 18 and 59 years, and was not felt to be unusual. There was only one female patient in the group of 25 cases. This correlates with the general predominance of systemic fungus infections in males, but the series could not be considered representative since 18 of the 25 cases were observed at the McGuire Veterans Hospital which has an almost negligible number of female patients. Fourteen patients were white and 11 Negro, and there was no evidence of racial susceptibility except in the four cases due to coccidioidomycosis infection. Three out of these four cases were among Negroes, and in two of these the disease was disseminated and progressive. The deeply pigmented races have been found to be more susceptible to this infection, and the disease is usually more serious.<sup>1, 2</sup> There has been a popular, although probably incorrect, conception that systemic fungus disease is restricted to rural areas, and to individuals in the lower income groups. In this series, 14 patients were from rural areas—eight farmers, five laborers, and one Pullman porter. Eleven patients were

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TABLE 1

Fungus Disease	Total Number of Cases	Number of Cases with Bone Involvement
Actinomycosis . . . . .	3	0
Blastomycosis . . . . .	11	5
Coccidioidomycosis . . . . .	4	1
Cryptococcosis . . . . .	4	2
Histoplasmosis . . . . .	2	0
Nocardiosis . . . . .	1	0
Total . . . . .	25	8

from urban centers—three laborers, two executives, one teacher, one policeman, one clerk, one student, one textile worker, and one who at the moment was unemployed but who had been discharged recently from the United States Marine Corps (Table 2).

Of the total number of 25 cases reviewed, three types of mycotic organisms produced joint and bone lesions. These were *Blastomyces Dermatitidis*, *Cryptococcus Neoformans*, and *Coccidioides Immitis*. A brief review of the disease pattern produced by these organisms will be made and representative case histories presented (Table 3).

*Blastomycosis*<sup>1, 2, 3, 10</sup>

North American blastomycosis is probably limited to the United States and Canada. The causative organism is the *Blastomyces Dermatitidis* which is a single budding, yeast-like cell with a thick refractile wall. The source of this organism and its mode of invasion are unknown. The infection may take either of two clinical forms: Cutaneous or systemic. In the systemic form, the skin, lungs and bone are chiefly involved, with the latter occurring probably in over half of the cases. Any of the bones of the body may be affected, but the cancellous more often than the tubular. The process is usually an osteolytic one with little or no surrounding bone reaction or production. Recent reports have shown that stilbamidine and 2-hydroxystilbamidine have been effective therapeutic agents.

*Case Report:* J.D., A 50 year old Negro male was admitted to St. Philip Hospital, of the Medical College of Virginia, on September 14, 1954. The general health had been good until six weeks prior to admission at which time multiple furuncles in the region of the right wrist, right great toe, and the dorsum of the left foot developed. One week prior to admission pain, swelling, and redness developed in the right knee, both ankles and the right wrist. For two weeks there had been slight anorexia, malaise and a low grade fever. *Physical examination:* Draining sinuses of the right

TABLE 2

Patient	Age	Sex	Race	Occupation	Residence	Diagnosis	Bone Involvement	Involvement Other Than Bones
S.E.	30	M	W	Farmer	Rural	Actinomycosis	0	Cervical nodes
M.R.	41	M	W	Farmer	Rural	Actinomycosis	0	Cervical nodes
J.R.	23	M	W	Lumber mill worker	City	Actinomycosis	0	Cervical nodes
W.D.	29	M	W	Laborer	Rural	Blastomycosis	0	Lungs and skin
M.G.	47	M	W	Executive	City	Blastomycosis	0	Lung
K.U.	40	M	C	Laborer	Rural	Blastomycosis	+	Lungs
J.D.	57	M	C	Laborer	Rural	Blastomycosis	+	Disseminated
C.T.	59	M	W	Farmer	Rural	Blastomycosis	+	Disseminated
A.H.	59	M	C	Farmer	Rural	Blastomycosis	0	Disseminated
R.M.	59	M	W	Lumberman	Rural	Blastomycosis	0	Skin
E.T.	32	M	C	Farmer	Rural	Blastomycosis	0	Disseminated
I.B.	43	M	W	Policeman	City	Blastomycosis	+	Disseminated
E.T.	32	M	C	Farmer	Rural	Blastomycosis	0	Disseminated
J.T.	23	M	W	Textile worker	City	Blastomycosis	+	Lungs
U.H.	37	M	C	Pullman porter	Rural	Coccidioidomycosis	0	Disseminated
M.D.	43	M	C	Farmer	Rural	Coccidioidomycosis	+	Lungs
W.J.	37	M	C	Carpenter	Rural	Coccidioidomycosis	0	Lung
J.W.	24	M	W	Store clerk	City	Coccidioidomycosis	0	Lung
J.H.	35	M	W	Executive	City	Cryptococcosis	0	Lung
R.J.	18	F	C	Student	City	Cryptococcosis	+	Disseminated
A.P.	44	M	C	Laborer	City	Cryptococcosis	0	Meninges
B.G.	27	M	C	Farmer	Rural	Cryptococcosis	+	Disseminated
H.S.	31	M	W	Laborer	City	Histoplasmosis	0	Lung
A.C.	46	M	W	Teacher	City	Histoplasmosis	0	Lungs and skin
J.B.	24	M	W	None	City	Nocardiosis	0	Disseminated

wrist, right great toe and dorsum of the left foot were present. There was painful swelling and redness of both ankles, the right knee and right wrist. Both the liver and spleen were barely felt on deep inspiration. Inspiratory and expiratory crepitant rales were heard in both lung bases. *Laboratory data:* A direct smear from the sinus of the right wrist area was positive for *Blastomyces Dermatitidis*. The hemoglobin was 7.8 gm.; erythrocytes

TABLE 3

Patient	Diagnosis	Extent of Bone Involvement
K.U.	Blastomycosis	Right patella and tibia
J.D.	Blastomycosis	Right ulna, proximal phalanx of right great toe, right sacro-iliac joint and 3rd and 4th lumbar vertebrae
C.T.	Blastomycosis	Cuneiforms, scaphoid, cuboid and the 1st, 2nd, and 3rd metatarsals of the left foot
I.B.	Blastomycosis	Sacrum
J.T.	Blastomycosis	Talus, calcaneous, tarsals and the 2nd and 3rd cuneiforms of right foot
M.D.	Coccidioidomycosis	Cervical and dorsal vertebrae
R.J.	Cryptococcosis	Ribs, sternum and pelvis
B.G.	Cryptococcosis	Skull, pelvis, right acromial process, right humerus, right tibia and the right 1st metacarpal

2,620,000; leukocytes 17,400; polymorphoneutrophils 97%. A urinalysis showed an albumin of 1 plus, and many white cells in the sediment. Six blood cultures were negative, and three sputa specimens showed no tubercle bacilli. X-ray examinations: There was extensive bone destruction of the distal third of the right ulna with a pathologic fracture present, moderate destruction of the proximal phalanx of the right great toe, a few punched out areas in the region of the right sacroiliac joint, a mottled "moth-eaten" appearance of the bodies of L-3 and L-4 vertebrae with necrosis and fracture of the transverse process of L-4 and moderate destruction of the right patella. A chest film showed mottled infiltration throughout the right lung field and the mid zone of the left. There was a small amount of fluid in the right costophrenic angle. Course in hospital: The patient was considered acutely ill at the time of admission, and died four days after entering the hospital. A single, 100 mg. dose of 2-hydroxystilbamidine was given intravenously on the day prior to death without any noticeable clinical effect (Fig. 1).

#### *Cryptococcosis*<sup>4, 5, 6</sup>

Cryptococcosis is world-wide in distribution. The infection is caused by the *Cryptococcus Neoformans*, a single budding yeast-like cell, with a thick capsule which can be clearly demonstrated by an India ink preparation. The organism has a known saprophytic existence in nature, but the mode of invasion in man is not understood. The disease has a marked predilection for the central nervous system, but the skin, lungs and other organs may also be affected. Joint and bone involvement is said to be rare, but does occur. The process is almost purely an osteolytic one with little or no reaction occurring in the surrounding bone or periosteum, and no



FIG. 1. Case No. 1. Osteolytic changes, distal one-third of right radius and ulna with pathologic fracture of right ulna. Blastomycosis.

tendency to bone production. There seems to be an affinity for various bony prominences; otherwise, almost any bone in the body may be affected. Encouraging results in treatment with stilbamidine and 2-hydroxystilbamidine have been reported recently although the organism does not appear to be influenced as strongly by these drugs as does the *Blastomyces Dermatitidis*. The central nervous system involvement is particularly resistant to treatment.

*Case report:* B.G., A 27 year old Negro male was admitted to St. Philip Hospital, of the Medical College of Virginia, on January 20, 1953. There had been a cough productive of clear sputum for five months, and pain, swelling and limitation of motion of the right shoulder for two. There was an additional history of weight loss, malaise, and temperature elevation. At the age of five years, osteomyelitis of the right leg had developed follow-

ing trauma, and the use of a leg brace since that time had been necessary. *Physical examination:* The temperature was 103.2 degrees Fahrenheit, the skin was hot and dry, and the patient was described as being lethargic. A tender, fluctuant,  $8 \times 3$  cm. mass was present over the right acromial process. There was a moderate generalized discrete lymphadenopathy, and the spleen was barely palpable. *Laboratory data:* The *Cryptococcus Neoformans* was found on smear and culture in material aspirated from a mass over the acromium and on culture of the urine. The urine otherwise was negative except for a slight amount of albumin. There was a persistent eosinophilia of 10%, but the hemogram otherwise was not remarkable. Spinal fluid examination was entirely normal. *X-ray examinations:* Sharply defined punched out areas were present in the skull, proximal end of the first left metacarpal, the right acromial process, the shaft of the right humerus, and in several ribs. There was also extensive widening and thickening of the right tibia indicative of marked bone productive changes, and probably resulting from the old osteomyelitis, presumably bacterial. Chest x-ray showed a moderate hilar adenopathy, and a moderate degree of diffuse fibrosis. *Hospital course:* Initial treatment consisted of the use of symptomatic and supportive measures with no appreciable change in the

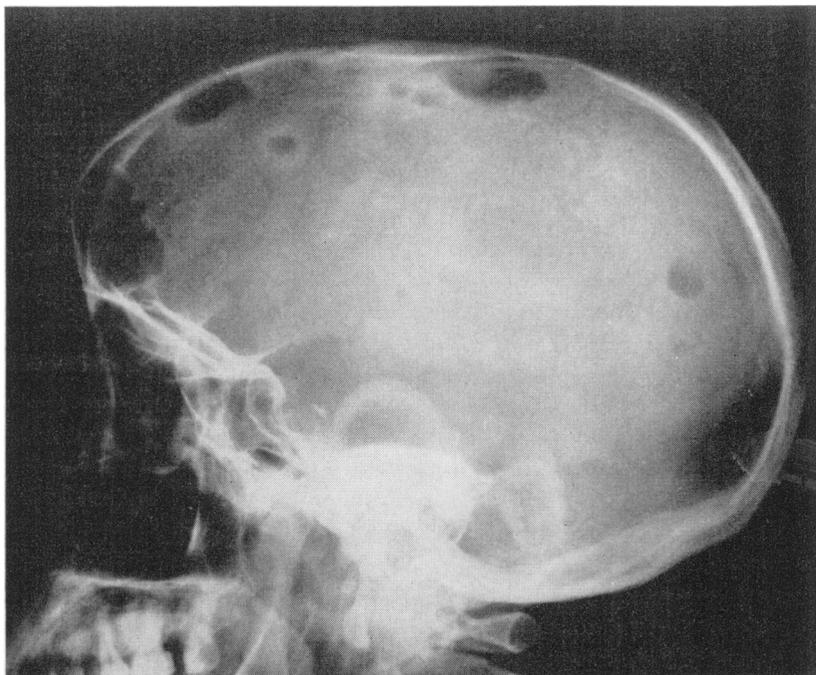


FIG. 2. Case No. 2. Osteolytic changes of the skull. Cryptococcosis

clinical status, and the patient left the hospital against medical advice after one week. He returned six weeks later after having developed fluctuant masses over the forearm and sternum. *Cryptococcus Neoformans* were cultured from these areas as well as from the sputa, and the urine continued positive. Treatment with 2-hydroxystilbamidine intravenously was then instituted for 20 days in a daily dose of 225 mg. Following a rest period of 10 days, this same course of treatment was repeated. Clinical improvement was prompt and quite marked with a return of temperature to normal, weight gain, disappearance of malaise, and disappearance of the fluctuant masses in the various areas mentioned. A two months follow-up x-ray study of the bones, however, showed no change. This is a characteristic experience. The patient was last seen six months following therapy, and appeared to be doing well clinically; but efforts to have him return to the hospital for more detailed studies have not been successful. His present status is not known although casual information obtained from friends and members of the family indicates that his condition is quite satisfactory (Fig. 2).

*Coccidioidomycosis*<sup>2, 7, 8, 15</sup>

Coccidioidomycosis is endemic in the southwestern part of the United States, and is particularly prevalent in the San Joaquin Valley region of California. The causative agent is the *Coccidioides Immitis* which is a round, thick walled organism containing numerous endospores. It is found in the soil, and it is believed that invasion occurs by inhalation. The disease takes one of two forms: The benign pulmonary infection or the chronic, progressive, and often fatal, systemic. In the latter, the skin, bones, and other organs may be involved by spread from the original pulmonary infection which usually is progressive. Bone lesions are quite common, and usually appear as cyst-like areas of osteolysis. Proliferative periostitis may be present although frequently there is no surrounding bone reaction. To date no effective therapy has been reported for the progressive systemic type of coccidioidomycosis.

*Case report:* M.D., A 42 year old Negro male farmer, while serving with the Army at Mather Field, California, in 1946, had been found to have an infiltration of the left lung field which was presumed to be tuberculosis although no organism was identified. For the next year symptomatic treatment was instituted with improvement of the pulmonary infiltration, but with the appearance of a destructive process involving several of the dorsal vertebrae. Shortly after discharge from the Army in 1947, he entered a Veterans Administration hospital. No definite diagnosis was established, but a year's therapy with streptomycin and para-aminosalicylic acid was given. Nine months following this course of treatment a fluctuant

mass in the upper dorsal region became evident. In 1950, he was admitted to McGuire Veterans Hospital, in Richmond, Virginia, because of this, and the mass was incised and drained. Smear and culture of the purulent material obtained were positive for *Coccidioides Immitis*. Symptomatic and supportive treatment was continued, principally at home, and the process apparently became stable. In 1951, he was recalled to McGuire Veterans Hospital for further evaluation. There were two small draining sinuses present in the upper right dorsal region of the back, and complete fixation of the cervical spine. Laboratory studies: Smear and culture made from material removed from the draining sinuses were positive for *Coccidioides Immitis*. The hemoglobin was 8.9 gm.; erythrocytes 3,090,000; leukocytes 15,000 with a normal differential count. The urine showed a 3 plus albuminuria and was otherwise negative. X-ray examinations: The chest x-ray was reported as being negative, and showed no evidence of any residual infiltration. The cervical and dorsal spine showed productive bone changes with bridging between the last four cervical vertebrae. There was evidence

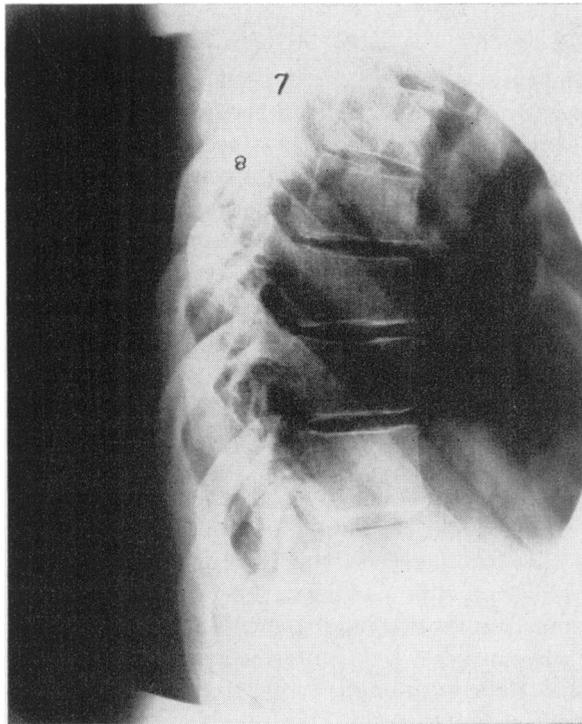


FIG. 3 Case No. 3. Irregular destructive changes along the anterior margin of D-7 with bone productive changes of the body of this vertebra. Coccidioidomycosis.

of bone destructive and productive changes in the seventh, eighth and ninth dorsal vertebrae. Shortly thereafter the patient left the hospital against medical advice. In November, 1953, the patient was admitted to another Veterans Administration hospital, and expired the following day. Postmortem examination showed a large paravertebral abscess in the right upper dorsal area with bone destructive and productive changes in the lower cervical and upper dorsal vertebrae. *Coccidioides Immitis* was identified in the material obtained (Fig. 3).

### *Comment*

Pathogenic fungi must be considered in the differential diagnosis of all infections involving bones and joints. Although neither clinical studies nor x-ray examination can make an absolute distinction between a mycotic and a bacterial infection, there are certain distinguishing features that will aid in the differentiation. Mycotic joint and bone disease occurs as a part of a systemic infection. Dissemination or spread is by means of the blood stream with the possible exception of actinomycosis in which case direct extension occurs. The lesions are usually multiple, wide spread, and in general show a predilection for cancellous rather than tubular bone. In the case of cryptococcosis there is a tendency towards involvement of the bony prominences.<sup>1, 2</sup> The x-ray appearance is that of an almost pure osteolytic process with little bone or periosteal reaction except, again, in occasional cases of actinomycosis. Sequestrae, if present, are usually small; a contrast with the usual reaction resulting from bacterial infection. When joints are involved, it is usually by direct extension from the initial bone lesion, and extensive damage occurs to the bone, cartilage and synovial membrane. Roentgen evidence of bone damage may exist for many months after skeletal pain and signs of systemic infection have disappeared. Tuberculous bone and joint lesions are most apt to be confused with mycotic infections, and it may be almost impossible to differentiate the two. Solely from a roentgen standpoint, mycotic infection of the bone may be difficult to distinguish from multiple myeloma, certain cases of metastatic carcinoma, eosinophilic granuloma and other conditions. The clinical features of these varying diseases, however, should not offer real difficulty.<sup>2, 3, 4, 5, 6, 7, 8</sup>

The failure to respond to the usual antibiotic and chemotherapeutic agents should arouse suspicion that the infection is not one resulting from the usual pathogenic bacteria. The diagnosis, however, can only be made by recovering the organism from the joint, bone, abscess cavity, sinus tract, skin, sputum, urine or spinal fluid.

The prognosis for certain of this group of diseases has improved due to the introduction of the aromatic diamidines as more effective treatment

measures. Stilbamidine is unstable in solution, and has been found to be toxic for the trigeminal nerve; but 2-hydroxystilbamidine does not have these disadvantages and is equally effective. Blastomycosis, cryptococcosis (except of the central nervous system) and actinomycosis have proven to be the most effectively treated. The various sulfonamides and antibiotics have been effective in some cases of actinomycosis and nocardiosis. Iodides in various forms and quantities have formerly been the drugs used most extensively, and for the longest period of time. This drug had been effective to a limited degree in the treatment of blastomycosis, cryptococcosis, actinomycosis and nocardiosis. Otherwise, the management has been largely symptomatic, supportive or with the use of a wide variety of drugs and other treatment measures that enjoyed brief and unwarranted periods of popularity. To date, no treatment of value is available for coccidioidomycosis, histoplasmosis or central nervous system cryptococcosis.<sup>9-15</sup>

### *Summary*

1. Eight cases of bone and joint disease were found in 25 cases of pathogenic mycotic infection observed in a period of five years. Five cases were due to the *Blastomyces Dermatitidis*, two to the *Cryptococcus Neoformans*, and one to the *Coccidioides Immitis*. The number and character of the mycotic infections were not considered unusual for this area.

2. Bone lesions, as a rule, are osteolytic in nature, usually multiple, and involve cancellous rather than tubular bone. Joint involvement occurs by extension from the adjacent infected bone. In cases responding to treatment, roentgen evidence of bone damage may exist long after the systemic features and evidence of involvement of other organs have disappeared.

3. The aromatic diamidines, particularly 2-hydroxystilbamidine, have been found to be effective in treating blastomycosis, actinomycosis and cryptococcosis (except of the central nervous system). Various sulfonamides and antibiotics have been helpful in some cases of actinomycosis and nocardiosis. Iodides in various forms are still being used in the treatment of a number of these diseases, but their use is limited. To date, no treatment of value is available for coccidioidomycosis, histoplasmosis or cryptococcosis of the central nervous system.

4. Diagnosis can be established only by recovering the organism from the joint, bone, abscess cavity, sinus tract, skin, sputum, urine or spinal fluid.

### REFERENCES

1. CONANT, N. F., SMITH, D. T., BAKER, R. D., CALLAWAY, J. L., AND MARTIN, D. S.: Manual of clinical mycology, 2nd. Ed., 1954, W. B. Saunders Co., Philadelphia

2. CARTER, R. A.: Infectious granulomas of bones and joints with special reference to coccidioidal granuloma, *Radiology*, *23*: 1-16, 1934.
3. HALL, R. H. AND MENDELLOFF, J.: Blastomycotic osteomyelitis with case report, *J. Bone and Joint Surg.*, *34-A*: 977-980, 1952.
4. COLLINS, V. P.: Bone involvement in cryptococcosis, *Am. J. Roentgenol.*, *63*: 102-112, 1950.
5. WIENER, M. F.: Generalized torulosis with bone involvement, *Arch. Int. Med.*, *87*: 713-726, 1951.
6. LEOPOLD, S. S.: Pulmonary moniliasis and cryptococcal osteomyelitis in the same patient, *Med. Clin. N. A.*, *37*: 1737-1746, 1953.
7. DYKES, J., SEGESMAN, J. K., AND BIRSNER, J. W.: Coccidioidomycosis of bone in children, *Am. J. Dis. Child.*, *85*: 34-42, 1953.
8. MILLER, D., AND BIRSNER, J. W.: Coccidioidal granuloma of bone, *Am. J. Roentgenol.*, *62*: 229-236, 1949.
9. SCHOENBACH, E. B., MILLER, J. M., AND LONG, P. H.: Treatment of systemic blastomycosis with stilbamidine, *Ann. Int. Med.*, *37*: 31-47, 1952.
10. SNAPPER, I., AND McVAY, L. V., JR.: The treatment of North American blastomycosis with 2-hydroxystilbamidine, *Am. J. Med.*, *15*: 603-693, 1953.
11. MILLER, J. M., SCHOENBACH, E. B., LONG, P. H., SHUTTLEWORTH, J. S., AND SNIDER, G. E.: Treatment of infections due to *Cryptococcus neoformans* with stilbamidine, *Antibiotics and Chemother.*, *2*: 444-446, 1952.
12. MILLER, J. M., SMITH, G. W., AND HEADLEY, W. H.: Treatment of *Cryptococcus neoformans* in mice with stilbamidine, *Science*, *118*: 31, 1953.
13. WHITEHILL, M. R. AND RAWSON, A. J.: Treatment of generalized cryptococcosis with 2-hydroxystilbamidine, *Va. Med. Monthly*, *81*: 591-594, 1954.
14. GORDON, L. E., SMITH, C. E., TOMPKINS, M., AND SAITO, M. T.: Sensitivity of coccidioides immitis to 2-hydroxystilbamidine and the failure of the drug in the treatment of experimental coccidioidomycosis, *J. Lab. Clin. Med.*, *43*: 942-945, 1954.
15. SNAPPER, I., BAKER, L. A., EDDIN, B. D., AND KUSHNER, D. S.: The results of 2-hydroxystilbamidine therapy in disseminated coccidioidomycosis, *Ann. Int. Med.*, *43*: 271-286, 1955.

#### DISCUSSION

DR. ROGER O. EGERBERG (Los Angeles): I think Dr. Toone's paper is very timely, if our experience out west is any criterion. We still see tuberculosis of the bone; but, certainly, the other granulomatous diseases, the fungi particularly, seem to be popping up more and more frequently.

I would like to bring out that, in the treatment of at least coccidioidomycosis involving bone, the treatment which existed for tuberculosis of the bone many, many years ago still holds true; and we have people, both Negro and white, who, purely on a supportive and rest regime, have had improvement and apparent cure, both from the complement-fixation test and from the clinical picture, by rest in bed, by nourishing diet, which has to be continued, as with tuberculosis, over a period of years.

One of these cases had a badly involved ankle, which did not look quite as bad as the foot Dr. Toone has shown. The other was a white man who had to have one leg amputated; but the lesions, which were many in the other leg, gradually healed, and he later died of other causes and had no evidence of coccidioidomycosis.

DR. THORNTON SCOTT (Lexington): I should like to ask Dr. Toone how many of

his patients with blastomycosis showed central nervous system involvement; and if he found any therapeutic regimen to which those patients would respond.

We have had five in the last two years in our community who responded systemically to stilbamidine, but showed no response of the peculiar meningitis with which they were suffering.

It is interesting to note that none of these patients was suspected of central nervous-system involvement at the time they were referred to the hospital. The course was very insidious; and the meningitis presented none of the outstanding features of other forms of meningitis.

At autopsy, they showed healing of their systemic lesions in bone and lungs with stilbamidine, but showed no response at all in the meninges.

DR. DAVID T. SMITH (Durham): This excellent paper of Dr. Toone's and Dr. Kelly's certainly emphasizes the increasing importance of the fungus infections, both as diagnostic and therapeutic problems. I was particularly impressed with his case of cryptococcosis (Torulosis) which recovered, because I think this fungus has the highest over-all mortality of all.

There are many unsolved problems connected with cryptococcosis. We have studied a number of the brain cases, and they show neither skin sensitivity nor agglutinins to the organism. One case which I studied had both pulmonary and bone lesions and did show a positive skin test to her own organism and also agglutinins which were easily demonstrable by ordinary test-tube reaction. Since this one did show agglutinins which were easily demonstrable, that gives additional weight to the uniform absence of agglutinin in the meningeal cases.

The organism itself is vaguely reminiscent of the pneumococcus, having a large, diffuse polysaccharide capsule, and also showing some evidence of response to sulfadiazine therapy. In other words, an occasional patient has recovered after sulfadiazine therapy.

All this suggests, purely theoretically, the possibility that we have here an analogous situation to the pneumococcus polysaccharide which may flood the body and paralyze the immune mechanism as was first described by Dr. Lloyd Felton. If a large amount of the polysaccharide is injected into a mouse, the mouse is unable to produce effective antibodies, and will die from a very few organisms introduced; furthermore, he cannot be immunized by ordinary methods.

All this adds up to the suggestion that, in the case of cryptococcosis, if the infection is limited and not too much of this capsule is produced, ordinary immune bodies may result and the patients recover. On the other hand, if the body is overwhelmed with this polysaccharide you expect no immune response, and the inevitable death of the patient.

I believe it is worth trying 2-hydroxystilbamidine. It is an inhibitor, not a direct fungicidal agent the way it is for blastomycosis. Dr. Snapper reported four cases of coccidioidomycosis in the *Annals of Internal Medicine* a few months ago which suggests that 2-hydroxystilbamidine is helpful. We recently had a very acute case contracted in the laboratory, which was rapidly disseminating, who made rather rapid recovery with this drug. Of course, that is just one case, but the drug is harmless; and, since we do not know anything better, it might be worth trying.

DR. WORTH B. DANIELS (Washington, D. C.): We had a patient recently at our hospital, who died with Hodgkin's Disease and cryptococcosis of the brain. It might be interesting to call attention to the fact that the incidence of cryptococcosis is much higher in patients with Hodgkin's Disease than in other diseases. Infection with cryptococcus neoformans should be suspected when any patient with Hodgkin's Disease develops symptoms suggestive of central nervous system involvement.

DR. L. WHITTINGTON GORHAM (New York): These large osteolytic lesions are of considerable interest. I would like to ask Dr. Toone if he had an opportunity to study either biopsy material or material at postmortem. I would be particularly interested to know whether osteoblasts were found, or whether the tissue resembled the panus formation which we see occasionally in cases of rheumatoid arthritis, where there is marked absorption of bone.

DR. ELAM C. TOONE (Closing): I believe Dr. Smith's remarks answered Dr. Egeberg's question regarding the treatment of coccidioidomycosis. Snapper has recently reported four cases treated with 2-hydroxystilbamidine with equivocal results. He summarized his article, however, by stating that he felt that the drug might have some controlling influence on the disease. Otherwise, the only treatment has been that of rest and supportive measures.

Dr. Scott's remarks referable to the central nervous system involvement in blastomycosis are very interesting. We did have one case with central nervous system involvement, and that patient died. It was the patient with the initial lesion in the sacrum, later developing an overwhelming disseminated infection. We have been aware, of course, that cryptococcosis is often associated with central nervous system involvement, but had felt that this was rare in blastomycosis.

In answer to Dr. Gorham's question: The bone and joint lesion here is not like that of rheumatoid arthritis. In mycotic infection the initial lesion is usually in the subchondral bone area with a direct extension into the joint. The lesion is primarily a destructive one with osteolytic changes in the bone and little evidence of soft tissue resistance. In rheumatoid arthritis the initial lesion is in the synovial membrane with spread to the cartilage and subchondral bone. The tissue response in rheumatoid disease is characterized by an overproduction of granulation tissue.

I would like to thank the discussants for their questions and remarks, and have nothing to add to the points brought up by Dr. Smith.