

John F. Fulton, Coccidioidomycosis, and Penicillin

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When the late Dr. John F. Fulton contracted severe pulmonary coccidioidomycosis in January, 1942, a metastatic lesion posed the threat of further progression and fatal dissemination. The possibility that an untested and generally unavailable antibiotic, penicillin, might be of value in Fulton's illness led his physician, Dr. John Bumstead, to appeal directly to Fulton to obtain this antibiotic, but ostensibly for the benefit of another patient succumbing to hemolytic streptococcal infection. While of no value for Fulton, penicillin was highly successful in the treatment of his other patient and soon of a second one with staphylococcal sepsis and pneumonia. This penicillin, administered in March, 1942, was the first clinical trial of penicillin under the control of the Office of Scientific Research and Development. The unique contribution of Dr. Fulton and of his illness to this event is described.

A recent account by Dohrmann (1) has described the significant role played by the late Dr. John F. Fulton in the early history of penicillin. Fulton provided much behind-the-scenes support for his friend, Sir Howard Florey, in the initiation of massive penicillin production in the United States during the critical early years of World War II. It was also through Fulton's good offices that his personal physician, Dr. John Bumstead, was able to secure the first penicillin released by the Office of Scientific Research and Development for clinical use at a time when penicillin for all practical purposes was still "unavailable." Dohrmann's excellent account is documented by extensive references to Fulton's diary and to other contemporary sources of information. Dr. Fulton had no reason to suspect that his own serious illness directly contributed to the decision to seek penicillin; as far as he was concerned, it was in behalf of another patient of Dr. Bumstead, Mrs. Ogden Miller, who was rapidly succumbing to streptococcal sepsis in spite of vigorous sulfonamide therapy.

Dohrmann's account has revived many personal recollections of this first encounter with penicillin. On November 14, 1942, Dr. Fulton wrote to me that: "If at any time you wish to report the case itself, I would be glad to have you do this provided you give Dr. Blake credit for having made the diagnosis! I am sure this would meet with Dr. Bumstead's approval." This report therefore also affords me the welcome privilege of honoring, although not in unseemly haste, his implied invitation to present the story of his serious brush with coccidioidomycosis.

Sad to relate, four of the principals involved in this incident have since died: Dr. John F. Fulton, Sterling Professor and Chairman of the Department of Physiology at the Yale Medical School, distinguished neurophysiologist, medical historian, and bibliophile; Dr. Francis G. Blake, Sterling Professor and Chairman, Department of Medicine and Dean of the Yale Medical School; Dr. John Bumstead, Assistant Clinical Professor of Medicine at Yale; and, across the continent, Dr. Charles E. Smith, Professor and Chairman of Preventive Medicine and Public Health at Stanford University School of Medicine at San Francisco. Dr. Smith, as the foremost authority on coccidioidomycosis, was at that time serving as Special Consultant to the Secretary of War on the program to contain this disease in the military bases operat-



FIG. 1. Dr. Charles E. Smith examining cultures of *C. immitis* in his Stanford University Medical School laboratory. Photograph by John Guttman, from an article entitled "The Mystery of the Deadly Dust," by Myron Silverman, appearing in *The Saturday Evening Post*, 1949, p. 41. Reprinted with permission from *The Saturday Evening Post*. © 1949, The Curtis Publishing Company.

ing in the heart of the *Coccidioides* endemic zone. He also served as President of the California State Board of Health and was soon to become Dean of the University of California School of Public Health at Berkeley.

As a member of the Committee on Aviation Medicine of the National Research Council, Dr. Fulton deplaned in California on January 9, 1942. Five days of travel to a variety of military installations and other institutions in the vicinity of Los Angeles and San Diego culminated in a visit to Dr. Smith on January 13 at his laboratory in San Francisco. This facility was dedicated to coccidioidal research, and required the large-scale cultivation of *Coccidioides immitis*. Although Dr. Fulton entertained no special zeal for coccidioidomycosis at that time, he went about the laboratory closely inspecting the cultures as a courtesy to his gracious and enthusiastic host. Indeed, as he subsequently wrote to Smith: "I recall sniffing one of your cultures, and I suspected that this indiscretion on my part might be the source of the infection." The hazards of infection from cultures of *C. immitis* have achieved considerable notoriety. Figure 1, which depicts Dr. Smith in his laboratory working with cultures of *C. immitis*, illustrates the risks to which Dr. Fulton was exposed. Indeed, over the years, Dr. Smith's laboratory proved to be a fertile source of infection for its denizens, for casual visitors, and even for personnel and experimental animals on other floors of the building.

Dr. Fulton dates the onset of his illness to January 16, when he first noted a "sticky bronchitis." This persisted until January 27, when, as he wrote to Smith, he developed "a massive atelectasis of the right lung a few hours before reaching New

Haven . . . I was not aware of having had a temperature or of feeling particularly poorly between the 16th and the 27th, save for the bronchitis which was not particularly disturbing.”

The incubation period of primary coccidioidomycosis is well established as from 10–16 days, with extremes of 7–28 days (2). While “sniffing the culture” makes a good story, it is difficult to reconcile with an onset 3 days later. Indeed, even if we assume massive exposure upon arrival in California on January 9, this would still place the incubation period at the lowest limit for acceptance. Possibly, Dr. Fulton erred in his appraisal of the date of onset, in which case the exposure in Dr. Smith’s laboratory would provide a very tempting probable source of infection.

When a critically ill Dr. Fulton entered New Haven Hospital on January 29, 1942, the California connection was on no one’s mind, although Dr. Bumstead had noted that his illustrious patient “had been flying about the country.” On January 25, Fulton had been subjected to a drop of 35,000 feet in a compression chamber in connection with his important studies in aviation physiology. A few days later, this was followed by a spasm of coughing, sharp pain in the chest, and shortness of breath. On admission, the fever was 104° F, the pulse at 106, and respiration at 24/min. The initial impression was atelectasis and pneumonia of the right lower lobe.

X rays of the chest only contributed to the diagnostic dilemma. These were interpreted as showing pneumonic infiltration of the entire right lung, compression atelectasis of the right lower and middle lobes, right perimediastinal hydrothorax, a markedly elevated right leaf of the diaphragm, and loculated fluid beneath the right anterior diaphragmatic pleura. They raised the possibility of a subdiaphragmatic origin of the illness, possibly an amoebic abscess of the liver which had ruptured into the right hemithorax. As late as February 11, both the Physician-in-Chief, Dr. Francis G. Blake, and The Surgeon-in-Chief, Dr. Samuel C. Harvey, concurred that an intraabdominal basis for the elevation of the diaphragm was a likely possibility. However, the pursuit of this lead proved unrewarding. Supradiaphragmatic alternatives were also vigorously explored and included such forbidding choices as malignancy, actinomycosis, tuberculosis, and unspecified pneumonia, again with no success.

Three weeks after admission to the hospital, Dr. Blake finally cleared the air. With his legendary diagnostic acumen, he related the California experience to the pulmonary lesion, the pleural effusion, the febrile course, and the leukocytosis with eosinophilia, and on February 20 proposed San Joaquin Valley Fever, or primary pulmonary coccidioidomycosis, as the diagnosis. To the best of my knowledge, this is the first time that this diagnosis had been made at New Haven Hospital.¹ His diagnosis is all the more noteworthy since, in 1942, this disease was hardly within the orbit of choices as a possible cause of obscure pulmonary disease encountered in the Eastern United States.

¹Actually, there was a patient with primary coccidioidomycosis in New Haven Hospital in 1934, but the diagnosis had not been made. In 1941, I received a number of strains of *C. immitis* from Dr. Norman Conant of Duke University. Upon subsequent inquiry, Conant revealed that his strain #190 had originated at New Haven Hospital. In tracking down the source of this culture, I found that it was recovered from the sputum of a Yale College student who had developed pneumonia after returning from a vacation in California. Dr. Robert Graves, Assistant Resident in Medicine, wrote an excellent description of the fungus but did not identify it as *C. immitis*. This is understandable; the patient recovered, and, in 1934, patients with coccidioidomycosis were expected to disseminate the infection and frequently die. It was not until 1937–1938 (3,4) that the classical reports of Dickson and Gifford established the concept of primary nondisseminating coccidioidomycosis.

As a member of the Department of Bacteriology, diagnostic problems from time to time gravitated to my laboratory. I had received earlier sputum specimens for study, and both Drs. Blake and Bumstead frequently came to my laboratory to study the preparations. Cultures for possible fungus isolation were first planted on February 18 and subsequently at Dr. Blake's request on the 21st, 23d, 25th. Although there was a heavy overgrowth with bacteria and saprophytic fungi, closer inspection revealed telltale white cottony and stellate colonies with mycelial penetration of the medium. These cultures were grossly and microscopically indistinguishable from cultures on hand in my laboratory of known strains of *C. immitis*. Inoculation into mice and guinea pigs readily yielded endosporeulating spherules, thus fully confirming Dr. Blake's clinical diagnosis.

Four days after admission to the hospital there was noted an area of erythema and 2-3 cm of induration on the right upper abdomen, interpreted as an early furuncle, or possibly an insect bite. In a subsequent letter to Dr. Smith, Fulton carefully detailed the evolution of this lesion. "This started," he wrote, "as a deep lesion in the fat and continued to enlarge during sulfadiazine therapy which was continued for 2½ weeks. It seemed at first like an ordinary boil, but it failed to point, and it presently developed a tough egg-shaped capsule which was about 30 mm in length and 20 mm in width. This began to point to the surface about 10 days ago (March 2) . . . Dr. Bumstead has been aspirating its content every three or four days, and usually gets 1 cc of purulent material from its centre."

Much to everyone's dismay, my cultures of this lesion were positive for *C. immitis*. Could this metastasis be a harbinger of fatal dissemination? Fulton's own close observation of its development strongly suggested that this lesion was blood borne and not a chance autoinoculation from the outside. I immediately communicated this development to Smith. He replied by return mail (March 7) as follows: "As you surmised, the prognostic significance of the abdominal furuncle is very grave. The only times we have seen patients with such lesions, they have lacked the ability to focalize the infection." More out of desperation than conviction, he recommended such measures as the direct inoculation of thymol into the abdominal lesion, further intensive sulfonamide therapy, a trial of coccidioidin vaccine, and even artificial pneumothorax. Needless to say, Smith's letter only increased the growing concern for Dr. Fulton's chances of survival.

It was at this time that penicillin first entered the scene. In the course of some prior conversations, Fulton had told Bumstead concerning this new antibiotic and of the beginning efforts to produce it in the United States. Indeed, a few preliminary reports of its extraordinary antibacterial activity had already been published in England (5). Having just viewed the positive cultures of the abdominal furuncle in my laboratory, he raised the question of the possibility that penicillin might turn the tide in Fulton's favor. We agreed that there was nothing to lose and perhaps much to gain if only some penicillin might be procured. At the least, I might test its activity *in vitro* against *C. immitis*. Penicillin distribution was under the most rigid control of the National Research Council, in behalf of the Office of Scientific Research and Development. Since Fulton had so many close ties to the National Research Council, perhaps he himself might succeed in obtaining a sample of penicillin. Besides, Bumstead added, he had a valid basis on which to appeal, and that was the desperate straits of his other patient, Mrs. Ogden Miller, who was close to death from streptococcal sepsis.

Not aware that his own possible plight was in the picture, Fulton responded with

characteristic vigor to Bumstead's plea. As Fulton had recorded in his diary, and as is also recounted by Dohrmann (1), Fulton first wired Dr. Norman Heatley at Merck. Heatley was Sir Howard Florey's colleague who came to the United States to expedite the production of penicillin. Heatley channeled the request to the Medical Director at Merck's, who felt that he lacked the authority to release any penicillin and referred Fulton to the eminent Dr. A. N. Richards, Chairman of the Committee on Medical Research of the National Research Council. Not discouraged, Fulton proceeded to track down Richards by the phone at his bedside. Even Dr. Richards would not authorize the release but directed Fulton to Dr. Perrin Long of Johns Hopkins, Chairman of the N.R.C. Committee on Chemotherapy. Long promptly got in touch with Bumstead, and within 2 days after the appeal was made, the first lot of penicillin reached New Haven on March 14, 1942. Although Dohrmann, quoting Fulton's diary, states that this was the only lot of penicillin forwarded by Merck, actually a second similar lot of 5.54 g was forwarded on March 27. As a memento of the occasion, Dr. Bumstead kindly presented to me the second empty vial and its mailing case (Fig. 2).

When Dr. Bumstead, accompanied by the Assistant Resident in Medicine, Dr.



FIG. 2. The vial of penicillin used in the treatment of the "first" patient and its mailing case (Dr. Bumstead's name is misspelled). The full label on the vial is as follows: 5.54 grams, penicillin, (about 60 units per mg.), 42RD491. Caution: new drug, limited by Federal Law to investigational use. From the Chemical Laboratories of Merck & Co., Inc., Rahway, N. J., manufacturing chemists.

Charles Grossman, brought the vial of penicillin to my laboratory, we viewed it with some concern and suspicion. It had a pungent odor, was coarse, and dark brown to red in color; when the powder was dissolved, it resembled a solution of iodine. We decided that discretion was the better part of valor and passed the penicillin through an EK Seitz (asbestos) filter pad to sterilize it. The penicillin was immediately administered to Mrs. Ogden Miller intravenously at dosage levels of 10,000 to 20,000 units every 4 hr, day and night. Her clinical course was summarized in 1944 by Dr. Blake (6), and actually a fuller description of her illness and response to penicillin is found in Goodman and Gilman's book (7). Although the response of Mrs. Miller to penicillin was prompt and dramatic, fever recurred, and, after an interruption, therapy was resumed on March 25 and continued until April 9, primarily with the second lot of penicillin. Enough penicillin remained to treat successfully a second patient, a 64-year-old man with *Staphylococcus aureus* septicemia. As Dohrmann reported, Mrs. Miller is alive and well today.

The penicillin was considered so precious that Dr. Heatley personally journeyed to New Haven to retrieve the urine for subsequent reextraction of the antibiotic at Merck. With his permission, and with helpful suggestions for performing the assays, a few milliliters of penicillin were diverted for *in vitro* tests against the strain of *C. immitis* recovered from Dr. Fulton. The results were most disappointing: Penicillin was about 1000 times less effective against the fungus than against a susceptible strain of *Staphylococcus aureus*. When apprised of the results, Heatley concluded that "in view of the impossibility of preparing enough penicillin for even part of the experimental needs, it might be better to postpone further work on its effects on *Coccidioides*."

In spite of many desperate needs, several months followed during which penicillin ceased to be available. Dr. Smith himself urgently appealed for it in behalf of a moribund young soldier with disseminated coccidioidomycosis, but Perrin Long, on the basis of our *in vitro* results, denied the request. It was not before June 1942 that the National Research Council Committee on Chemotherapeutic and Other Agents organized a program of clinical investigation of penicillin in 22 designated civilian medical centers (8). By 1944, Dr. Blake (6), as one of the designated principal investigators, was able to report on the clinical trial of penicillin in 200 patients at New Haven Hospital. Mrs. Ogden Miller was his Case #1. Only after the conclusion of the war did the floodgates open up.

In an editorial (9) on the history of penicillin published in 1944, Mrs. Miller is acknowledged to be "the earliest patient to be studied in this country under the auspices of the Office of Scientific Research and Development." Goodman and Gilman (7) refer to this case as the "first clinical trial of penicillin in the United States." Sir Alexander Fleming, who visited New Haven in 1945 and met Mrs. Miller, called her "his most important patient" (1). It is only fair to point out, however, that several pioneering studies on penicillin were reported in the United States in 1943 (10-12), so that the experimental work on animals and on human volunteers may actually have been at about the same time as the New Haven experience.

To return to Dr. Fulton: For almost a month, his course was significantly febrile. The leukocyte level of 22,000 on admission, with 88% polymorphonuclear leukocytes, did not return to normal for a month, excepting for some persistent increase in eosinophilia. The administration of a full course of sulfadiazine for 2.5 weeks had no demonstrable effect. Dr. Smith forwarded some coccidioidin, and 0.1 ml of a 1:100 di-

lution was administered on February 28. The reaction was strongly positive, measuring 7 by 3.5 cm, with central vesiculation, a most favorable omen. Although Fulton felt quite well, the X ray of the chest remained stubbornly unchanging and as late as May, 1942, showed only slight and questionable improvement. Dr. Fulton soon regained his high spirits and dictated a stream of letters to his secretray, and the telephone was constantly in use. His interest in coccidioidomycosis had become keen, and he soon amassed a formidable collection of reprints on this subject. He carried on a lively correspondence with Dr. Smith, including many aspects of his own illness, not to mention a case of coccidioidomycosis in M'Bongo, a gorilla at the San Diego Zoo.

Dr. Fulton was discharged from New Haven Hospital on March 20, 1942, with strong admonitions from Dr. Smith to curb his activities. Soon, however, he was chafing at the bit, and, by April 18, Smith gave him his reluctant consent to liberalize his daily work program. It was not long before Dr. Fulton was on the road, and, on May 5, he wrote to Smith: "As for my coccidioidal self, I am glad to report that the three days in Baltimore (I sneaked over to Washington for one day) did not leave me any the worse for the trip. I get out of breath pretty easily still, and find it convenient to look at pretty faces until my wind returns."

In spite of the favorable clinical course and the vigorous reaction to the coccidioidin skin test, the metastatic lesion continued to be a source of concern over the ultimate prognosis. It is well known that coccidioidomycosis may disseminate insidiously over a long period of time. Extensive studies, in which Dr. Smith himself had been a pioneer, have established the prognostic value of the serological response in coccidioidomycosis. Therefore, for a period of about 2 years, until July 5, 1944, I forwarded 10 serum samples to Dr. Smith for complement fixation and precipitin tests. These determinations showed a steady decline in titer, reinforcing the conclusion that the infection was healing. Nevertheless, the sputum was still positive 6 months after the onset of the disease.

Dr. Fulton died in 1960 of causes unrelated to his serious encounter with coccidioidomycosis.

One may only speculate whether Fulton's own prominence and potentially desperate need in any way contributed to the decision to release penicillin at that time. Letters of inquiry came from various parts of the country. On March 10, Smith wrote to him: "Your illness has already achieved national prominence: a very good friend of ours named Amos Christie who is now in Washington just wrote me about it yesterday, and the University of California and Stanford faculties are all expecting daily bulletins."

In a study (13) of experimental infection with *C. immitis*, Fulton's strain was utilized and designated as "Strain J.F.F." When Fulton spotted this report, he wrote, in part: "I am greatly interested in your paper in the October number of the Yale Journal on *Coccidioides immitis*. The fact that you were able to get something worthwhile out of my illness last winter makes me feel very much better about it. . . . I hope that you will be able to spare me four or five copies so that I can send them to my friends pointing proudly to 'Strain J.F.F.'" Perhaps he would have had a far sounder basis for deriving some satisfaction from his severe bout of coccidioidomycosis had he realized the key role his illness played in the decision to seek penicillin at that time. As a direct consequence of his own ordeal, two other lives were saved, and penicillin was launched on its fateful course in American medicine.

ACKNOWLEDGMENTS

Over 30 letters relevant to this episode have survived and have reinforced personal recollections. These have included direct correspondence with Dr. Charles E. Smith and Dr. Fulton, as well as carbon copies of the correspondence between Fulton and Smith which they shared with me.

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