

Mahoney J F, Arnold R C & Harris A. Penicillin treatment of early syphilis: a preliminary report. *Venerereal Disease Inform.* 24:355-7, 1943.
[US Public Health Service, US Marine Hospital, Staten Island, NY]

Four patients with early syphilis were treated with penicillin. Each patient had a dark-field positive chancre of syphilis and a positive blood test for syphilis by both qualitative and quantitative examinations. The clinical lesions healed rapidly, and over a two-month period the blood tests became negative. This work was later discussed in JAMA's "Landmark Perspective" series. [This is the most-cited article in this journal.]

Richard C. Arnold
814 Yale
Columbia, MO 65201

February 3, 1986

Syphilis was once a dreaded and dreadful disease involving millions of US citizens. Before the introduction of penicillin, the heavy-metal cure often caused thousands of deaths each year. The morbidity and mortality of the disease itself was horrendous, involving all ages from the fetus to the elderly.

I had demonstrated in *in vitro* studies that penicillin would not kill the infecting organism of syphilis. Nonetheless, I gave two rabbits with early scrotal chancres of syphilis injections of penicillin every 4 hours for 48 hours. To my surprise the chancres healed quickly and no organisms could be found by intensive examinations. This amazing discovery led J.F. Mahoney and me to treat five additional acutely infectious rabbits, and we observed the same results. Then began an intensive lymph node study to determine if the animals were actually cured. The cure was evident, so we undertook numerous studies to determine the time-dose relationship necessary to produce a cure in animals and then to determine human dosage. In June of that year, four young men with early chancres of syphilis were selected, each having a lesion that was dark-field positive for the syphilis organism, and each with blood tests positive for syphilis.

Each patient was given 25,000 units of penicillin intramuscularly every four hours for eight days. The dosage was determined by the fact that peni-

cillin came in ampoules containing just 25,000 units, and the frequency was determined by our early animal studies. The length of treatment was based on the early continuous arsenical intravenous therapy, which lasted for eight days.

Within four hours the lesions had become edematous and exuded serum for several hours, then showed a beginning of the healing process. Each patient had an elevated temperature due to the toxins released from the killed treponemes. In all patients, the chancres showed a rapid diminution in the number of treponemes (to zero by 12 hours). Within 24 hours the patients felt well and had no local or systemic ill feelings. The serological tests for syphilis first showed a diminution of titer by the quantitative tests, and later the qualitative tests were completely negative, remaining so at a six-year follow-up examination.

Needless to say, there was many a doubting Thomas about the work and the early reports that seemed so optimistic. Standing alone and taking the criticism and doubts of the experts was not easy but well worth the bombardment of words. What the experts did not know was that, although I was just a young, inexperienced clinical research physician, I had previously checked every new idea, treatment, or report of reinfection, and studied relapse and proof of cure in the experimental rabbits. So I knew I was right regardless of what the "books" or expert clinicians said.

I was very fortunate in having a laboratory chief who never interfered with my studies and, even more important, in having a medical director who had faith in my laboratory studies and who believed I would not intentionally do any harm to patients while trying new treatments. I was aided by a small but very loyal staff in the necessary round-the-clock work. They helped to develop a follow-up loyalty in the treated patients. The patients felt it was most important to come back for the tests to help prove that penicillin cured the disease, despite the fact that they often sacrificed brief leave periods to do so.

I was surprised and pleased by the honor that our later work¹ received when it was discussed 40 years later as a landmark article in the *Journal of the American Medical Association*.² The treatment of syphilis has changed very little. Few realized that the best prevention of the disease would eventually arise from treatment of the more common venereal disease—gonorrhea. For years the treatment of that disease has cured incipient, undiagnosable syphilis as well; therefore, we see far fewer new primary infections of syphilis today.

1. Mahoney J F, Arnold R C, Sterner B L, Harris A & Zwally M R. Penicillin treatment of early syphilis: II. *JAMA* 126:63-7, 1944.
2. Arnold H L, Jr. Penicillin and early syphilis. *JAMA* 251:2011-12, 1984.