

Brucellosis Therapy: A Historical Overview

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In 1886 David Bruce (1855-1931), a British army surgeon, isolated a coccobacillus that he named “*Micrococcus melitensis*” from the spleen of a man who had died of “Malta Fever”(1). This disease was endemic, but confused with other diseases, especially malaria. The average annual incidence in Malta during 1901-06 was 652 civilian and 605 military cases, with a death rate, respectively of 10.4% and 2.3% (2). The human disease was associated with people who consumed goat milk and had other close contact with goats. The organism soon was isolated from these animals. In 1897 a similar microbe was isolated from the udder of cows, and in 1914 from swine. In about 1920 the genus was renamed *Brucella* and its species became respectively *Br. Melitensis*, *Br. Abortus*, and *Br. Suis*. The pathogens are not entirely species specific, e.g., cattle may be infected with *Br. Suis*. The disease has had numerous names, with “undulant fever” becoming predominant in the United States until the 1940s, when it began to be called Brucellosis. The first cases identified in the U.S. resulted from exposure during the Spanish-American War, presumably from infection in the Philippines (3). The first North American infections were probably recognized in 1894, but were not published until 1911, included with the experience of others (4). These patients, like the Mediterranean cases, herded goats and drank their milk. They were located in the Mexican border region of Texas. The first human blood culture of *Br. abortus* (rather than *Br. melitensis*) was obtained in Baltimore in 1924 (5). Infection of cattle became recognized as far more wide spread than that of goats or swine. In the mid-1930s 13-16% of all U.S. cattle in 70% of the herds were estimated to be infected, as well as 10% of the milk goats in Texas (6).

In 1926 46 human cases were reported in the U.S. (7). The first cases to be recognized in Iowa or Minnesota, where Brucellosis became a major endemic problem, occurred in 1927 (8). The prevalence of the disease increased rapidly, but the extent to which this merely indicated better diagnosis is uncertain. In the 14 years 1930-1943

36,513 cases of Brucellosis were reported in the U.S., 59% of these during the latter seven years (9,10).

Brucellosis has been difficult to diagnose conclusively because blood cultures in chronic cases usually are negative and, conversely, the agglutination reaction may be falsely negative and a positive reaction may not indicate currently active disease or cross-reaction with another pathogen.⁸ These factors, as well as the marked variability of symptoms have made treatments difficult to evaluate. The disease may be self-limited. The best diagnostic clue has been the occupational history. Since most milk has been pasteurized most at risk have been slaughterhouse workers and farmers.

The greatest reliance in the 1930s was placed on various therapeutic vaccines (11) although they “appear to be very uncertain in their effect.”¹² Nevertheless, there were small trials of numerous drugs. There appears to have been particular interest in metallic drugs which were available for the treatment of other diseases: e.g., I.V. neoarsphenamine (arsenical), I.V. Mercurochrome (mercurial) (12), I.M. Enesol (bismuth-mercury),¹¹ I.M. Fouadin (antimonial) (13). However, the first drug to be tried widely that appeared to hold promise for a rapid effect was sulfanilamide. The first of numerous English language reports appeared in 1938 (14,15), but failures already began to be reported in 1939 (16). Subsequent sulfonamides as monotherapy were equally ineffective.

Between 1947 and 1951 antibiotic therapy became established, although also without complete reliability. The first hope was accorded to I.M. streptomycin (17), although another report deemed it worthless as monotherapy. The latter report was the first to find streptomycin combined with oral sulfadiazine to possibly be effective (18). This was rapidly confirmed (19). However, the parenteral administration of streptomycin made the treatment frequently impractical. Next, in 1948, the first trial of chlor-tetracycline (Aureomycin) was made in Mexico, initially combined with sulfadiazine, but soon by itself. This drug had the practical advantage over streptomycin of oral administration and lack of oto-toxicity. Some cases who had failed streptomycin – sulfadiazine were cured (19). As with previous drugs, in 1950 cases in which Aureomycin failed were reported (20). Spink et al., in 1951 adhered to the superiority of Aureomycin monotherapy (21). The last drugs to be cited in this brief review are

chloramphenicol (Chloromycetin) and oxy-tetracycline (Terramycin). Harris (1950) found the former drug to be equally effective and better tolerated than Aureomycin (22). In 1951, also initially in Mexico, oxy-tetracycline (Terramycin) was introduced. These investigators concluded that “all three of the agents (Aureomycin, chloramphenicol, Terramycin) are far superior to the combination of streptomycin and sulfadiazine...”(23) In 1960 Spink concluded that the tetracycline drugs “constitute the treatment of choice and are recommended in an oral dose of 500 mg. every six hours for a minimum of 21 days.” If there is a relapse this course should be repeated combined with 14 days of I.M. streptomycin (24).

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