of relapse, but they acknowledge that combination regimens are associated with higher rates of adverse events and poor adherence, which are important considerations for patients with a potentially life-threatening infection that requires prolonged oral antibiotic therapy. Between the data presented by Low et al. [1] and those presented in other published reports [2–5], there are a total of 18 reported episodes of maintenance therapy with oral antibiotics among 14 individuals with mycotic aneurysm due to B. pseudomallei. If successful therapy is defined as the absence of further episodes of relapse or complication during the reported follow-up period, the success ratios for episodes of maintenance therapy with antibiotics were as follows: 0/3 (0%) for doxycycline; 2/4 (50%) for amoxicillin clavulanate; 1/2 (50%) for doxycycline and amoxicillin clavulanate; 2/2 (100%) for trimethoprim-sulfamethoxazole (TMP-SMZ); 5/5 (100%) for TMP-SMZ and doxycycline; 1/1 (100%) for TMP-SMZ and tetracycline; and 1/1 (100%) for TMP-SMZ, minocycline, and ampicillin-sulbactam. In summary, the efficacy of single-drug or combination treatment regimens with TMP-SMZ was high (9 [100%] of 9 regimens were successful). The only combination treatment that failed was the one that did not contain TMP-SMZ. The use of TMP-SMZ monotherapy for the maintenance phase of treatment of melioidosis is supported by data regarding in vitro susceptibility [6] and outcomes from the Darwin prospective melioidosis study [7]. In that study, the concept of “eradication,” instead of “maintenance therapy,” is supported by the absence of relapse after the discontinuation of therapy, provided that the adherence to and the duration of treatment are adequate. A randomized, controlled trial of treatment with TMP-SMZ versus treatment with TMP-SMZ plus doxycycline is proposed for Thailand. Meanwhile, we recommend that, as with other presentations of melioidosis, eradication therapy with oral antibiotics for mycotic aneurysm due to B. pseudomallei should usually contain TMP-SMZ. On the basis of our data and the known difficulties with combination therapy, TMP-SMZ monotherapy seems to be preferable at a dose of 8/40 mg/kg (320/1600 mg for an adult) twice per day. If combination therapy is used, the regimen should include TMP-SMZ, possibly even in the occasional case in which in vitro susceptibility testing suggests resistance to TMP-SMZ.

Acknowledgments

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Syphilis in History: A Response to 2 Articles
Sir—the editors of Clinical Infectious Diseases should be congratulated for publishing 2 articles on the history of syphilis this year (by Ross [1] and Rothschild [2]) and thereby drawing readers’ attention to the long history of this disease. What a shame, however, that neither author worked with a historian to broaden his perspective about the historical impact of syphilis. Historians could direct researchers to the rich historical records about human populations, including their migration to and from areas affected by syphilis; about hospitals and other charitable institutions that cared for the sick, especially the indigent; and about the thriving marketplace in cures for syphilis from the mid-16th century onwards. An audience of clinical infectious diseases specialists might be interested to know that syphilis had an even greater historical impact on societies than either author’s work suggests.

Rothschild [2] poses questions that historians have already tackled—for example, whether the epidemic of syphilis in the late 15th century was new or a clinical misdiagnosis of leprosy. Carmichael [3] addressed this question in her analysis of Milan’s mortality records from the 15th century. Milanese physicians had been regularly attributing deaths to leprosy since at least 1452, whereas they attributed deaths to the “French disease” (or syphilis) only after 1503, thereby suggesting an ability to distinguish between the 2 diseases clinically. The French disease was probably new to the Italian peninsula, if not to all of Europe. Physicians and the wider public did, however, often draw analogies between syphilis and leprosy, which is not the same as misdiagnosis. Foa [4] has explained how the new disease was disori-
ent to physicians and the public. Analogies between the new disease and older diseases, including leprosy—a widely feared but familiar disease—helped physicians and the wider public understand and cope with the psychological devastations of the new disease.

Written records are evidence that can be subject to analysis with the appropriate skills in language, culture, historical context, and a clear methodology, thereby making Rothschild’s distinction between the “literary record” and evidence-based analysis somewhat arbitrary [2]. Given that Rothschild wants to explain how disease moved from one region to another, it is important to study population migration, for which historical evidence exists. Fortunately for researchers, the first European syphilis epidemic took place in precisely the location with the richest archival evidence: Renaissance Italy, with its proliferation of bureaucracies, including public health magistracies that tracked plague and other diseases, in addition to information about household composition and demographic characteristics [5–8].

Rothschild [2] missed an opportunity to explain the conditions in which the first European syphilis epidemic occurred: massive warfare. No one has disputed that this epidemic erupted during the French invasion of Italy. Mercenary soldiers from throughout Europe defended the Italian city-states, while the European powers (the Holy Roman Empire, France, Spain, and the Papal States) vied for control of the Italian peninsula. This large-scale war endured for >30 years. Foreign troops were billeted in local towns long enough for marriages and long-term sexual relationships to occur, not to mention rape and prostitution associated with the war [9]. Columbus’s ships are not the key to unraveling this epidemic’s origins; the Italian Wars are.

Whereas Rothschild [2] was trying to diagnose disease at the population level, Ross [1] took this approach one step further and tried to diagnose disease at the individual level—specifically, the person of William Shakespeare. Historians call this practice “retrospective diagnosis,” an exercise that requires the utmost caution. Ross presents rather thin evidence to conclude that Shakespeare had syphilis: Shakespeare wrote about syphilis, his marriage was apparently shaky at times and he may have had sex with others, and his extraordinary literary productivity eventually declined. It is not true, as Ross asserts, that “Shakespeare was more preoccupied than his contemporaries with sexually transmitted diseases” (p. 399). On the contrary, English literature was filled with references to the “pox,” precisely because the disease carried so much symbolic power to evoke shame and individual and collective immorality [10–12].

Ross reduces Shakespeare’s complex poetry and plays to autobiography of the narrowest sort. For Ross, Shakespeare’s sonnet 129 is a confession of his “lasciviousness”; his bawdy vocabulary is not evidence of his skill in appealing to the masses and in inventively using vernacular expressions, but rather of his “high level of sexual awareness.” The problem with retrospective diagnosis is not just that it relies on shaky evidence, but that it so often reduces an individual’s life—with the complex interplay of historical, literary, and personal influences—to the mere expression of disease.

Ross [1] has also missed a larger opportunity: to explore the impact of syphilis on the imaginations, personal and public lives, and institutions of large numbers of people living in Elizabethan England. Far more effective is Siena’s [13] careful study of how the pox affected the residents and institutions of London: the poor often opted for suicide rather than face painful treatment, and London’s workhouses could not fulfill their intended function, because so many of the poor, disabled by pox, could not work. The pox was one of the major engines of poverty in 17th and 18th century London. Although we cannot be certain which specific individuals had syphilis, we do know that the disease was widespread. Closer attention to social processes explains how syphilis became stigmatized and why stigma fell more heavily on some groups, especially women and the poor [14].

A collaborative effort between paleontologists, infectious diseases specialists, historians, and scholars of literature could be fruitful and more productive than work done in isolation. An ecological approach to the history of syphilis could bring together these disciplines. Whereas paleontologists and infectious diseases experts can supply information about pathogens and disease, historians can provide information about host populations and large-scale demographic changes. Literary scholars can elucidate how the disease was represented and perceived.

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Reply to McGough

Sir—I share the cogent sentiments expressed by Laura McGough [1], so much so that I presented the treponematosis issue at the Society for the History of Medicine national meeting in Pittsburgh, Pennsylvania, several years ago, in the unrequited hope that I could stimulate a medical historian to perform analyses that we both obviously perceive as necessary to the question. There are, however, several comments and a basic concept that need to be clarified.

Analysis of any record is predicated on validated criteria and techniques. Although validated criteria and techniques are available for the skeletal record [2–4], issues regarding semantics/word usage and medical diagnostic clarity (especially for the 15th and 16th centuries) make the literary record more difficult to interpret. Analysis of that record is even more complicated, because physicians typically do not record all of their findings; rather, they record what is perceived to be pertinent. Delineation of definitive characteristics of a new disease, however, is refined by the “retrospectoscope.” Thus, findings amenable to interpretations of the literary record may not be sufficiently diagnostic or pathognomonic today for confident diagnosis.

An example of a modern semantic issue might be McGough’s [1] suggestion that “Columbus’s ships are not the key to unraveling this epidemic’s origins; the Italian Wars are.” In a sense, both are responsible. From a historical point of view, the Italian Wars (and the biological warfare apparently practiced therein) were responsible for the spread of syphilis. However, those wars could not have spread the disease had it not had been present in Europe—and that was Columbus’ contribution [5].

McGough [1] cites tertiary references (i.e., distillations of at least some of what has been published on the subject). To try to avoid “coloring” of information, the original articles would actually need to be reviewed and cited. However, even that is not sufficient. Modern paleopathology has become a true science, transcending opinion-based pronouncements to offer assessments based on validated, data-based criteria; the pursuit of historical medicine also requires such attention to detail. My history of medicine colleagues tell me that their analyses must be performed on the clinical notes and correspondence letters from the time in question. I hope this correspondence may stimulate pursuit of this topic by those with the appropriate language and medical skills and interest in the history of medicine.

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References


Reply to McGough

Sir—I thank Dr. McGough [1] for drawing the attention of readers of Clinical Infectious Diseases to the abundant scholarly literature documenting the rampant spread of syphilis in early modern England. Will Shakespeare, a spirited man of means, living apart from his wife, and keeping bohemian company in the epidemic’s London epicenter, was at high risk for the disease. Furthermore, Shakespeare’s venerable illness was the subject of gossip during his lifetime [2]. Reading autobiography into the writings of Shakespeare, or anyone else, can be a fatuous and superficial exercise, but the hysterical, raving references to syphilis in the problem plays, such as Timon of Athens, suggest that the subject cut deeper with Shakespeare than his contemporaries. (I doubt that a life of Shakespeare has been written that did not extrapolate biography from his work, although this does not necessarily justify the practice.)

I defend retrospective diagnosis as an instructive exercise for physicians and also as a means to gain new understanding of the past. I agree that facile reductionism is a grave danger. Attempting to explain Shakespeare’s astonishing career entirely.