The Tale of Infective Endocarditis: Fatal Then Curable but Rarely Preventable

Harold Smulyan, MD and Donald C. Blair, MD

Abstract: The story of infective endocarditis (IE) is a miracle of medical progress. In retrospect, it seems as a logical and orderly progression of remarkable events leading to the nearly complete conquest of the disease. IE was almost uniformly fatal until the 1st cures by surgery, followed by frequent cures with antibiotics, further improved when combined with valve surgery. Most recently, it has become almost a new disease with a change in the offending organisms, a change in the type of afflicted patients and the infection of implanted medical devices. Despite therapeutic success, prevention of IE has been elusive. In this review, the authors tell the story by highlighting major events, illustrating interconnections among branches of science that brought the authors to their present state and describing some well-known patients. For this summary, the authors are indebted to the more detailed descriptions of the IE history readily available for interested readers.

Key Indexing Terms: Osler; Penicillin; Surgery; Bacteria; Prophylaxis.
[Am J Med Sci 2015;350(2):140–146.]

BEFORE OSLER

Although excrescences on heart valves were described many years earlier,[1,2] the authors begin in 1806, when the name "vegetation" was 1st applied to the valvular lesions seen at autopsy by Corvisart in France. He incorrectly attributed them to syphilis.[3] Laennec,[4] a student of Corvisart, who unknowingly contributed to the field in 1819 by inventing the stethoscope, disagreed with his mentor regarding the relationship to syphilis in his 1821 treatise on diseases of the chest.[5] His disagreement arose from the rarity of the vegetations versus the frequency of venereal disease. Although vegetations were well recognized by that time, there had been no clear connection to any specific disease.

Between 1800 and 1850, Paris had become a center for autopsy study and, in 1841, Bouillaud[6] began to relate autopsy findings to such clinical findings as cardiac murmurs and fever. The international contributions to the field began to emerge when, in 1852, an Englishman, Kirkes,[7] showed that bits of the vegetations of any size could embolize—from the right heart to the lungs and from the left heart to any systemic organ. Then in 1855, Von Rokitansky,[8] in Germany, described "small, round, oblong, cylindric, sausage-shaped bodies" within the vegetations of the mitral valve. These were also identified in 1871 by Virchow[9] who suggested that they could be bacteria. Photomicrographs were not available then to display what they saw but are now readily available (Figure 1).

Another major contribution was made in 1869 but not widely appreciated at the time since it was published in a relatively obscure Norwegian journal. The author Winge,[10] in a single case report, observed that organisms from a severe skin infection could enter the blood stream and be transported to both the left- and right-sided heart valves. He identified the same organism from all the 3 sites and thereby demonstrated the route by which the heart could be infected. In 1878, Klebs[11] from Germany was able to demonstrate in 27 autopsies microorganisms in the vegetations of each case. The study was provocative, but not all concurrent publications on this subject described this degree of consistency. It was in the same year, also in Germany, that the first animal model of infective endocarditis (IE) was described by Rosenbach.[12] He showed that stylet-induced injury to the aortic valve of a rabbit was insufficient to produce endocarditis unless organisms were also introduced. This work was confirmed by Orth,[13] also in Germany, in 1885.

In a different direction, a major advance was the identification of specific organisms and the practical use of the blood culture in the budding field of microbiology. If the blood carried the organisms to the heart from a peripheral site as shown by Winge, it was reasonable to assume that the germs could be isolated from the blood. Pasteur[14] had shown that circulating organisms could be cultured and identified from peripheral blood in infectious diseases other than IE but this was technically difficult, because the blood samples from multiple skin pricks were small. The problem was solved by the French invention of the sterilizable piston syringe by Straus[15] in 1886. Several other versions were developed culminating in a syringe completely made of glass and also designed in France in 1891 by Malassez.[16] The ability to sample larger volumes of blood made the blood culture a readily available clinical tool that permitted correct bacteriologic diagnoses during life. Subsequent studies showed that, as a disease, IE could be caused by many different organisms.

OSLER—THE CLINICAL DEFINITION OF IE

The name of William Osler has become inextricably linked to IE—not because of original experiments but rather for his ability at clinical observation and synthesis. In 1885, he was honored by the Royal Society of Physicians in London when asked to deliver 3 Gulstonian Lectures.[17] These lectures had been given annually for the previous 250 years by "one of the 4 youngest doctors in Physic in the Society."[18] Osler had been elected as a fellow 2 years earlier at age 35, having completed distinguished service as a professor of the Institutes of Medicine at McGill University and physician to the Montreal General Hospital in Canada. Only 13 years out of medical school, he had just taken up the Chair of Clinical Medicine at the University of Pennsylvania[18] (Figure 2).

In these lectures, Osler summarized, organized and classified the previous clinical descriptions of "malignant endocarditis." His presentations were based on a review of the previous literature, the records of 209 cases and on 23 cases of his own. The lectures were a landmark in the history of the disease because they

From the Department of Medicine, Upstate Medical University, Syracuse, New York.
Submitted January 5, 2015; accepted in revised form April 2, 2015.
The authors have no financial or other conflicts of interest to disclose.
Correspondence: Harold Smulyan, MD, Upstate Medical University, 90 Presidential Plaza, Syracuse, NY 13208 (E-mail: smulyanh@upstate.edu).

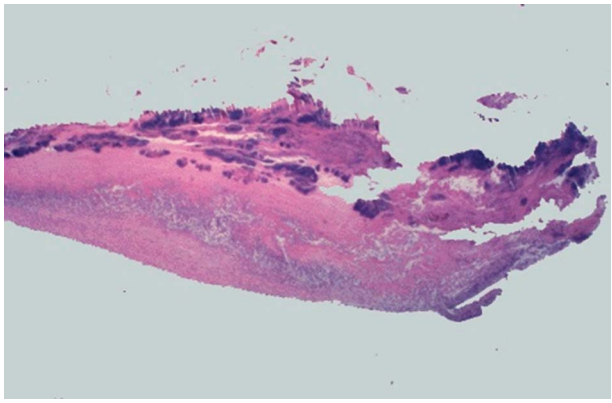

FIGURE 1. Photomicrograph of a valve with endocarditis. Demonstrates friable vegetations and platelets (pink) mixed with inflammatory cells and bacterial colonies (blue). http://library.med.utah.edu/WebPath/CVHTML/CV041.html with permission from Edward C. Klatt, MD, Professor of Pathology, Mercer School of Medicine, Mercer University.

collected and reviewed a disparate literature, added a large number of case descriptions, stressed the importance of previously damaged valves and importantly brought the subject to wide clinical attention.[19] He summarized the current confused clinical state of affairs … "Few diseases present greater difficulties in the way of diagnosis than malignant endocarditis, difficulties which in many cases are practically insurmountable. It is no disparagement to the many skilled physicians who have put their cases upon record to say that in fully one-half of them the diagnosis was made post mortem," … in other words, a 50/50 chance for a correct diagnosis during life. In retrospect, the lectures also had a number of drawbacks. They were observational only with cases drawn from different sources, there was no attempt at statistical analysis and the offered classification was incomplete at best. Also missing from the lectures was an accounting of the related microbiology of the times, a subject with which Osler was largely unfamiliar.[18] At the end of the last lecture, Osler concluded "that we should follow an important rule too much neglected and get a definite outline for our ignorance." This may have been the most important result of the lectures—recommending that unknowns be indentified to point the way for future investigation.

AFTER OSLER

In the years after the lectures, Osler followed developments and wrote frequently about the disease. During that time, there were many studies confirming that IE could be produced by different organisms although the Streptococcus and Staphylococcus were most common. In his last publication on IE[20] (Figure 3), Osler further refined the clinical description, stressed the predilection of previously damaged valves, the constancy of fever as a symptom and the growing importance of the blood culture. In this article, he also described the "ephemeral spots of a painful nodular erythema, chiefly in the skin of the hands and feet" to which his name was later appended—Osler's nodes (Figure 4). A major subsequent advance was the widespread use of the blood culture, advanced by Horder[21] in England in 1905 and in the United States by Libman[22] in 1906. Libman's multiple publications not only established the value of a positive blood culture for the diagnosis of IE but also required that the

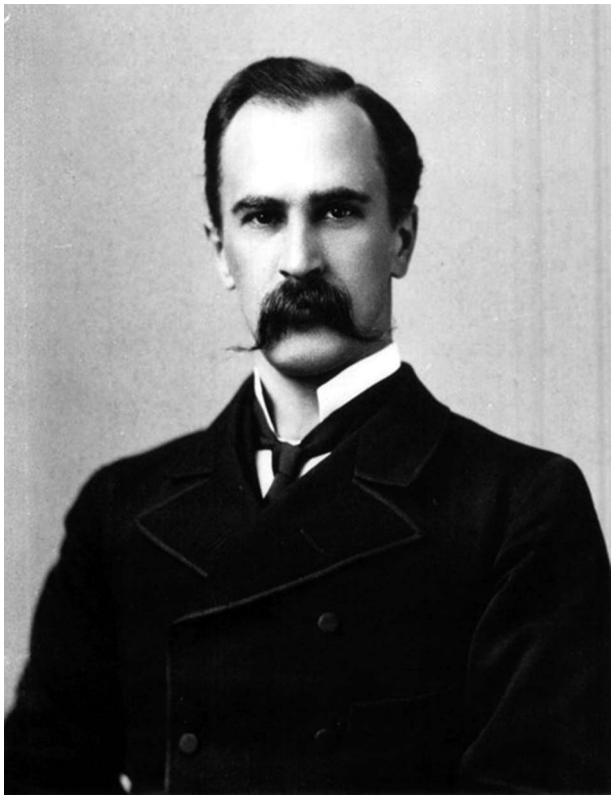

FIGURE 2. William Osler 1881, age 32. Rowland CC. In the dictionary of Canadian biography. Vol 14. University of Toronto, 1998.

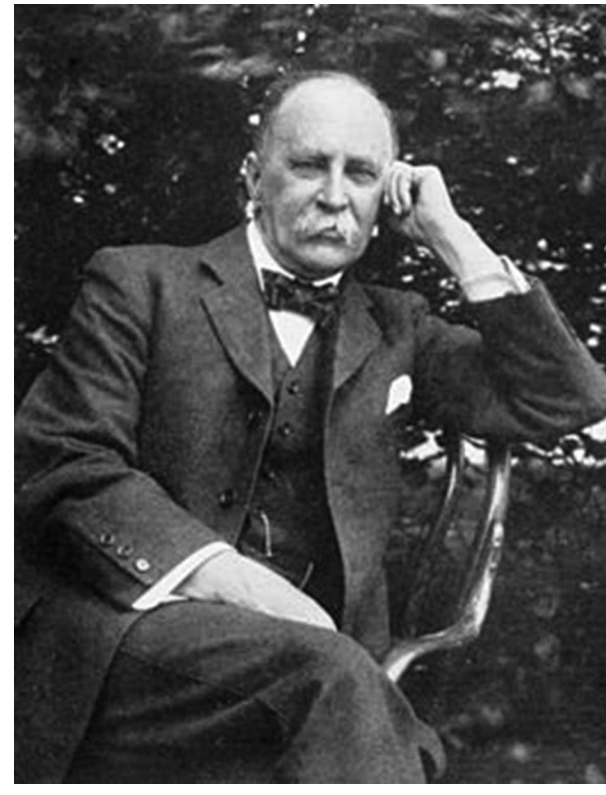

FIGURE 3. Sir William Osler—circa 1912, age 63. Professorships at the Johns Hopkins University.