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Infective endocarditis: a history of the development of its understanding

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ABSTRACT

Inflammation of the inner layer of the heart, especially the valvular endothelium, chordae tendinae and mural endocardium was first recognized almost 350 years ago. Over the years it has had many names, but is now generally designated infective endocarditis (IE) and has an associated infectious agent. A sterile vegetative process can also affect the valves and is usually referred to as Libman-Sacks endocarditis. The developments of medical science that allowed for our understanding of this entity included refinement of the autopsy, medical microscopy, microbiology, and in recent years, molecular studies. Some observations were misleading but clarification particularly followed the reports of Morgagni, Osler and Libman. As understanding of the pathobiology of infective endocarditis grew so did the effectiveness of therapy. This paper provides a detailed history of the development of the concept of Infective endocarditis citing many key morphological observations and concludes with brief comments about current concepts of pathogenesis as well as a few remarks about therapy.

Keywords: Endocarditis/diagnosis; Endocarditis/history.

Endocarditis is the inflammation of the inner layer of the heart, usually involving the heart valves, both native and prosthetic. Other cardiac structures including the chordae tendinae, the mural endocardium, the sinuses of Valsalva and the interventricular septum can also be involved. The typical lesion of endocarditis is the vegetation, which in its earliest stages, consists of fibrin and platelets with no or few inflammatory cells. This beginning vegetation, characteristic of coagulopathic states, is known as non-bacterial thrombotic endocarditis or endocardiosis (NBTE). These uncomplicated histopathologic features are also typical of the vegetations of acute rheumatic fever[1] and systemic lupus erythematosus, also known as Libman-Sacks endocarditis.[2]

When infectious agents and inflammatory cells supervene the term “infective” or “infectious” endocarditis is applied. Bacteria are most often the cause, but fungi can also be seen, particularly in immunodeficient (e.g., AIDS) or immunosuppressed (e.g., post-chemotherapy or post-transplantation) patients. For many years the terms “acute bacterial endocarditis” (ABE) and “subacute bacterial endocarditis” (SBE) were applied but, with the increasing recognition of a variety of causative organisms and their variable clinical presentations, the term “infective endocarditis” has come to be the standard. *Staphylococci* or *streptococci* were often identified in the “acute” cases, typically affecting a chronically damaged (e.g., calcific aortic stenosis) or congenitally deformed (e.g., bicuspid aortic) valve.

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These forms of endocarditis were often destructive and many of the earliest descriptions of endocarditis highlighted the ulcero-necrotic behavior of the infection.

Streptococcus viridans was recognized as the prototypic organism of subacute bacterial endocarditis[3] which, characteristically, affected damaged and fibrotic valves of chronic rheumatic fever and which, also characteristically, usually took four to six months from diagnosis to death. The final illness of Gustav Mahler (1860-1911), the great conductor and composer, exemplifies this illness.[4,5] Mahler had well-documented childhood rheumatic fever. His endocarditis developed while he was conductor of the New York Philharmonic Orchestra. Emanuel Libman (1872-1946), the brilliant physician who had studied with Theodor Escherich (1857-1911) and was himself an expert microbiologist, as well as a superb pianist, advised Mahler of his prognosis, allowing Mahler time to return to his beloved Vienna where he died approximately six months after consulting with Libman.

Although endocarditis almost certainly occurred throughout the ages, there is no documentation of cardiac valvular/endothelial inflammation until **Lazare Rivière** (1589-1655) described,[6-8] in 1646 (Table 1), a patient presenting with palpitations and irregular pulse who died after a relatively short course. At autopsy, "round carbuncles" were found in the left ventricle, resembling a "cluster of hazelnuts" and filling up the "opening of the aorta." His description also suggested that the aortic valve was "hardened".[8] Although not unequivocally evocative of endocarditis, Laennec credited this report as the first account of aortic valve disease with vegetations of endocarditis.[9] Rivière, who introduced the teaching of chemistry at Montpellier, was an advocate of the medicinal uses of antimony.[10]

De sedibus, et causis morborum per anatomen indagatis (the sites and causes of disease by anatomic investigations) is, along with Andreas Vesalius' (1514-1564) 1543 *De humani corporis fabrica libri septem* (the structure of the human body in seen books), William Harvey's (1578-1657) 1628 *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus* (an anatomical study of the motion of the heart and blood in animals) and James Watson's and Francis Crick's (1916-2004) 1953 paper on the structure of DNA,[11] one of the four most important and influential publications in the history of medicine. This great work of **Giovanni Battista Morgagni** (1682-1771) (Figure 1) set the firm foundation for the practice of medicine by establishing clinical and pathologic correlations as the basis for the understanding of disease.[12] In Section II of *De sedibus …* Morgagni described chronic rheumatic valvulitis with aortic valve endocarditis, correlated in great detail with the clinical course of the patient with the findings at autopsy. Both Giovanni Maria Lancisi (1654-1720) and Raymond de Vieussens (1641-1715) described lesions likely representing aortic valve infective endocarditis prior to Morgagni[7], but neither the descriptive details nor the clinical correlations are as clear.

Jean-Nicolas Corvisart (1755-1821) provided the first description of mitral valve endocarditis and introduced the term "vegetation," alluding to soft valvular excrescences easily detached from the valves.[13] The lesions reminded Corvisart of syphilitic warts and he incorrectly concluded that the cardiac lesions were another manifestation of that disease, even suggesting that anti-venereal treatment might be useful if the diagnosis could be established.[7] Corvisart was physician to Napoleon. Every case dying on

Figure 1 – Giovanni Battista Morgagni (1682-1771). Dr. Stephen A Geller private collection.

Table 1 – Key figures in the history of the pathology of endocarditis

Year	Author Key publication
1674	Lazare Riviére (1589-1655) *Opera Medica Universa*
1771	Giovanni Battista Morgagni (1682-1771) *De sedibus, et causis morborum per anatomen indagatis*
1806	Jean-Nicolas Corvisart (1755-1821) *Essai sur les maladies et les lésions organiques du Coeur et des gros vaisseaux*
1815	Joseph Hodgson (1788-1869) *On the Diseases of Arteries and Veins*
1826	René-Theophile Hyacinthe Laennec (1781-1826) *Traité des maladies des poumons et du coeur*
1824	Jean Baptiste Bouillaud (1796-1881) *Traité clinique des maladies du coeur*
1852	William Senhouse Kirkes (1823-1864) *On the effects which may result from the separation of fibrinous deposits from the valves or interior of the left side of the heart, and their mixture with the systemic blood* *On the effects which may result from the detachment of fibrinous deposits from the right valves of the heart*
1869	Emanuel Fredrik Hagbarth Winge (1827-1894) *[Mycosis endocardii]* (Norwegian)
1870	Samuel Wilks (1824-1911) *Capillary embolism or arterial pyaemia*
1872	Hjalmar Heiberg (1837-1897) *Ein Fall von Endocarditis ulcerosa puerperalis mit Pilzhildungen in Herzen (Mycoses endocardia)*
1878	Edwin Klebs (1834-1913) *Weitere Beiträge zur Enststehungsceshichte der endocarditis*
1884	Byrom Bramwell (1847-1931) *Diseases of the Heart and Thoracic Aorta*
1885-1909	William Osler (1849-1919) *On some points in the etiology and pathology of ulcerative endocarditis* *Galstonian lectures on malignant endocarditis* *Endocarditis infectieuses chroniques* *Chronic infectious endocarditis*
1903	Hugo Schottmuller (1867-1936) *Die Artunterscheidung der fur den Menschen pathogenen Streptokokken Munchen*
1910	Max Friedrich Löhlein (1877-1921) *Uber hamorrhagische Nierenaffectionen bei chronischer ulceroser Endocarditis*
1910	Emanuel Libman (1872-1946) *The etiology of subacute infective endocarditis*
1912	George Baehr (1887-1978) *Glomerular lesions of subacute bacterial endocarditis*

Corvisart's wards was autopsied[14] and his book, *Essai sur les maladies et les lésions organiques du coeur et des gros vaisseaux*, is one of the classic texts of cardiac literature.[10]

Although best known for his studies of aneurysms, excellent illustrations of fungating as well as ulcerating/perforating aortic valve endocarditis were provided by **Joseph Hodgson** (1788-1869) in his 1815 book *On the Diseases of Arteries and Veins.*[15] He used the term "fungus" to describe "wart-like excrescences" occurring in an 18-year-old patient who also had abscess formation at the aortic root. This report was also the first to document peripheral embolization, later described in greater detail almost a century later by Löhlein and Baehr.[16,17]

A towering figure in the history of medicine, **René-Theophile Hyacinthe Laennec** (1781-1826) provided physicians with the first and, for the next two centuries, the most important aid to studying

cardiac disease when he invented the stethoscope.[9] In addition to many detailed studies of diseases of the heart valves he reported on a number of patients with infective endocarditis. Laennec noted that several of his endocarditis patients had no history of syphilis and he doubted that association proposed by his teacher Corvisart. Laennec described two forms of vegetations (verrucal and globular), suggesting that the globular form represented thrombus formation, a hypothesis eventually confirmed by others.[7,8]

Renowned as "the last of the great blood-letters," **Jean Baptiste Bouillaud** (1796-1881) was, nonetheless, a fine physician who recognized the connection between rheumatic fever and heart disease and also recognized the value of digitalis as the "opium of the heart".[10,18] In his 1824 monograph, *Traité cliniques des maladies du coeur et des gros vaisseaux,* written with René-Joseph-Hyacinthe Bertin (1757-1828)[10,19], and a year later in his own book, Traité Clinique des maladies du Coeur, he introduced the terms "endocardium" and "endocarditis." He described the various stages of endocarditis, from acute, early inflammatory changes with edema as well as suppurative cases to a second period of organization of the inflammatory process and, in the patients who survived, fibrotic valvular change with ultimate calcification and ossification, noting the regurgitation was associated with valvular retraction. His acute lesions correlate with both acute rheumatic valvulitis and, in those examples of suppuration, acute infective endocarditis.

William Senhouse Kirkes (1823-1864) described a number of cases of infective endocarditis with peripheral embolization, emphasizing both systemic signs and symptoms.[20] He greatly expanded the understanding of the embolic potential of vegetations of both the left and right heart valves. He particularly emphasized the effects of relatively large systemic emboli. William Osler would later acknowledge a debt to Kirkes for his lucid studies. Others, who studied infectious endocarditis, both before and after Kirkes, included Jean-Martin Charcot (1825-1893), Alfred Vulpian (1826-1887), Rudolf Virchow (1821-1902), Karl von Rokitansky (1804-1878) and others.[7,8] It may be that both Virchow and Rokitansky recognized, but incorrectly interpreted, bacteria as "small granulations" in the vegetations they studied.[7]

The earliest suggestion that microbials were the cause of an endocarditis came from **Emanuel Fredrik Hagbarth Winge** (1827-1894), a student of Rudolf Virchow. Winge suggested that "parasitic particles" could penetrate the skin to enter the circulatory system and be disseminated to the cardiac valves, although the basis of his conclusion is not clear.[7,21] The experimental injection of material from vegetation did not cause the death of a rabbit.[7]

Sir **Samuel Wilks** (1824-1911), the great physician at Guy's Hospital, London, cited the work of Kirkes but concentrated his attention on the effects of embolic vegetations when they involved the small vessels of organs.[22] He postulated that the systemic effects of "arterial pyemia" were usually the cause of death in patients with infective endocarditis, rather than the valvular vegetations themselves and emphasized that infective endocarditis should always be considered as a possible diagnosis in patients with fevers of unknown origin. He also suggested scarlet fever as the cause of the local valvular lesions.[7]

Three years after Winge a countryman, **Hjalmar Heiberg** (1837-1897) described a 22-year-old postpartum woman who became critically ill ten days after delivery and died a few weeks later. He described chains of cocci within the vegetation[23,24] although his original interpretation of them was incorrect.

Theodor Albrecht Edwin Klebs (1824-1913), also a student of Virchow, was a pioneering microbiologist who determined the etiology of diphtheria (*Corynebacterium diphtheriae*) and for whom the genus *Klebsiella* was named. In 1878 he proposed that all cases of endocarditis were due to an infectious organism.[25] Other students of microbial organisms, including Louis Pasteur (1822-1895) and Robert Koch (1843-1910), helped develop microbiology as a distinct and increasingly sophisticated specialty and, although only peripherally involved with the study of endocarditis, certainly contributed to its understanding. Pasteur advocated newer approaches to obtaining blood cultures, including obtaining samples from various sites, evidence of his understanding of the vascular dissemination of infectious agents.

Although the 1884 monograph by Sir **Byrom Bramwell** (1847-1931)[26] provided little in the way of new information, it does offer a comprehensive, highly readable review of the information available at the time of its writing. There are outstanding and highly accurate illustrations of the macro- and microscopic features of the various forms of endocarditis, which he described in considerable

detail. By the time of publication of Bramwell's book, Gram staining for bacteria had become available and he noted their presence in both the vegetations and in the embolized material. Bramwell was one of the first to emphasize that left-sided valves were more often involved than right. He also highlighted the various ways, in which infective endocarditis presents, nothing that death was inevitable.

One of the greatest physicians of all time, and one of the four principal founding physicians of the Johns Hopkins School of Medicine, Sir **William Osler** (1849-1919) (Figure 2) was a brilliant diagnostician, pathologist, writer and lecturer. He expanded greatly the understanding of the clinical manifestations and the pathology of infectious endocarditis.[27] His Gulstonian lectures, emphasizing clinical-pathologic correlations, were based on his personal experience with more than 200 patients.[28] He recommended simplification of the relatively complex classifications previously used, advocating that endocarditis be clinically distinguished as *simple*, with few or slight symptoms, and *malignant*, in which there were prominent, often destructive valvular lesions, and severe constitutional disturbances.[27-30] He also emphasized that "sclerotic or malformed" valves were more prone to endocarditis. He pointed to the Gram stain as the best way to identify bacterial cocci, which, in his estimation, were always present. A prolific writer, Osler's clinical and morphologic descriptions are as valid today as they were then and remain valuable reading. Among other phenomena he clarified and clearly described are the characteristic painful red cutaneous nodules of bacterial endocarditis ("Osler's nodes"), which were first described by Kirkes.[20] Osler was the first to mention the association of platelets and fibrin in the vegetations postulating that they were derived from the blood stream and were not a product of the valve lesions.[28]

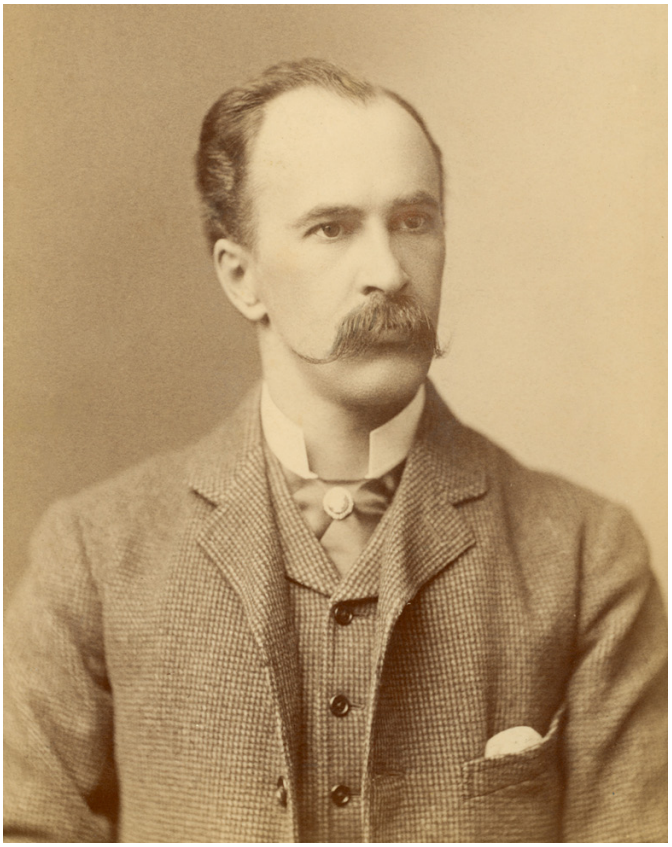

Figure 2 – William Osler (1849-1919). (William Osler Photo Collection - image CUS_044-004_P – McGill Osler Library).

Hugo Schottmuller (1867-1936) was the first to isolate *Streptococcus viridans* from cases of what was then called chronic or subacute bacterial endocarditis, showing that "ordinary" streptococci produced hemolysis on blood agar plates, whereas the "little bacteria" from endocarditis patients did not.[31] Others, including Libman, soon confirmed his 1910 report.

1910 was also the year of publication of **Max Löhlein**'s report of the hemorrhagic kidney lesions associated with infective endocarditis.[16] Although embolic lesions were well known at this time, Löhlein provided a clear description of the histopathology of what came to be called "Löhlein embolic glomerulonephritis", while also highlighting the renal manifestations of this complication.

Emanuel Libman (1872-1946) (Figure 3) was a brilliant physician and was referred to as "the Jewish Osler." He made invaluable contributions to the knowledge of infective endocarditis and helped refine understanding of the subacute forms of the disease.[3,32] As Osler, he was a skilled pathologist as well as a particularly astute diagnostician. His 1909 paper, with Herbert Celler, described 43 patients, including 19 who were autopsied.[32] Libman had studied with Theodor Escherich (1857-1911) and was a skilled and highly knowledgeable microbiologist. Importantly, blood cultures were obtained from 36 patients, 35 of whom had an "atypical," non-hemolytic streptococcus. The paper also reviewed the 2,750 blood cultures made over a ten year period noting that the organism found in subacute bacterial endocarditis, which Libman determined to be identical to the *Streptococcus viridans* identified by Schottmuller two years previously[31], was not found in any other form of endocarditis and that blood culture established the diagnosis. In another paper that year he showed that, despite the fact that bacteria may not be detectable and that healing

Figure 3 – Emanuel Libman (1872-1946). Courtesy of Barbara Niss, Archivist, Mount Sinai Medical Center, New York.

can occur in a subgroup of patients with subacute bacterial endocarditis, the prognosis remained grim with patients dying from complications such as embolization to various organs as well as from glomerulonephritis.

Although subacute endocarditis is sometimes referred to as "Osler disease" it was Libman who proposed the term. In 1924 Libman, along with Benjamin Sacks (1896-1971), described a previously unrecognized form a vegetative endocarditis from which organisms could not be isolated occurring in patients with systemic lupus erythematosus (SLE).[2] This byproduct of a coagulopathy, later shown to be part of the antiphospholipid syndrome, is the same as the endocardial fibrin-platelet vegetation associated with various other coagulopathies and, in the non-SLE patient, is known as nonbacterial thrombotic endocarditis or endocardiosis (NBTE). It was noted that the vegetations could localize on either the atrial or the ventricular surfaces of the valve with extensions from the leaflet to the ventricular endocardium. The Libman-Sachs lesions was distinguished from the endocarditis of acute rheumatic fever, which it histologically resembles, by the absence of clinical evidence for rheumatic fever and, especially, by the absence of Aschoff bodies in the myocardium.[2]

George Baehr (1887-1978), Libman's student and then colleague at The Mount Sinai Hospital, New York, expanded on the contributions of Kirkes, Osler, Löhlein and others with comprehensive descriptions of the renal pathology in patients with subacute bacterial endocarditis.[17] His 1912 report of morphologic studies of 34 patients, in 25 of whom *Streptococcus viridans* had been cultured, outlined the progression of the glomerular lesions from epithelial swelling to eventual necrosis and inflammatory cell infiltration. It was the young George Baehr, then a house officer, who was dispatched by Libman to Gustav Mahler's hospital bed to obtain the blood culture sample from which *Streptococcus viridans* was isolated.[4,7] In another version of the story, Baehr took the Fifth Avenue trolley carrying the necessary paraphernalia the two miles from Mount Sinai to New York's Plaza Hotel to obtain the specimen.

Two decades later sulfur drugs would prove effective in treating at least a few patients with this dread disease[33] to be followed, in another decade, by the highly effective penicillin[34] and succeeding antibiotics.

Infective endocarditis remains a potentially fatal disorder and establishing the diagnosis can be elusive.[35-39] Newer organisms, requiring newer treatments, have been recognized. Controversies about therapy, including medical and surgical approaches, persist.[36,40,41] Even the importance of pathology studies of infective endocarditis has come into question[42] at the same time that the value of autopsy has been reaffirmed.[43] In the last four hundred years this disorder has prompted some of the great writings in medical literature.

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