Centenary of William Osler's 1885 Gulstonian Lectures and their place in the history of bacterial endocarditis[1]

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One hundred years ago, in March 1885, the young William Osler (1849–1919), recently appointed Professor of Clinical Medicine at the University of Pennsylvania, delivered his three Gulstonian Lectures on 'Malignant Endocarditis' to the Royal College of Physicians. They were soon published in the *British Medical Journal* (Osler 1885). The subject was then, as now, of major medical importance. A century on, the intellectual scope of Osler's extensive and acute observations on the disease still provide us with object lessons for the conduct of clinical investigation.

As Pruitt (1982) has remarked, the lectures themselves were, as Osler himself realized, not revolutionary in either content or intention. They contain a historical résumé of accounts of the condition and a detailed study of 23 cases which he had personally supervised at Montreal General Hospital, reinforced with evidence drawn from two very large unselected post-mortem series which he had also seen and noted, though he is not specific about their origin. Although his knowledge of the relatively new science of microbiology was not first-hand, or profound, he summarized all the recent developments which seemed to him to be relevant and quite obviously realized their implications. Osler's characteristic clarity and thoroughness allowed him to dissect from his various series certain fundamental strands of thought on the classification and clinical presentation of the disease, and thereby forge a conceptual route which found its final expression in his 1909 paper on endocarditis. In his longstanding role as a medical educator and as the author of the pre-eminent medical textbook of its time, he was able to draw the attention of his contemporaries to a poorly understood disease and its detailed clinical signs, and thereby hoped to improve on the then ante-mortem diagnosis rate of only about 50%.

Osler had a profound sense of medical history. It is clear that he thought these lectures should not be taken out of historical context, and that they represented simply another step towards understanding a disease which had baffled succeeding generations of medical scientists. Historically, the importance of these lectures is Osler's summary of the existing state of knowledge and the use he puts this to in exploring possible future paths of research.

Early studies of endocarditis

Since there have been no recent accounts of early developments in the study of endocarditis, it may not be out of place to summarize them here.

The gross cardiac lesions of bacterial endocarditis, together with the whole question of intracardiac masses, had been a focus of much heated speculation by the early physicians. Laennec (1781–1826) devoted much attention to endocarditis in his great treatise 'On mediate auscultation' (English translation, 1846), and attributed to Lazarus Riverius (1589–1655) the first description of the vegetations of what would now be regarded as bacterial endocarditis. A clearer but later description was given by Giovanni Lancisi (1654–1720) in 'De Subitaneis Mortibus' (1709), written during his tenure as physician to Pope Clement XI (Wright 1952). Both discussed the cause of the lesions in terms of the prevailing theories, and argued at length over the contribution of changes in the blood and of the regularity of the heartbeat in their formation. There is a long discussion of cardiac masses in 'The Seats and Causes of

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Diseases . . . ' by Morgagni (1682–1771) (1769), though he had little new to say on their cause. Corvisart (1755–1821), misled by the gross appearance of the vegetations, firmly attributed them to syphilis (Corvisart 1806), a view Laennec refuted.

In the nineteenth century, the descriptions attained a greater precision, largely through the work of Jean Baptiste Bouillaud (1796–1881), who was the first to define the endocardium and its state of inflammation. He was probably also the first to describe the association between a 'typhoid' state and 'gangrenous endocarditis' (his term) (Bouillaud 1841). Osler himself credited the first account to Kirkes (1823–1864), whose work on embolism, as important as that of Virchow (1821–1902), was carried out in patients with endocarditis (Kirkes 1852). More recently, in 1868, Sir Samuel Wilks (1824–1911) had made a distinction between 'arterial' and 'venous pyaemia' (Wilks 1868), that is, infection originating in the heart itself, or peripherally, respectively. Rokitansky (1804–1878) had postulated that the constitutional symptoms accompanying the disease were caused by the process of 'capillary phlebitis' – microscopical particles which became detached from the vegetations and impacted peripherally – the microscopic counterparts of the emboli obstructing major vessels, so clearly described by Kirkes. Osler mentions Wilks' 'arterial pyaemia' as a concise and useful term, though in general he disapproved of the confusing proliferation of terms in the disease.

Diagnostic problem faced by Osler

When Osler approached the problem of endocarditis, therefore, the disease was recognized as an acute febrile one, sometimes in association with an obvious external infection, for example infected surgical wounds, with peripheral embolism as a prominent feature, and which terminated invariably in death. The association of the disease with pre-existing chronic rheumatic valvular damage was becoming increasingly evident. Osler credits Sir James Paget (1814–1899) with this discovery (Paget 1844), and an earlier Gulstonian lecturer (Ormerod 1851) had remarked on the link between rheumatic endocarditis and large valvular vegetations, associated with a short-lived febrile illness. Osler himself noted that about three-quarters of his Montreal cases had evidence of previous rheumatic fever, considerably more than the current state of knowledge had led him to expect. He reinforces the view hinted at by Ormerod, that congenitally bicuspid aortic valves are unusually likely to become infected (about 50% of cases). Osler published a more complete account of this condition a year after these lectures (Osler 1886) and Thomas Horder (1871–1955) aired the subject some years later (Horder 1909).

While the acute and fulminating forms of the disease were well known, if poorly understood, Osler was able to give an identity to the chronic forms of the illness. Since the 1850s there had been several isolated instances reported in the medical and pathological journals (for example, the celebrated and much quoted case of Dr Ray, a London general practitioner: Wilks 1868, Wilks *et al.* 1968) of a prolonged illness of insidious onset, with fever but without prominent cardiac symptoms, which caused diagnostic confusion during life. At post-mortem, however, abundant valvular vegetations were found.

New attempt at classification

The problem of nomenclature had become severe. Adopting the approach used in many diseases other than endocarditis, Osler suggests a simple distinction, based on the clinical course of the disease, between 'simple' and 'malignant' endocarditis:

> '. . . the simple being those with few or slight symptoms, and which run a favourable course; the malignant, the cases with severe constitutional disturbance and extensive valve-lesions, whether ulcerative or vegetative, the term being more clinical than anatomical'.

Osler's attempt to maintain the distinction is laudable, and viewed from 1985 remarkably farsighted, but the spectrum of disease he so carefully observed did not allow the differentiation consistently to be maintained throughout the lectures. Nevertheless, this broad classification allowed him much valuable room to manoeuvre within the 'malignant' group, and to define certain clinically useful diagnostic pointers towards delineating subgroups of the 'malignant'

variety. It is not surprising, therefore, that he tries to abandon the morphological terms in popular use (ulcerative, verrucose, vegetative and suppurative among many others), since on the basis of his extensive studies he was unable to correlate his post-mortem findings with specific clinical forms of the disease.

Osler was able to identify three groups of patients particularly at risk from 'malignant' endocarditis. The 'debilitated and dissipated' were likely to suffer it as a primary affection of the endocardium or valves. Some twenty years later Glynn, in his Lumleian Lectures of 1903, emphasized this characteristically 19th century viewpoint, with its hint of moralistic Victorian overtones (Glynn 1903). Discussing a case reported by Corvisart, he acknowledges that a previous attack of rheumatism is the most important factor in predisposing to the disease, but also directs our attention to the contribution of 'habits of intemperance, and exposure to vicissitudes of heat and cold'. Consideration of the importance of environmental factors in the development of the disease continued for many years, even after its bacterial aetiology had been firmly established. It was further stimulated by the surge of cases diagnosed after the First World War by Carey Coombs (1922) and Cotton (1920).

Osler's second group comprises those cases where the endocarditis was secondary to various other diseases, commonly one of the prevalent infectious diseases of the time, particularly scarlet fever and diphtheria. He also includes rheumatic fever itself, even though it was recognized that an episode of 'simple' endocarditis rarely progressed directly to a 'malignant' state. Two others were of particular importance for Osler. Ague (malaria) was thought by many French physicians to be a possible cause of the indolent and chronic forms of endocarditis. Both Osler and Horder recognized its importance in the differential diagnosis of endocarditis, even in their later papers, but aetiologically gave it short shrift. Numerically, pneumonia was the most important single underlying disease; it was present in 11 of 23 patients in Osler's Montreal series. It was only lack of knowledge of the infective nature of pneumonia that prevented Osler classifying the cases associated with pneumonia together with those with obvious external septic lesions, surgical, traumatic or puerpural, which comprised Osler's third predisposing factor. Bacteriological unification was close at hand, however. Billroth (1829–1894) and in this country Ogston (1844–1929) (1881), had proven the pathogenic role of microorganisms in abscesses and pyaemia in the early 1870s. Osler himself had seen teeming microbes in the air-cells of the lungs in pneumonia, and suspicion in endocarditis had been high ever since 1870 when the Norwegian Winge (1827–1894) had reported the presence of 'micrococci' in the endocardial lesions of the disease he graphically termed 'mycosis endocardii' (Winge 1870). They had been repeatedly demonstrated since then, and even if Osler was not familiar with Winge's account, which had been published in an obscure Norwegian journal, he was well acquainted with the many subsequent German papers illustrating the same point.

Emergence of prolonged forms of endocarditis

With one half of Osler's Montreal patients suffering an underlying pneumonia, and 18% of his larger combined series a septic 'surgical' lesion, it was quite clear to Osler that his Gulstonian view of endocarditis was a snapshot one, of a continuous spectrum of disease within which he was somewhat arbitrarily defining subgroups:

'The different modes of onset, and the extraordinary diversity of symptoms which may arise, render it very difficult to present a satisfactory clinical picture.'

The change in the natural history of the disease in the intervening years between these lectures and his 1909 paper itself played an important part in aiding the separation of the acute and subacute/chronic forms of the disease. Thus in Horder's very large series of 150 patients gathered between 1901–8, only a small proportion fell into the acute/surgical variety. Improved standards of surgical care had helped reduce the numerical importance of this group, and thus bring the subacute/chronic variety gradually into pre-eminence (Horder 1909). Ironically, later the advent of more refined bacteriological techniques allowed a similar

classification problem to recur, and as late as 1937 Gross & Fried stated, with an air of some discomfiture:

'... the division of the bacterial endocarditides into the acute and subacute form based on the duration of the illness is largely arbitrary, inasmuch as on the one hand the clinical course may be prolonged for a number of months in frank cases of bacterial endocarditis which are known generally to run a very acute course (eg *Staphylococcus aureus*), and on the other hand death may supervene within a few weeks in such usually protracted conditions as *Streptococcus viridans* endocarditis'.

This uneasy relationship between the pathological/bacteriological classification and the clinical time course classification remains.

Osler's discussion of the protracted forms of the disease is illuminating, though they formed only a small proportion of his series. He describes no fewer than five types; these are a rich and inconsistent mixture of syndromes, some defined in terms of the commonly seen diseases they mimicked, others according to the organ predominantly affected. Thus Osler discusses a 'pyaemic' form of the disease; a 'typhoid-like condition'; those with intermittent, ague-like symptoms; and he emphasized the importance of one group presenting with cerebral or cerebrospinal features, and another with prominent cardiac symptoms. His classification seems inelegant to us today, but it reveals not only his customary clinical and pathological acumen, but most importantly his striving towards a practical system of differential diagnosis which would allow those cases with a confusing clinical picture to be treated appropriately – that is those with, for example, surgical sepsis or malaria. While he was still unclear about the cause of the disease, he makes the best pragmatic use of the currently held views for the furtherance of his clinical expertise. We would do well to note his approach.

Osler recognized a partial clinical overlap between the 'pyaemic' cases, and those with endocarditis secondary to external, 'surgical' suppuration, that is, in Wilks' classification, 'venous pyaemia'. These all ran a short course, with rigors and sweating. However, it was already recognized that the endocarditis in the latter cases was merely incidental to the overwhelming septicaemic state, and Osler is anxious to convey that although numerically important, they lay properly within the domain of the surgeon. More interesting to the physician were those patients with an intermittent pyrexia, 'simulating a quotidian or tertian ague'. Though Osler found no cases of this type in his small Montreal group, he regarded it as most important, and he refers extensively to the past literature, including Ormerod's and Wilks' cases mentioned above. They could continue for between six weeks and four months, and generally occurred in patients with pre-existing chronic valvular damage. Osler's distinction between this and the next 'typhoid-like' group is subtle, but at a time when typhoid fever was a common disease, the clinical distinction, based on the pattern of fever, the mode of onset, and the presence of diarrhoea and 'severe nervous prostration', was of crucial importance in management and prognosis.

Osler painted a dramatic picture of a typical case in his 'cardiac' group:

'The patient has, perhaps, aortic-valve disease, and is under treatment for failing compensation, when he begins to have slight irregular fever, an evening exacerbation of two or three degrees, some increase in cardiac pain, and a sense of restlessness and distress. Embolic phenomena may develop; a sudden hemiplegia; pain in the region of the spleen, and signs of enlargement of the organ; or there is pain in the back, with bloody urine. In other instances, peripheral embolism may take place, with gangrene of the foot or hand. There may be hebetude or a low delirium. Instances such as these are extremely common; and while, in some, the process may be very intense, in others it is essentially chronic, and may last for weeks and months ... In very many instances, there is no history of rheumatic fever or of other constitutional disorder; but the endocarditis appears to attack the sclerotic valves as a primary process ... '

He recognized that not all cases were as clear-cut as this and issues the following caveats for the clinician:

'In those cases with [known] chronic valve-disease, there is usually no difficulty, but where the affection sets in with marked constitutional symptoms, the local trouble is very apt not to attract attention. Even on examination, there may be no murmur present, with extensive vegetations, or it may be variable. There are many instances on record, by careful observers, in which the examination of the heart was negative'.

Within the cardiac group itself he was particularly careful to draw attention to the features distinguishing infective and degenerative valve disease. Pathologically:

'atheromatous degeneration in sclerotic valves . . . leads to ulceration and extensive destruction of segments, which has nothing in common, except in its effects upon the valves, with the acute ulcerative changes . . . but is similar to the atheromatous processes in the aorta'.

In his second lecture he ventures a crucial clinical extension of this view:

'In my experience, the existence of fever is invariable when the ulcerative processes are due to micrococci, whereas most extensive destructive changes may occur in atheromatous disease without elevation of temperature'.

At this stage Osler's diagnostic caution is mirrored in some uncertainty over prognosis, and he does not absolutely exclude the possibility of recovery from the disease. He therefore seems less inclined to designate all cases of this variety as 'malignant'. His views on the ultimate fate of these patients had, nonetheless, altered by the time he wrote his 1909 paper. None of his 10 patients reported there lived, and even in Horder's series, only one of his 150 patients survived the inexorably debilitating disease (and this was not a bacteriologically proven case). Various attempts at therapy with vaccines derived from the patient's serum or from specifically raised antistreptococcal sera were made from about 1905 onward. These were pursued particularly by Horder (1908), but Osler makes cautious reference to them. Disappointment with the results of these apparently rational therapies was universal, apart from an occasional and only temporary remission of symptoms and fever. It was left to Emanuel Libman (1872–1943) and his collaborator Celler (1878–1928), who wrote a bacteriologically orientated paper on subacute infective endocarditis to resurrect the concept of 'healing' or 'healed' disease, and of a 'bacteria-free' stage of the disease (Libman & Celler 1910). This, however, was a histological diagnosis, not a clinical one, and though Libman made out a convincing case for the existence of healed lesions of 'subacute bacterial endocarditis' (as he designated the disease), these were presumably due to subclinical rather than full-blown episodes as, like all contemporary workers, he found there were virtually no survivors of a clinically and bacteriologically diagnosed endocarditis.

Conclusions and prospects for future research

In his peroration Osler turns to a series of predictions and speculations based on current pathological work. Their clarity and perception elevate the series of lectures to the level of, for example, Kirkes' (1852) monumental paper on endocarditis. It is characteristic of the man that he should state he does not consider himself competent to discuss the pathology of the disease, even though in morbid anatomy, clinical methods and histology he had few equals.

In common with Virchow, and in spite of the absence of conclusive microbiological evidence, he believed that 'malignant' endocarditis in all its protean forms would turn out to be a 'mycotic' process. Whether 'simple' endocarditis could be similarly universally attributed to a microbial cause was open to speculation at this stage. It was a question which was debated fiercely over the next 30 years. In all his own 'malignant' cases, examined both histologically and with specific bacterial stains (recall that in 1885 Gram's method, which was to become standard, was only a year old) he confirmed that 'the micrococci are constant elements in the vegetations'. Further:

'the only one [theory of acute endocarditis] to which I shall refer, is, that it is in all its forms, an essentially mycotic process; the local and constitutional effects being produced by the growth on the valves, and the transference to distant parts of microbes, which vary in character with the disease in which it develops. This very attractive theory can be adjusted to meet every requirement of the case . . . '

Osler quickly perceived that this was a likely unifying theory, with wide possibilities for expansion and experimental and clinical confirmation. For example, he speculates that once pneumonia had been established as an infective disorder, then the associated endocarditis, pleurisy, meningitis and intestinal inflammation could readily be explained on the basis of spread of microorganisms across adjacent membranes. Even greater simplicity could be obtained if microorganisms could be shown to be circulating in the bloodstream, and there

Figure 1. Portrait of Sir William Osler (1849–1919) painted around 1909, the time of his second major study on bacterial endocarditis. (Courtesy Library of the Royal Society of Medicine)

was very recent evidence from France that this occurred. Intensive experimental work in Germany, but not reported here by Osler, was continuing, to establish a uniformly infective aetiology for all forms of endocarditis, and to assess the necessity of pre-existing valvular damage in the production of endocarditis (Prudden 1886).

There was no theoretical problem in explaining the involvement of the right-sided heart valves in cases of overwhelming puerpural and traumatic septicaemia, but Osler surmises that in those without obvious sources of sepsis, the origin of the organisms might be the intestine or lungs. Clearly, he envisaged that this would occur by direct transfer from the environment, rather than from endogenous infection, a concept introduced much later, from about 1909 onwards, by Schottmüller (1910), Horder (1909) and Libman & Celler (1910) in relation to their work on streptococci of low virulence. In arbitrating over whether the organisms reach the valves via the general circulation or through the coronary arteries (a typically Germanic controversy which had generated an immense amount of academic heat, though astonishingly little light) Osler accepts the former, on the basis of his own observations that the microbes seem to be pressed into the endocardium along the lines of closure of the valves. In discussing the variable clinical picture of endocarditis, Osler is able to synthesize a typical explanation based on his unifying microbiological theory together with his accumulated clinical wisdom; the different microorganisms involved, and the variable interaction between the pre-existing state of the heart valves and the general condition of the patient. Hence, healthy valves may be able to resist infection during a septicaemia; debilitated patients would be more susceptible even in the presence of normal valves; and, quoting Goodhart, and making use of a Virchovian analogy, 'those with chronically sclerotic valves are walking mushroom-beds, in common times without spawn, but in periods of epidemics taking in germs by various channels'.

Osler (Figure 1) developed his views on malignant endocarditis in his many subsequent journal articles and in the several editions of his textbook. His final statement of 1909 was made in an early issue of the journal he himself founded, the *Quarterly Journal of Medicine*. But though solid and wise, it demonstrates the gap which was opening up between his predominantly clinical methods and the increasing expertise of the younger microbiologically-

trained physician. Blood culture was pioneered in the UK by Horder (1905) and in the USA by Libman (1906), and was in regular clinical use from the early 1900s onwards. It had become a vital part of the diagnosis of subacute infective endocarditis, particularly in those cases to which Osler had alerted the profession in his Gulstonian lectures, namely those which presented with either nonspecific or frankly misleading clinical features, with few symptoms or signs from the diseased heart valves. Nevertheless, Osler continued to stress that clinical suspicion was the most important factor in the prompt diagnosis of the disease, and his example was being followed by the discovery of further specific diagnostic clues. 'Osler's nodes', for instance (in fact, pointed out to him in 1888 by a certain Dr Mullen of Hamilton, Ontario, and described many years previously in the French literature: Weber 1912) became important as an early sign of embolism in the disease. Several other cutaneous signs were subsequently described, as well as retinal signs, optic neuritis (Falconer 1909) and clubbing of the fingers (Cotton 1920). Löhlein and, later, Baehr (1912) described the early specific renal lesions of subacute bacterial endocarditis, the histological counterparts of the almost invariable microscopic haematuria described by Horder and Osler. The cynical view would be that all these detailed clinical signs only allowed a rather earlier diagnosis of an untreatable and invariably fatal disease. However, they were to pave the way for vital early clinical suspicion when specific antimicrobial treatments became available in the late 1940s and 1950s (Dormer 1958). Their importance remains little diminished today, particularly when the clinical or bacteriological setting of endocarditis is novel or unfamiliar.

Osler's 1885 lectures initiated a new era of diagnostic optimism in bacterial endocarditis, which was to reach its climax around 1910. Osler and Horder's later papers have an unmistakably 'modern' feel to them and, apart from their dismal therapeutic aspects, convey a buoyant and confident tone provided by the intellectual satisfaction of the synthesis of clinical medicine, pathology and thoroughly up-to-date scientific microbiology. The hiatus between the 1920s and 1940s was filled with papers describing further details, but few authors attempted again an overall view of the disease with such vigour. Even Horder's 1926 Lumleian Lectures, scholarly though they are, are shot through with the therapeutic pessimism resulting from the palpable failure of the 'specific' therapies discussed earlier (Horder 1926). Horder at least had the satisfaction of living to see the partial successes of the early antibiotics. Osler, who died in 1919, would certainly have had the vision to see the future of bacterial endocarditis as a clinician's disease – eminently treatable, but still lethal without the keen suspicion of a watchful physician. The minutiae may have changed, but the results of his omnivorous clinical and scientific skills shown in these lectures are well worth our notice 100 years on.

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