

HEART

Editorial

Immune responses in endocarditis

In 1885 William Osler delivered the Gulstonian lectures describing the broad clinical manifestations of bacterial endocarditis.¹ The past 30 years have seen concerted attempts to explain the pathogenetic mechanisms behind the syndrome: heart failure out of proportion to the valve insufficiency; the presence of renal lesions in the majority of cases; arthritis, vasculitis, and splenomegaly as well as the classic cutaneous signs. What is clear is that an encounter between a circulating bacterium and an abnormal valve, with subsequent embolisation, can explain neither the initial establishment of the vegetation nor the myriad of extracardiac sequelae. Moreover, in most cases the microorganisms implicated are of low virulence, but when sequestered in a vegetation they are capable of inducing uncharacteristically severe disease.

The understanding of endocarditis as an immune complex mediated syndrome and the identification of factors necessary for the genesis of the vegetation have clarified some of these contradictions. Recent appreciation of the specific roles for cytokines in inflammation and control of sepsis enable further understanding of the diverse pathophysiological findings in infective endocarditis.

Pathogenesis of the cardiac vegetation

The animal model of endocarditis, in which a polyethylene catheter is passed across the aortic valve of a rabbit, producing initially a non-bacterial thrombotic vegetation and subsequently bacterial colonisation, has been a useful pathophysiological tool.^{2,3} Bacterial factors such as dextran, slime, fibronectin binding, and teichoic acid have been implicated in bacterial adherence to the platelet-fibrin matrices on the damaged valve. Other studies, investigating the role of the host immune response in protection against endocarditis, employed whole cell vaccines with varied results. In some cases, active (but not passive) immunisation prevented endocarditis without accelerating the rate of bacterial clearance from the circulation, suggesting a mechanism related to interference with bacterial adherence to the vegetation. The requirement for active rather than passive immunisation implicates additional components of the immune system. Rabbits challenged with *Escherichia coli* develop endocarditis if they are genetically deficient in C6, providing strong evidence for the protective role of complement against bacterial endocarditis in this lupine model. Other studies in right sided lupine experimental endocarditis demonstrated failure of spontaneous sterilisation in the presence of dexamethasone or agranulocytosis. Recent work with viridans streptococci has implicated platelet released bactericidal factors in the clearance of bacteria early after adherence,⁴ and interestingly reduction in vegetation weight and bacterial concentration in rabbits treated with aspirin has been demonstrated.⁵ The development of endocarditis depends on a balance between the abilities of the organism to adhere to vegetations and to resist the array of host responses.

Immune complexes

Necropsy studies have shown the presence of glomerulonephritis in a large proportion of cases of human endocarditis, and immunofluorescence studies have characterised the lesion as mediated by immune complex deposition. The "lumpy bumpy" distribution of immunoglobulin and complement components, typical of immune complex mediated injury, is more common with streptococci, which appear to involve the classic complement pathway. In contrast, staphylococci, which initiate the alternative pathway, deposit antigen and not antibody with complement in the kidney. Evidence suggests deposition of circulating immune complexes (CICs) rather than formation intrarenally, and CICs have been identified in other sites, such as the spleen and cutaneous lesions in endocarditis. Assays developed to detect CICs have shown correlations between CIC concentrations and duration of illness, extravalvar manifestations, and hypocomplementaemia as well as a fall in CIC in response to treatment.

Antibody specific to the infecting organism and bacterial cell wall constituents have been identified within CICs. Under normal conditions antigen-antibody complexes should be solubilised and phagocytosed. Clearly other factors are operating to prevent solubilisation of these complexes, with consequent deposition in tissues. Evidence suggests that rheumatoid factors, detectable in 50% of endocarditis cases, mask the receptor sites for phagocytosis and hence prevent clearance of CICs. This would explain why patients with endocarditis may suffer long term bacteraemia despite high level specific IgG antibody, adequate complement, and functioning neutrophils.⁶

Antibodies directed against myocardial proteins

Another feature of endocarditis that has received attention from immunologists is the presence of myocardial dysfunction out of proportion to the valve lesion, often even in the absence of significant valve destruction. Maisch found that the polyclonal antibody response in endocarditis included antimyolemmal and antisarcolemmal antibodies.⁷ The antisarcolemmal antibodies could be shown to cross react with streptococcal antigens, as demonstrated previously in rheumatic fever and for viral antigen in myocarditis. This may represent deliberate antigenic mimicry on the part of the bacteria, but the pathological role of these antibodies in cardiac dysfunction, rather than just as innocent bystanders, is not proven. The antimyolemmal antibodies (AMLA) were cytolytic to cardiac cells in vitro in the presence of complement, and cytolytic serum activity in some patients was present only when AMLA were also found and correlated with AMLA titre.

In addition, studies examining myocardial protein synthesis in rats receiving endotoxin to simulate acute phase response, demonstrated overall reduction in such protein synthesis⁸ and a switch in myosin isoenzyme transcription.⁹ Such profound changes in myocardial

protein synthesis in this rodent model may partially explain alterations in myocardial performance seen in inflammatory conditions such as infectious endocarditis.

Lymphocyte activity

White cell function in endocarditis has been analysed, until now fairly crudely, showing an increase in number of monocytes and granulocytes, but a decrease in number and activity of T helper, T suppressor, and natural killer cells during infection.⁷⁻¹⁰ The reduction in numbers in the peripheral blood may, however, be accounted for purely by trafficking to the site of injury. In some studies T suppressor cell activity corrected partially after treatment, suggesting a predisposition to endocarditis as a result of inherent reduced lymphocyte function in such patients, rather than lymphocyte dysfunction being purely a consequence of infection (note the increased risk of endocarditis in immune suppressed individuals).

A decrease in number of polymorphonuclear leucocytes in the circulation during severe bacterial infection may indicate consumption of these cells at sites of inflammation. However, in the setting of long term (four to six weeks) β lactam treatment for endocarditis, neutropenia is not unusual. Such neutropenia reverses spontaneously within days of stopping β lactam and is thought to be immune mediated. It is important to be aware of this iatrogenic phenomenon as its presence does not indicate uncontrolled disease but that antibiotic change is required.

Cytokines and the mechanisms of inflammation

The mechanisms of stimulation of phagocytosis and inflammation in general have come under more detailed scrutiny recently, with the study of cytokine responses to various organisms. Evidence suggests that interleukin 8 (IL-8), a member of the C-XC chemokine family that has predominant neutrophil stimulatory and chemotactic activities, is an important mediator of acute inflammation in response to infection. Lipopolysaccharide, mycobacterium tuberculosis,¹¹ and influenza A¹² have been shown to induce production of IL-8, and increased plasma concentrations of IL-8 have been detected in acute bacterial infections.¹³ Bacterial endocarditis provides a useful tool for studying the mechanisms by which Gram positive organisms initiate activation of phagocytes and subsequent inflammation. Enhanced IL-8 expression in macrophages present in the inflamed endocardium of patients with *Staphylococcus aureus* endocarditis has been demonstrated. Furthermore, lipoteichoic acid, a constituent of the Gram positive cell wall and known to have important macrophage stimulatory effects, is a potent stimulus for IL-8 production.¹⁴

IL-6, a cytokine involved in B cell stimulation, antibody production, and the release of acute phase proteins, has been found to be raised in streptococcal and Q fever endocarditis. In studies of patients with Q fever, tumour necrosis factor (TNF) and IL-1 are good markers of disease activity, concentrations being higher in patients with recent endocarditis than in those with stabilised endocarditis.¹⁵ In addition, immune complexes per se elicit release of eicosa-

noids and cytokines (for example, TNF from macrophages), and suppress protective cell mediated immunity by inducing IL-10 release from circulating phagocytes.¹⁶

Plasma levels of TNF have been measured in streptococcal endocarditis. While lipoteichoic acid stimulates TNF production by macrophages in vitro, a study of 10 patients with subacute endocarditis showed normal plasma concentrations of TNF in all except those with complications. However, soluble TNF receptor (sTNF-R) concentrations were significantly raised. In contrast, control patients with falciparum malaria had high ratios of TNF to sTNF-R.¹⁷ The presence of high concentrations of sTNF-R suggests chronic constitutive TNF activity perhaps principally at the tissue level with little direct spillover of TNF into the circulation. The pro-inflammatory activity of TNF inducing the acute phase response may be pivotal in the systemic manifestations of infective endocarditis. The site of cytokine production is not yet established, but as the endothelium is known to be a rich source of such molecules, investigation of the endothelial factors released in infective endocarditis is a high priority in understanding the pathogenesis of this condition.

MICHAEL BROWN
GEORGE E GRIFFIN

*Division of Infectious Diseases,
St George's Hospital Medical School,
Cranmer Terrace, London SW17 0RE, UK*

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