Immunopathogenetic Aspects of Infective Endocarditis

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Histopathologic Studies

A number of histopathologic observations have cast doubt on the concept that all extracardiac lesions in IE are related to septic embolization from the infected cardiac valve. For example, the report of Alpert et al of four patients with acute IE showed that histologic and bacteriologic data implicated bacterial or fungal microemboli in the pathogenesis of the Osler’s node; the authors theorized that the tender nature of the lesion was related to embolic lodgement in the dermal glomus apparatus of the densely packed tissue of the finger tip. In contrast, three reports from the French literature and one from the US stressed that Osler’s nodes were often histologically characterized by an intense perivasculitis in the absence of bacterial organisms, and suggested a “hypersensitivity phenomenon” as the basis for this lesion in IE. The major difference between the Alpert study and those in the French literature appears to relate to the timing of the lesion biopsy; the patients described by Alpert et al had their Osler’s nodes sampled early in their evolution phase (within 48 h of development), while those reported by French investigators were often sampled later in the course (e.g., ten days post-development). Thus, it seems likely that as the lesion ages, localized host defenses are able to sterilize the Osler’s node, leaving an intense inflammatory response.

Similar controversy has arisen over the etiology of other extracardiac manifestations of IE such as the chorioretinal Roth spot and the polyarthritis syndrome, since bacterial or fungal organisms rarely have been documented within these lesions.7,8

The most convincing evidence concerning the possible immunologic nature of the peripheral stigmata of IE have emanated from histopathologic analysis of renal tissue from patients with IE-related glomerulonephritis (GN). It has been recognized for many years that there are two main histologic forms of renal involvement in IE, “focal embolic” and “diffuse proliferative” GN.9 The former is a relatively trivial form of renal disease and is usually unassociated with functional impairment; the latter is universally asso-

IE = infective endocarditis; GN = glomerulonephritis; GBM = glomerular basement membrane; EM = electron microscopy; IC = immune complex; CIC = circulating immune complex; RF = rheumatoid factor

It has been over 100 years since the famous Gulstonian Lecture Series on the clinical features of chronic (malignant) endocarditis by Osler,1 in which many of the classic peripheral extracardiac manifestations of the disease were first delineated. Since that time, a number of histopathologic studies have raised the possibility that such extracardiac manifestations as glomerulonephritis, sterile arthritis, splenomegaly and oculo-cutaneous lesions may be the result of necrotizing vasculitis rather than from direct involvement by micro- or macroscopic embolism from the valvular vegetation. Although there remains controversy on the exact nature of the immune-mediated injury in endocarditis, there is little doubt that immune complexes play a major pathogenetic role in this infection.

This article will focus upon the histopathologic, immunopathologic, and circulating immune complex data that have been marshalled as evidence of the immune complex nature of endocarditis. We will also emphasize which immunologic pathways appear to be involved in the tissue injury phase of endocarditis, underlying the disease’s extracardiac manifestations. Lastly, we will stress the diagnostic and prognostic role of immune complex measurements in patients with infective endocarditis (IE).

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associated with an "active" renal sediment and is often accompanied by moderate to severe depression of creatinine clearances. The diffuse GN of IE has often been seen in concert with detectable antiglobulins (rheumatoid factors), cryoglobulins, and hypocomplementemia, suggesting an immune-mediated lesion. It had previously been thought that the "focal embolic" lesion was related to bland and/or septic emboli to the renal cortex. This theory became untenable with recognition that this renal lesion could be seen in cases of pure right-sided IE in which the "pulmonary artery-pulmonary alveolar barrier" serves as an efficient filter for micro- and macro-embolization. It now appears certain from immunopathologic investigations that these two forms of renal disease are on the same continuum of immune complex-mediated, extracardiac tissue injury in IE.

Prevalence figures on these two forms of IE-related GN are very variable depending upon the clinical diagnostic criteria utilized. Studies employing hematuria, pyuria and proteinuria as markers of diffuse GN tend to overestimate the prevalence, since cases of focal embolic and frank embolic renal infarction surely will be included. Conversely, studies that utilize only clinically-manifest renal functional impairment probably underestimate the prevalence of the disease, as autopsy studies of IE patients confirm that "silent" GN may exist in the absence of such perturbations. The best data on IE-related GN prevalence have come from autopsy studies such as that of Spain and King in 1952. Of 52 untreated patients dying of subacute IE, 33 percent had diffuse GN and 48 percent had focal GN. Of interest, in 25 additional patients dying of subacute IE despite penicillin treatment, no cases of diffuse GN were observed, suggesting that this renal lesion in IE was amenable to cure by antimicrobial therapy. Most cases in this latter study were associated with viridans streptococci in patients with long-standing infection; these findings implied a relationship between duration of infection in streptococcal IE and development of diffuse GN. More recent autopsy studies in the antibiotic era by Neugarten et al have shown a somewhat different spectrum of GN in IE cases. These investigators found focal GN in 5 percent and diffuse GN in 14 percent of their cases dying of IE despite antibiotic therapy. Of note, their patient population was strikingly different from that reported by Spain and King in that: 1) S aureus was disproportionately represented as a cause of both death and GN; 2) parenteral drug abuse was a common risk factor for IE, while underlying valvular heart disease was less frequently seen; and 3) long duration of antecedent illness was less frequently observed in association with development of GN. Supporting their findings were two other reports which documented the prevalence of clinically manifest GN in S aureus IE to be as high as 40-78 percent despite a mean duration of illness of seven-ten days. The markedly different prevalence of GN in streptococcal vs staphylococcal IE, as well as the distinct differences in durations of underlying symptoms and nature of the underlying valvular disease raised the question as to whether IE-related renal lesions might have a different pathogenetic basis depending on the valvular pathogen. This concept has, in fact, been supported by study of complement activation and utilization in IE-associated GN. In series of patients with S aureus IE-related GN, levels of C3 and factor B were low, while early complement cascade components tended to be normal or high, suggesting activation of the alternate complement pathway. In contrast, studies of complement activation in streptococcal IE-associated GN tended to show utilization of early complement components (C1q, C4, C3) as well as C3 and factor B, suggesting classic complement pathway activation with perhaps secondary activation of the alternate complement pathway via the "amplification loop."

Immunopathologic and Ultrastructural Studies

Immunopathologic studies in IE-associated GN have mainly involved immunofluorescent microscopic delineation of the immunoglobulin and complement repertoire deposited within the glomerular basement membrane (GBM). These findings have been used to indirectly define the nature of the renal lesion as immunologic, as well as to ascertain the participating components of the antibody and complement systems. The bulk of the human studies in this regard have documented the frequent deposition of IgG and early complement components (C1q, C4, C3) in GBMs in a "granular" or "lumpy-bumpy" distribution typical of circulating immune complex (CIC) injury; such deposits are occasionally seen in the mesangial regions. Such granular depositions have been mainly observed in patients with either long-duration illness and/or viridans streptococcal IE, supporting the concept of CIC-mediated activation of the complement cascade as a participating, underlying pathogenetic mechanism. In contrast, some cases of S aureus IE-related GN have shown only antigen and complement deposition in the GBM, suggesting again that this organism has the capacity to directly activate the alternate complement pathway, perhaps through the action of cell-wall-bound protein A, peptidoglycan or teichoic acid. Occasionally, the renal lesion in IE can evolve into either rapidly progressive, crescentic or membranous GN. Immunofluorescent studies of the kidneys in such patients have revealed granular deposition of IgG, IgM and/or complement components similar to the typical streptococcal IE-related diffuse GN, suggesting a similar immunopathogenesis. Because of the nature and distribution of the immu-
noglobulin depositions in the GBM of streptococcal IE-related GN, it has been theorized that such lesions represent injury due to CICs formed intravascularly during antibody excess. In support of this theory has been the frequent subendothelial location of CICs in this renal lesion, a typical localization point for CICs formed in antibody excess due to the larger size of the complex. Studies in the experimental animal model have provided ample data to confirm this concept. In rabbits with viridans streptococcal IE, Arnold et al. could produce diffuse GN only in animals who had been preimmunized with a vaccine prepared from the eventual infecting streptococcal strain. Thus, animals with transaortic valve catheters had their IE induced at a time of antibody excess, and most developed diffuse proliferative GN featuring granular IgG and C3 GBM deposits in a subendothelial location. However, this study did not answer the question as to whether the pathogenesis of the diffuse GN of streptococcal IE related to: 1) initial renal GBM lodgement of bacterial antigen with secondary antigen-antibody complexing in situ; or 2) GBM deposition of CICs. Sindrey et al. clearly showed that the onset of proteinuria as a marker of underlying GN in preimmunized animals with streptococcal IE did not occur until ~two weeks after the induction of IE, at a time when CIC levels were peaking. This confirmed that GN in streptococcal IE was the result of GBM deposition of CICs formed in vivo during antibody excess, and not the consequence of in situ renal antigen-antibody complexing.

Ultrastructural electronmicroscopic (EM) studies of IE-related GN in both humans and experimental animals have tended to confirm the immunofluorescent findings above in situ putative pathogenetic pathways. Gutman et al. found that patients with staphylococcal IE-associated GN demonstrated subepithelial electron-dense GBM deposits, consistent with small CICs formed at antigen excess. In contrast, patients with either streptococcal or culture-negative IE who had long-duration antecedent syndromes tended to have subendothelial electron-dense lesions suggesting the deposition of larger CICs at antibody excess. Other ultrastructural studies of patients or experimental animals with either streptococcal or staphylococcal IE-associated GN have confirmed the relationship between the EM site-localization of the CIC dependent upon pathogen and duration of disease.

Studies of kidneys from patients and experimental animals with IE-related GN have attempted to define the antibody specificities and the antigenic nature of the CIC-mediated renal lesion. Investigations into experimentally-induced CIC nephritis by Wilson and Dixon showed that antigens often become obscured to direct immunofluorescent reagents by extensive antibody deposits. Thus, strategies in IE-related GN centered around acid elution of antibody from renal tissue with subsequent immunoglobulin isolation and specificity analyses, with the potential secondary gain of "unmasking" GBM-localized antigen lodged as part of the initial CIC deposit. Yum et al. studied a patient with diffuse GN associated with staphylococcal IE. After elution of antibody from renal tissue, the presence of renally lodged staphylococcal antigen was defined by direct immunofluorescent GBM staining by IgG antibody raised in rabbits to a non-protein A-bearing S. aureus strain. Of interest, the pattern of intrarenal antigen staining was in the same granular distribution as that for the immunoglobulin and complement repertoire deposition. Normal rabbit IgG did not bind to the glomerular staphylococcal antigen confirming the specificity of immunofluorescent binding through F(ab)2 mechanisms. In contrast to studies with staphylococcal IE, it has been difficult to demonstrate GBM streptococcal antigen in cases of IE-related GN. Sindrey et al. were unable to detect streptococcal antigen by direct immunofluorescence in the kidneys of pre-immunized animals with experimental IE and GN despite extensive acid elution of antibody. They hypothesized that CIC renal lodgement might be a transient event, with clearance of antigen after initiation of the GN. An alternative hypothesis is the lack of the elution procedures to unmask antigen from an extensive envelope of complexed antibody.

Several studies have examined the antigen specificities of antibody eluted from kidneys of humans with typical CIC-mediated GN of IE. In an elegant study of a patient with enterococcal subacute IE and diffuse GN, Levy and Hong made several important observations. First, renally eluted antibody was predominantly IgG and not a mixture of diverse serum proteins as one would expect if the eluate represented only a release of GBM-trapped serum components. Second, the IgG eluate bound specifically to the patient's own blood stream enterococcal isolate and not to other bacterial pathogens. Finally, the eluate specifically bound to heterologous and homologous GBM preparations, but not to renal tubule preparations. The authors theorized that the initial CIC-mediated renal injury led to exposure of sequestered GBM antigens, stimulating secondary production of anti-GBM antibody as part of the renal eluate. Similarly, Iida et al. demonstrated specific interaction of the renal antibody eluate of a patient with enterococcal IE and CIC-mediated membranous GBM with his own bacteremic isolate by indirect immunofluorescence techniques. In contrast, Pertschuk et al. were unable to detect anti-staphylococcal antibody activity of the renal eluate from a patient with S. aureus IE and GBM, despite detection of staphylococcal antigen in the GBM. The studies of Levy and Hong and Iida et al. with strep-
toxococal IE on one hand, and that of Pertshuk et al. with staphylococcal IE on the other hand, further support the proposed divergent immunopathogenetic pathways in GN caused by the two organisms. The ready demonstration of eluted organism-specific IgG antibody from kidneys of patients with streptococcal IE and GN support the concept that antigen-antibody complexes participate in the immunopathogenetic injury in this setting via the classic complement pathway. Conversely, the inability to demonstrate organism-specific antibody from eluates of kidneys of patients with staphylococcal IE and GN lends credence to the theory that this renal injury results from in situ activation of the alternate complement pathway by organism-specific antigens.

As anticipated, evidence of CIC-mediated tissue injury in IE is not unique to the kidney. Tissues in which such injury has been documented have included the skin, synovium, choroid plexus and spleen. For example, Nast et al. from our own institution, recently described a patient with streptococcal subacute IE with crescentic GN in whom typical granular mesangial deposits of IgG and C3 were noted by immunofluorescence, and electron-dense mesangial deposits were seen by electron microscopy. Splenic tissue also showed similar CIC deposits within intrasplenic arterioles. Williams and Kilpatrick performed immunofluorescent analyses of cardiac valve and vegetations from a patient undergoing emergency valve replacement for decompensated, untreated streptococcal IE. Both valvular tissue and vegetations showed evidence of IgG and IgM deposition. Similarly, immunofluorescent stains for C3 and the terminal complement complex of neoantigens (C5-C9) were positive, with the latter complement components being extensively present on both the endocardial surface, as well as in the subendocardial layers. Of note, prominent streptococcal bacterial antigen depositions were also detected within cardiac vegetations by using Fα-specific fragments from rabbit IgG prepared against the patient's infecting strain. The authors' data implied in situ formation of cardiac vegetation antigen-antibody complexes, since their own previous studies had demonstrated no evidence for Fc or Cγb receptors on human valvular endothelium. These observations are intriguing as they provide evidence that CICs could have their origin in in situ-derived ICS within cardiac vegetations that periodically enter the bloodstream to circulate and cause secondary immunologic injury in other organs (eg, kidney). These observations by Williams and Kilpatrick also raise the question as to whether a portion of the destructive valvulitis seen in patients with IE may be of immunopathologic nature, rather than purely "infectious" in etiology.

Detection of Circulating Immune Complexes (CICs) in IE

The immunopathologic investigations of Gutman et al. and others had confirmed that the GN in patients with IE was compatible with CIC-mediated injury. In addition, the findings of Williams and Kunke and others of serum antiglobulins (rheumatoid factors), cryoglobulins, conglutinins and hypocomplementemia in patients with subacute IE led to the suspicion of CICs in this disease. It was not until Theofilopoulos et al. and others developed relatively rapid, sensitive and specific assays for the detection of complement-containing and/or complement-binding CICs in serum and other body fluids that the immune complex nature of IE was confirmed. These techniques, including the Raji cell radioimmunoassay, the bovine conglutinin assay, the C1q-binding assay and the polyethylene glycol precipitation assay, not only allowed direct detection of CICs in biologic fluids, but also served as techniques to help isolate CICs in order to identify and characterize the putative bacterial antigens within the complex. Studies from our own laboratory were the first to directly document the high prevalences of CICs in IE. Ninety-seven percent of patients with IE from our institution had detectable CICs with mean levels significantly higher than normal control subjects and patients with non-IE septicemias. CIC levels were correlated with longer duration of antecedent illness, presence of extravascular manifestations of IE (eg, sterile arthritis) and hypocomplementemia. We also confirmed that CIC levels tended to fall in parallel with successful clinical response to antimicrobial therapy, sterilization of blood cultures and rises in serum complement levels. Conversely, in several patients, persistent or recrudescent elevations of CICs heralded the onset of ongoing IE often requiring valvulectomy for salutary clinical outcome. We also confirmed these observations in the experimental model of streptococcal IE in rabbits. All animals developed elevated CICs by Raji cell radioimmunoassay after induction of IE. Of interest, untreated animals continued to have ongoing streptococcal IE at autopsy, coincident with persistent elevations of CICs. In contrast, CIC levels in animals cured of IE with penicillin therapy experienced sharp declines in CIC levels, while animals with refractory IE, despite penicillin treatment, demonstrated persistent elevations of CICs. Since our initial studies, a number of other investigators have confirmed the high prevalences of CICs in patients and experimental animals with IE. Prevalences of CICs in initial serum specimens of IE patients in these other studies have ranged from 63 to 93 percent, including analyses of patients with both native and prosthetic valve IE (Table). These latter studies have also served to confirm our initial correlations of CIC levels with subacute clinical
course and extravalvular manifestations, as well as CIC disappearance with effective treatment of IE, and persistence with refractory IE.

Our initial studies with CICs in IE had suggested also that clinicians might be able to utilize CIC levels during the early part of a patient's hospitalization to serodifferentiate IE from non-IE-related septicemias. In one study from our institution,\(^5\) significantly more patients with native valve IE (90 percent) had detectable CICs in admission serum samples than their non-IE septicemic counterparts (50 percent). Additionally, nearly one-third of IE patients had very high CIC levels (>100 \(\mu g/ml\)) as opposed to only ~5 percent of non-IE patients. In a followup study we performed in conjunction with the Massachusetts General Hospital, Hooper et al\(^{14}\) found that most patients with prosthetic valve IE had detectable CICs in serum, and the majority (63 percent) had CIC levels >100 \(\mu g/ml\). Febrile prosthetic valve recipients without IE had a lower prevalence of CICs and few had high levels. The study of Kaufmann et al\(^{22}\) put the diagnostic abilities of CIC determinations regarding ability to utilize such assays to distinguish IE from non-cardiac septicemias into perspective. Their study showed that in patients with more acutely presenting IE (<four weeks duration), the prevalence of positive serum CIC assays (23 percent) was not different from septicemic controls. In contrast, in patients with more subacute IE (≥four weeks duration), the prevalence of detectable CICs (91 percent) and the CIC levels were significantly greater than the non-IE septicemic controls; these findings correlating duration of illness with CIC levels in IE have been subsequently confirmed by Pocidalo et al.\(^{30}\)

The most consistent association of CIC levels and extracardiac stigmata of IE has been with GN and hypocomplementemia. Kaufman et al showed\(^{21}\) that their 24 IE patients with clinical evidence of GN had significantly higher CIC levels than their IE counterparts without evidence of GN. Also, there was a significant inverse relationship between CIC levels and complement levels of both \(C_{3b}\) and \(C_{4}\). Similarly, Hooper et al\(^{14}\) documented a relationship between evidence of IE-related GN (ie, hematuria) and CIC levels in patients with prosthetic valve infections. We observed an interesting relationship of high CIC levels with IE-related GN in two patients with a classic thrombotic thrombocytopenic purpura (TTP) syndrome associated with IE.\(^{39}\) Both patients had elevated levels of CICs, hypocomplementemia along with the TTP syndrome. The entire syndrome, including the renal, platelet and neurologic aberrations abated, CIC levels fell and hypocomplementemia reversed coincident with successful therapy of IE by both antibiotic and operative interventions.

**Determination of the Antibody Component of CICs**

As noted above, several investigators have shown that antibody eluted from tissue manifesting IE-related CIC injury has apparent specificity for the infecting bacterial organism, particularly for cell wall or cytoplasmic constituents.\(^{22}\) This relationship has been most clearly shown for eluted IgG antibody from kidneys of IE patients with GN. With use of the Raji cell radioimmunoassay,\(^{23}\) we were able to indirectly show that CICs in patients and experimental animals with IE contained both IgG and activated complement components. The Raji lymphoblastoid cell line expresses surface receptors for \(C_{3b}\), mediating initial CIC attachment in the assay system; the presence of IgG in the CIC is then revealed by either immunofluorescence in the qualitative assay or by competitive inhibition of radiolabeled IgG in the classic radioimmunoassay technique. Burton-Kee et al\(^{28}\) were able to directly characterize the antibody-complement repertoire contained directly within CICs of patients with IE. Using the polyethylene glycol precipitation technique for CIC detection, they were able to convincingly demonstrate that such complexes contained both IgG and IgA in addition to \(C_{3}\). These investigators, however, could not confirm the specificity of this complexed antibody for the infecting organism, as \(F_{ab}\) preparations from the complex did not bind with any bacterial antigens in a radioimmunoelectrophoresis system.

**Characterization of the Antigen Component of CICs**

There have been several pivotal studies regarding delineation of the putative bacterial antigen(s) contained within CICs in patients with IE from the laboratory of Inman et al.\(^{20,21}\) These authors isolated CICs from the serum of a patient with enterococcal IE by polyethylene glycol precipitation and competitive binding of the IgG-containing complex to staphylococcal protein A.\(^{29}\) Purified CICs were used to immunize rabbits and raise an anti-CIC serum, which was subsequently utilized in a crossed immunoelectrophoresis assay system. This electrophoretic technique demonstrated that the anti-CIC antibody had reactivity and specificity towards a cytoplasmic protein antigen of the infecting enterococcal organism in a
molecular weight range between 12-24 Kd. Direct surface labeling of the isolated, protein A-bound CIC by lactoperoxidase confirmed the molecular weight characteristics of this protein antigen. These investigators then sought to utilize more direct methods to characterize the antigenic identity of CICs in IE patients. They sequentially studied the CICs isolated by the same polyethylene glycol-protein A methodologies as before in a patient with lactobacillary IE.\(^{40}\) They then used Western blot immunassays to characterize the antigenic nature of the CICs. Thus, isolated CICs were electrophoresed on SDS-PAGE gels; protein antigens were then transferred onto nitrocellulose paper and probed with polyclonal anti-CIC antisera raised in rabbits. IgG bound to CIC-associated protein antigens were then detected by \(^{125}\)I-labeled protein A. These studies consistently showed that CICs obtained both early and later in the patient’s clinical course contained a similar 60 Kd protein antigen; this antigen was subsequently shown by absorption and other in vitro experiments to be a complexed (not free) protein derived from the infecting organism’s cytoplasm rather than from normal human serum components.

Other investigators have detected circulating complexed bacterial antigen within CICs in patients and experimental animals with IE. Wheat and co-workers,\(^{41}\) using radioimmunoassay detected staphylococcal teichoic acid antigenemia in rabbits with experimental IE. They showed in another study that the presence of pre-existing anti-teichoic acid antibodies masked and precluded direct detection of teichoic acid antigenemia in rabbits with IE, suggesting that this acidic polysaccharide cell wall antigen was being complexed in CICs.\(^{42}\) They then were able to confirm their hypothesis of CICs containing complexed teichoic acid by detecting this antigen following thermodissociation of serum from humans with staphylococcal IE (to destroy CIC-associated antibody\(^{43}\)). In a similar study, Lentino and Ryte\(^{44}\) demonstrated the presence of complexed staphylococcal teichoic acid antigen in the serum of most patients with \textit{S aureus} IE following acidic dissociation of CICs initially isolated by polyethylene glycol precipitation.

\textit{Role of Rheumatoid Factor as an Antiglobulin in IE}

Williams and Kunkel\(^{45}\) were the first to document the frequent occurrence of circulating rheumatoid factor (RF) in the serum of patients with streptococcal IE, confirming a sero-prevalence rate in such patients of ~50 percent. These investigators also showed that after therapy, many of the patients demonstrated a marked reduction of RF titers. Also, they characterized that IE-related RFs as 19S in size, similar to the factor from patients with rheumatoid arthritis. They predicted that such IgM rheumatoid factors were not the result of an antigen stimulus, but were, in fact, “anti-antibodies” developing against new groups of IgG antibody molecules exposed following intravascular complexing with bacterial antigen. In a followup study, Messner et al\(^{46}\) showed that the IgM RF produced in patients with IE had potentially important biologic properties, rather than merely representing an immunologic “epiphenomenon.” They showed, using an in vitro system, that polymorphonuclear phagocytosis and killing of bacteria preopsonized with IgG and complement could be inhibited in the presence of IE-related RF. This anti-opsonophagocytic property of IgM RF was not related to direct binding of IgM to the organism, but depended on the prior binding of IgG to the organism (postopsonization interference with phagocytic killing). This antiopsonic effect of IgM RF could be overcome by an excess of heat-labile, complement-rich serum. These studies indicated that IgM RF from patients with IE probably interfered with phagocytosis of opsonized bacteria either through masking of the IgG F\(_c\) terminus that binds to the polymorphonuclear F\(_c\) surface receptor site or by interference with complement fixation on the F\(_c\) terminus. The reversal of the antiopsonic effect of IgM RF by complement-rich serum was felt to be related to competition of the initially-reacting complement component (C\(_1\)q) to closely adjacent but separate sites on the F\(_c\) fragment to the IgM binding site (Fig 1). These studies were very important in offering a biological explanation as to why patients with IE could suffer such long duration bacteremias despite the presence of high-level, specific IgG antibodies to the infecting organism, adequate complement and functioning polymorphonuclear leukocytes in the circulation.

Carson et al\(^{46}\) in collaboration with our own laboratory were the first to document the sequential and phasic development of RFs in the serum of patients with IE, and their relationship to CIC productions in the same patients. We showed that in IE patients, the appearance of CICs and RF were temporally related. Clearly the production of both IgG and IgM RFs followed the peak production time of CICs. These studies suggested that RFs in IE were part of a polyvalent antibody response to elevated levels of CICs, probably against the IgG moiety complexed within the CIC. Elkon et al\(^{47}\) have recently confirmed that the serum of patients with IE may contain polymeric IgA-containing RFs, in addition to IgG and IgM RFs similar to patients with collagen-vascular disease such as Sjogren’s syndrome with the sicca complex. However, the IE patients had no obvious mucosal injury as a stimulus for the IgA RF, suggesting that the production of IgA RF in this setting might represent successive “class switching” of IgM RF-producing B cells.
Effect of CICs and Antiglobulins in IE on Host Defenses

The process by which intravascular CICs in IE patients become deposited in tissue to initiate the extracardiac immunologic lesions of this disease remain an important and largely unanswered question. It is known that an intact complement cascade is critically involved in the inhibition of precipitation and solubilization of preformed CICs, through the classic and alternate pathways, respectively. It has been shown that "CIC-mediated," collagen-vascular diseases such as rheumatoid arthritis and SLE are associated with an impairment in ability of sera from such patients to prevent precipitation of CICs. In SLE, this impaired CIC solubilization phenomenon has been linked to hypocomplementemia; in contrast, in rheumatoid arthritics, this defective solubilization phenomenon has been related to an inhibitory property of IgM RF. The exact mechanisms involved in IE patients in this regard (hypocomplementemia vs RF inhibitory activity) remain problematic, although Kerr et al. recently put this into somewhat clearer perspective. These investigators noted, as others have, that a high proportion of their IE patients had both elevated CIC levels and RF titers in sera prior to antimicrobial therapy. Of note, most of the IE sera contained normal or near-normal complement levels. They studied the ability of these IE sera to support or inhibit the solubilization of "artificial, preformed CICs" (BSA-anti-BSA complexes). Their data revealed a significant statistical inverse relationship between CIC levels and ability to solubilize ICs, related to the presence of RF (not hypocomplementemia) in these sera. The sera of these IE patients were able to initiate the IC solubilization process only after antimicrobial therapy of the infection at a time when CIC levels and RF activity had decreased markedly. These observations support those of Messner et al. above, that IgM rheumatoid factor binding to the Fc portion of complexed IgG interferes with complement fixation on adjacent binding sites on the IgG molecule, leading to interference with the complement-mediated processes of CIC solubilization. Although not directly proving the hypothesis, these findings suggest an important primary role for IgM RF produced in response to CICs in allowing tissue deposition of CICs.

Another mechanism by which CIC deposition could be enhanced might involve "immune saturation" of the phagocytic reticuloendothelial system's Fc receptor sites by CICs themselves during untreated IE. This might allow CICs to circulate freely in the intravascular tree and promote their eventual tissue deposition. Schned et al. investigated this possibility by studying the mononuclear phagocyte system function of IE patients in vitro through evaluation of Fc-dependent IgG-coated red blood cell clearance. Their data clearly showed that patients with IE, in fact, had an accelerated rather than impaired Fc-dependent clearance of IgG coated red blood cells. These observations in concert with those of Messner et al. on polymorphonuclear leukocyte function suggest that the phagocytic, Fc-dependent limb of host defenses is intact and functional in IE patients; moreover, it seems likely that the inability to clear bacteria from the circulation in IE relates more to impairment of complement fixation on the Fc portion of the complexed IgG and/or a masking of the Fc terminus by RF.

Specific Therapy of CIC-Mediated Syndromes in IE

As mentioned before, the primary therapy of CIC-mediated extracardiac manifestations of IE (eg, GN) involves antimicrobial and surgical treatment of the primary valvular infection. Most studies have shown that these extracardiac lesions of IE will abate or disappear with successful medical or surgical therapy of the underlying IE. These investigations have also shown clearly that the decline in CIC levels, RF titers, as well as the reversal of absolute or relative hypocom-
plementemia are useful predictors of a salutary clinical outcome.

Because of the clear-cut relationship of CICs with GN in IE, several investigators have utilized non-antibiotic modalities to remove or mitigate CICs in IE patients. For example, McKenzie et al\(^\text{80}\) used plasmapheresis on an IE patient with crescentic, CIC-mediated GN and severe renal failure (the patient was additionally given corticosteroids). Plasmapheresis was associated with a marked improvement of renal function. Of interest, however, following discontinuation of the plasmapheresis, the patient's GN syndrome recurred clinically and functionally, in association with persistent CICs and hypocomplementemia. The GN eventually resolved after the patient's aortic valve was replaced surgically. Rozvar et al\(^\text{81}\) treated a similar patient with IE-related crescentic GN and renal insufficiency with plasmapheresis, corticosteroids and azathioprine (in addition to antimicrobial therapy). Their patient experienced an improvement in renal function, a fall in CIC levels and a reversal of hypocomplementemia with plasmapheresis, immunosuppression, and eventual aortic valve replacement. It thus appears that in those IE patients with rapidly-progressive crescentic CIC-related GN, the institution of plasmapheresis with or without immunosuppressive therapy can ameliorate the course of the renal dysfunction.

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