IMMUNE COMPLEXES IN CLINICAL AND EXPERIMENTAL MEDICINE

Ralph C. Williams, Jr.

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Immune Complexes in Clinical and Experimental Medicine

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To Frank J. Dixon and Henry G. Kunkel

who were among the first to recognize the importance of immune complexes and who have clarified much of their mystery

Preface

There is today a rapidly growing mass of information relative to the physiological consequences of immune complexes. Interactions between cells, the evolution of important clinical syndromes, possibly the ultimate spread of metastatic cancer may be governed by mechanisms triggered by various types of immune complexes. Many physical and facultative effects of circulating as well as tissue-fixed immune complexes are not yet fully understood and await new approaches aimed at clarifying their behavior.

Within this volume I have attempted to assemble an overview of the subject, with the focus on areas where sufficient clinical or experimental information has accumulated to expand on what began as an explanation for some types of renal disease and is now recognized as an extremely significant aspect of the biologic response to many forms of tissue injury, infection, or neoplasia. The final importance of immune complexes in clinical medicine must still be determined; but it is now abundantly clear that immune regulation and many mechanisms of tissue destruction demand the precise understanding of this subject that will eventually be ours.

It is my hope that this book will provide a logical approach to a subject which during the past ten years has assumed more and more of a central role in the comprehension of many disease events as well as the more complex distant ripples that these disease states produce. A precise understanding of the physical, anatomic, theoretical, and practical effects of immune complexes will soon be fundamental to clear interpretation of the pathophysiology of a wide variety of diseases. I have not tried to set down a complete catalogue or encyclopedia of all diseases in which immune complexes have been implicated, but instead to present a broad view of the subject that I hope will be useful not only to the medical student or physician in training but to the practicing clinician, experimental pathologist, or basic research worker.

The first three chapters illustrate the importance of immune complexes in human bacterial, parasitic, and viral infections. Chapters 4 and 5 focus on physical and immunochemical factors, as well as host determinants, in the formation of immune complexes and their disposal in normal body homeostasis. Chapter 6 evaluates current methods used to detect immune complexes. Chapters 7 through 12 cover what is known of the role of immune complexes in a variety of specific organ sites or general disease states. Chapter 13 discusses the experimental models developed in animals for the study of immune complexes, and a brief Epilogue concludes the book.

I should like to express my deep gratitude to those who assisted in compiling this volume. I am particularly indebted to Carol Arnold, Jody Butterfield, Sophia Collaros, John Lingenfelter, Peggy Maddox, Carol Montman, Sophia Olona, Debbie Rindels, and Julie Weaks for their help with the manuscript. Sheila Foley, David McMullen, Donna Maurer, Mike Norviel, and David Tafoya assisted enormously with the illustrations and drawings, and the library staff at the Imperial Cancer Research Fund in London under Helen Flinders gave invaluable aid. I take pleasure in acknowledging the support of the Josiah Macy Foundation during a sabbatical leave in which the book was written, and the aid of the Commonwealth Fund in bringing the volume to fruition.

Contents

CHAPTER 1

Bacterial Infections

Most bacterial infections in both man and animals are associated with generation of an immune response in the host. In recent times—particularly in the immunosuppressed or immunologically compromised host—the immune response may be muted or low-key, but in general, infection by natural pathogens, potential pathogens, or relatively ubiquitous nosocomial agents engenders some kind of immunologic reaction in the host. Part of the immune response to foreign or infecting bacteria involves generation of humoral antibody. Early work on antibody response in experimental animals established that the primary or initial antibody formed may be largely IgM, whereas after the first week IgG antibody production is called forth, and as the immune response gains in momentum, IgG antibody gains ascendancy and IgM antibody declines (1–3).

Some modification of these basic principles may occur, depending largely on the types of antigen involved—protein, sugar, or protein-lipid-carbohydrate complex. Another important modulating factor is the actual antigenic load: very small doses of powerful immunogens may produce rapid but ephemeral 19S IgM antibody responses and virtually no detectable 7S IgG antibody. In all immune responses, whether principally 19S IgM or 7S IgG, memory cells are induced, which are then primed for a secondary, more prolonged IgG antibody response. As time of immunization or exposure to potential antigens increases, there is usually a marked increment in antibody-combining-site tightness of fit or avidity of IgG antibody formed. This principle has been documented in the elegant studies of Siskind and colleagues (4–6). In addition, the level of 7S IgG may actually regulate or monitor ongoing synthesis of antibody by the host (7, 8), through a process similar to feedback inhibition.

Some routes of immunization such as mucosal, oral, or even intrabronchial appear to be much more likely to produce an IgA or IgM antibody response than IgG. Although predominance of IgA antibody as the humoral product of mucosal immunization has been amply illustrated in studies by many groups (9–13), the totality of factors involved in determining immunoglobulin class of antibody molecules manufactured during the host response to any particular infecting bacterium is not yet clearly understood.

In bacterial infections several extenuating influences may substantially affect the humoral antibody response. First, the chemical characteristics of certain classes of antigens may predetermine a characteristic profile of humoral antibody. There is some evidence that many of the lipopolysaccharides found in a wide range of Gram-negative bacteria are particularly potent stimulators of IgM antibody. These same substances also appear to have powerful ancillary effects on the immune system—for instance in general activation of the reticuloendothelial system, direct activation of the complement pathways (14), or even in some circumstances as polyclonal B-cell activators (15).

Considerable adjuvant or antibody-enhanc-

ing activity of the lipopolysaccharides of Gram-negative bacteria has been documented in many laboratories. Digestion or partitioning off of some of the intrinsic immunologic properties of these materials was achieved by Parish and Ada (16), who showed that the immunogenic portion of *Salmonella adelaide* endotoxin could be separated from the mediating adjuvant effect by cyanogen bromide cleavage. The immunogenic fragment in this instance had a relatively low molecular weight (18,000 Daltons) compared to the whole endotoxin molecule. Another aspect that has been shown to be important in the humoral antibody response to bacterial antigens is the actual physical state of the antigen. There is now some evidence that particulate antigens, as in the case of *S. adelaide* studied by Ada and co-workers (17), preferentially stimulate an IgM response. In the same way it has been shown by others (18) that protein antigens such as thyroglobulin coated onto acrylic particles may result in a prolonged IgM antibody response, instead of inducing initial IgM antibody followed by gradually increasing IgG antibody of higher and higher avidity.

Other bacterial antigens, like the pneumococcal polysaccharides present in type III or type VIII pneumococci, are potent antigenic stimuli for the production of 7S IgG antibody. Studies by Jaton and colleagues (19, 20) have shown that hyperimmunization of rabbits with such pneumococcal serotypes can produce monoclonal IgG antibodies with specificities against precisely defined chemical determinants on the repeating sugar linkages that make up the structure of the various pneumococcal capsular polysaccharide antigens. In addition, other selected bacterial polysaccharides (for instance, those obtained from some variant strains of group C or G streptococci) are capable of inducing formation of homogeneous monoclonal antibodies of IgG type in rabbits (21). These models for the production of monoclonal M-components in experimental animals have also been utilized to extend knowledge of the genetic control, as well as the precise combining specificities, of such responses.

Of great practical importance in studying the humoral immune response produced in infected patients is precisely how the complete immunologic apparatus of the host reacts when it encounters lipopolysaccharide released from an invading *Escherichia coli,* or when it sees the pneumococcus surrounded by its fluffy capsule of repeating sugar units. The immune response broken down into its simplest parts can be defined as essentially B-cell or humoral-antibody related, and T-cell or mediated by immunologically competent cells. Some antigens appear to require interaction between various specialized types of immunocompetent cells to promote an adequate immune reaction. Present evidence indicates that B cells are involved directly in humoral antibody formation and T cells in mediating cell-directed immune reactions. Certain bacterial antigens appear to require T-cell–B-cell interaction or intercommunication in order to produce a protective immune response, whereas others do not. Current knowledge of these processes as applied to a number of important human bacterial pathogens lags far behind understanding of host reactions to simple chemically defined haptens or to protein antigens such as bovine serum albumin, which have been studied extensively in various experimental animal models.

There are several possible pathways by which an immune reaction in an infected host may proceed. Bacterial antigen may interact with the producer of humoral antibody—the B cell—directly, or after being processed and refined by an intermediary cell such as the macrophage. The subsequent B-cell activation is then sufficient for a successful, progressive synthesis and release of humoral antibody and presumably neutralization, complement activation and opsonization, and phagocytosis with eventual elimination of the invading bacteria. Other pathogenic bacteria or bacterial antigens may require considerable B-cell–T-cell interaction for an effective immune response. Such antigens have been termed T-dependent, since they seem to require help by various soluble helping intermediary T-cell factors that act on B cells for maximal effective humoral immunity.

Clear understanding of these basic principles is important when we consider the immune response to specific infecting bacteria. It is not yet known, for instance, what complete

repertoire of antigens exists in many of the important pathogens of man. Work in experimental animals has established that various pneumococcal polysaccharides are T-independent (22, 23). It is not known, however, whether other extracellular or intracellular pneumococcal antigens are T-dependent or independent. By the same token, we do not know whether the great variety of extracellular or cell-related bacterial antigens found in other common pathogens such as *Staphylococcus aureus,* β-hemolytic group A streptococci, Klebsiella, or even *Pseudomonas aeruginosa* are T-dependent or T-independent in evoking an immune response. In addition, it is clear that interactions between T cells and B cells in the immune response may be profoundly influenced by suppressor effects on B-cell function caused by T cells, macrophages, or other intermediary cells (24–27). Eventual complete understanding of the host response to individual bacterial pathogens must be based on a careful analysis of all of these factors, including antigenic repertoire, T-cell–B-cell interaction, knowledge of adjuvant properties of certain bacterial antigens, and the actual physical state of the key bacterial antigens involved.

Another extremely important aspect of the local tissue immune response to bacteria has recently been studied by Miller and associates (28), who showed that isolated renal cells were capable of in vitro suppression of T-cell proliferation. Such a phenomenon could obviate fundamental immunoregulatory cell processes, including T-cell support of the cell-mediated immune response. It seems likely that many local tissue factors may play an important role in the precise immune response associated with a variety of bacterial infections.

Of all sources of extrinsic antigens to which man is continually exposed, bacteria known to be associated with specific diseases have been the most elaborately characterized. Specific examples of the importance of immune complexes in determining the course or sequelae in a variety of bacterial reactions serve to illustrate the practical necessity for a clear understanding of the immune response in common clinical situations.

Subacute Bacterial Endocarditis (Infective Endocarditis)

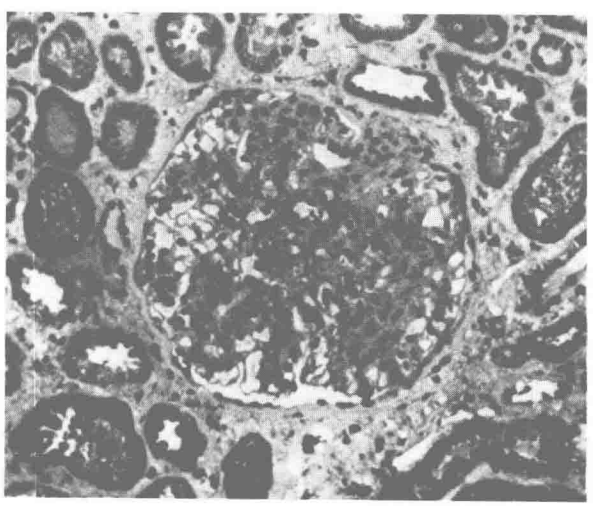
Subacute bacterial endocarditis, recently termed infective endocarditis (IE), is a disorder associated with a low-grade, often indolent

Figure 1-1 The typical gross appearance of aortic valvular vegetations seen in infective endocarditis. (Photograph courtesy of A. G. Stansfeld, St. Bartholomew's Hospital, London.)

infection in a nidus of fibrin, coagulum, and platelets within the arterial or venous circulation of the afflicted individual. Vegetations typical of this disease are shown in Figure 1-1. The most common organisms involved in this infection are represented by the α-hemolytic viridans streptococci, *Staphylococcus aureus, S. albus,* candida, or a wide variety of bacteria of low virulence or natural pathogenicity, but when entrenched as vegetations on heart valves fully capable of inducing severe disease and abundant distant sequelae.

Before the advent of antibiotics virtually all patients with IE died of cardiovascular complications as a consequence of progressive valvular dysfunction, embolic phenomena, heart failure, or occasionally progressive renal failure (29–35). Infective endocarditis may be associated with several forms of renal injury, including segmental infarction, focal abscess formation, diffuse glomerulonephritis, or a more localized form of glomerular injury originally termed focal embolic nephritis. For many years the glomerular lesions in the kidney associated with IE were felt by most pathologists to represent microemboli from the infected heart valves; the term *focal embolic nephritis* was often used to describe these findings. Examples of these microscopic renal lesions from patients studied postmortem are shown in Figure 1-2.

Various aspects of the renal involvement recorded in some patients with IE did not fit the pathological concept of minute bacterial or fibrin emboli producing segmental glomerular lesions. First, a certain proportion of patients were shown at autopsy or by renal biopsy to have lesions more typical of an acute diffuse glomerulonephritis. Second, patients with IE



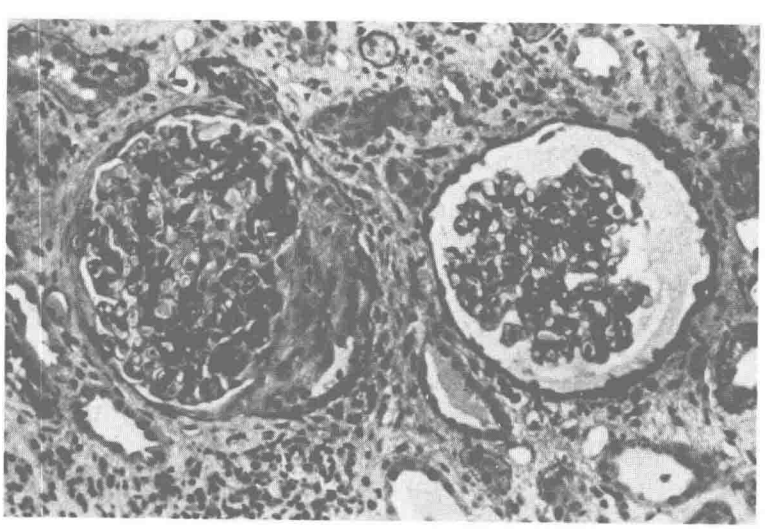


Figure 1-2 *Above,* light microscopy of renal tissue from a patient with culture-negative endocarditis showing diffuse glomerulonephritis with focal epithelial proliferation and crescent formation. *Below,* light microscopic picture of the same patient, again with culture-negative endocarditis showing diffuse glomerulonephritis with focal areas of fibrin deposition and necrosis. Magnification × 150. (Reproduced with permission, R. A. Gutman, G. E. Striker, B. C. Gilliland et al., *Medicine* 51:1, 1972.)

and the clinical or pathological picture of an acute glomerulonephritis sometimes showed vegetations only on the right side of the heart. In such instances direct embolization to the kidney through the efficient macrophage filter of the lungs seemed unlikely; however, in a series of 23 autopsied cases of right-sided IE studied by Bain and colleagues (36), renal lesions were noted in 14, and suppurative nephritis with either focal abscesses or involvement of the whole renal parenchyma was recorded in 8 patients. In this carefully studied group 3 patients were recorded with the lesion of so-called focal embolic nephritis.

Subsequently, a series of interrelated observations has provided a convincing body of evidence that the renal lesion in IE is often probably the result of glomerular deposition of circulating immune complexes. About half of a group of 51 patients with IE caused by a broad variety of organisms showed the presence of marked elevations of rheumatoid factors during the active phase of the disease (37). These anti-gamma-globulins or self-directed autoreacting antibodies showed broad reactivity for human as well as rabbit gamma-globulin preparations. Of great interest was the finding that upon initiation of appropriate antimicrobial therapy, a striking fall and ultimate complete disappearance of rheumatoid factors were recorded in most of these subjects. An example is shown in Figure 1-3. By contrast such rapid disappearance in rheumatoid factor elevations is not generally seen in patients with positive latex fixation reactions in connective-tissue diseases such as rheumatoid arthritis. These findings suggested that the rheumatoid factors may be generated in IE as antibodies against altered autologous gamma globulins. Thus disappearance of anti-γ-globulins after the course of successful antibiotic therapy might be interpreted as evidence that removal of autologous bacterial-antigen-antibody complexes by treatment was capable of turning off the stimulus toward rheumatoid factor production. Furthermore, these observations, viewed now in perspective, indicate that an ongoing self-immunization with autologous complexes may be involved in continued rheumatoid factor production even in rheumatoid arthritis itself.

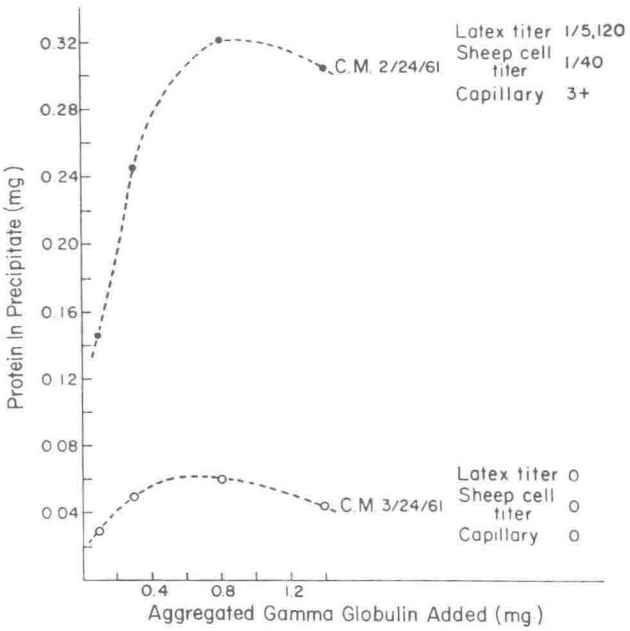


Figure 1-3 Serial changes in anti-γ-globulin activity before and after successful treatment for bacterial endocarditis. (Reproduced with permission, R. C. Williams, Jr., and H. G. Kunkel, *J. Clin. Invest.* 41: 666, 1962.)

Striking hypocomplementemia, as measured by total hemolytic complement or assay of individual complement components, has been documented in a substantial proportion of patients with acute diffuse nephritis and IE (37–39). Subsequent careful biopsy or postmortem studies of several groups of individual patients have also now provided strong evidence that glomerular immune complex deposition is fundamental to the pathogenesis of the lesion in such individuals (37–42). Pathological studies have demonstrated gamma globulin, complement components, and occasionally bacterial antigen by immunofluorescence in glomerular lesions. Moreover, a rabbit model that simulated the human disease using *Streptococcus viridans* showed that diffuse glomerulonephritis developed only in animals that had been immunized to the infecting agent prior to the experimental production of endocarditis (43). These results were of considerable interest, since they appeared to indicate that, for a diffuse proliferative glomerulonephritis to

occur, immunity to infecting organisms might be necessary prior to development of IE. To our knowledge this particular point has not been reinvestigated recently in patients with IE and acute diffuse nephritis; it would of course require studies of such individuals before and after onset of the clinical disorder.

Electron microscopic studies of biopsy and autopsy material have provided additional abundant support for the concept that many of the renal lesions in IE are produced by immune complex deposition (38–40). Examples of immunofluorescence studies as well as the ultrastructural appearance of subendothelial dense glomerular deposits recorded in subjects with IE are shown in Figures 1-4 and 1-5.

Several features of the clinical situation in IE have an important bearing on other less chronic or perhaps less dramatic infections. First, in IE renal disease, renal immune-complex disposition has not been restricted or especially limited to any particular organism but has been recorded in association with a wide variety of infecting organisms, including the pneumococcus, gonococcus, *Haemophilus influenzae, Staphylococcus aureus,* and *S. albus* and microaerophilic species (37–39, 44–46). Lesions in the renal glomeruli, while tending in many instances to be localized in the mesangium as well as in a lobular distribution, are often diffuse or granular in type and often closely resemble an acute diffuse nephritis seen after group A β-hemolytic streptococcus infections. Thus, in valvular or endocardial infections by a wide variety of both Gram-positive and Gram-negative organisms, there is a common feature capable of inducing progressive renal deposition of complexes in a certain proportion of patients at risk. This is an important aspect of bacterial endocarditis, which emphasizes the fact that intravascular and particularly intraarterial infection with organisms as diverse as proteus or *S. albus* may afford an opportunity for the formation of immune complexes potentially very dangerous for the host.

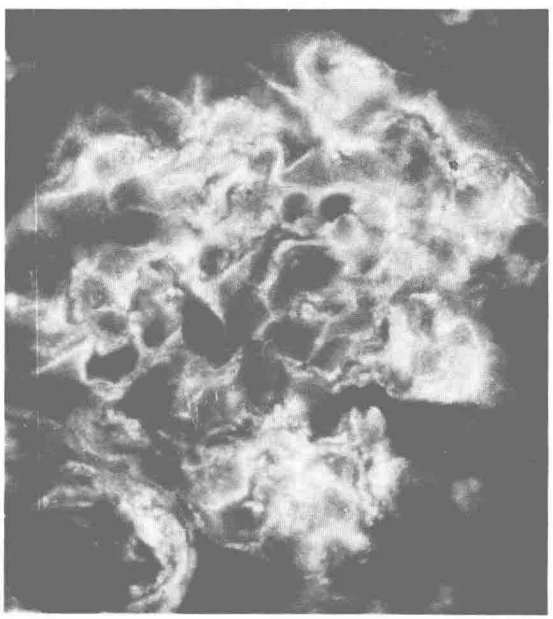


Figure 1-4 Immunofluorescence photomicrograph of IgG staining of glomeruli from the renal biopsy of a patient with infective endocarditis and renal involvement. Magnification × 122. (Photograph courtesy of Richard Hong, University of Wisconsin.)

An impressive parallel is presented by patients with infected intraventricular shunts. In this circumstance the causative organism is often an *S. albus* or *S. aureus* of relatively low virulence (47). Numerous examples of acute diffuse nephritis associated with such infections have now been documented (47–53). An example of the striking immune deposits associated with nephritis or nephrotic syndrome in such patients is shown in Figure 1-6. It is obvious that an infected nidus directly contiguous to the circulation provides a ready avenue for the infected patient to receive a small steady antigenic load over a prolonged period of time. Studies by several groups have indicated that the degree of bacteremia occurring in IE is remarkably constant, seldom varying over 100 organisms/ml, and more often falling in the range of 10 to 20 bacteria/ml (54, 55). Such prolonged low-dose antigenic stimulation provides an ideal opportunity for the infected individual to manufacture a steadily increasing and maximum humoral antibody response. In such a circumstance, from a theoretical standpoint, the humoral IgG antibody response would show progressive increments in antibody avidity over time. An increase in immu-

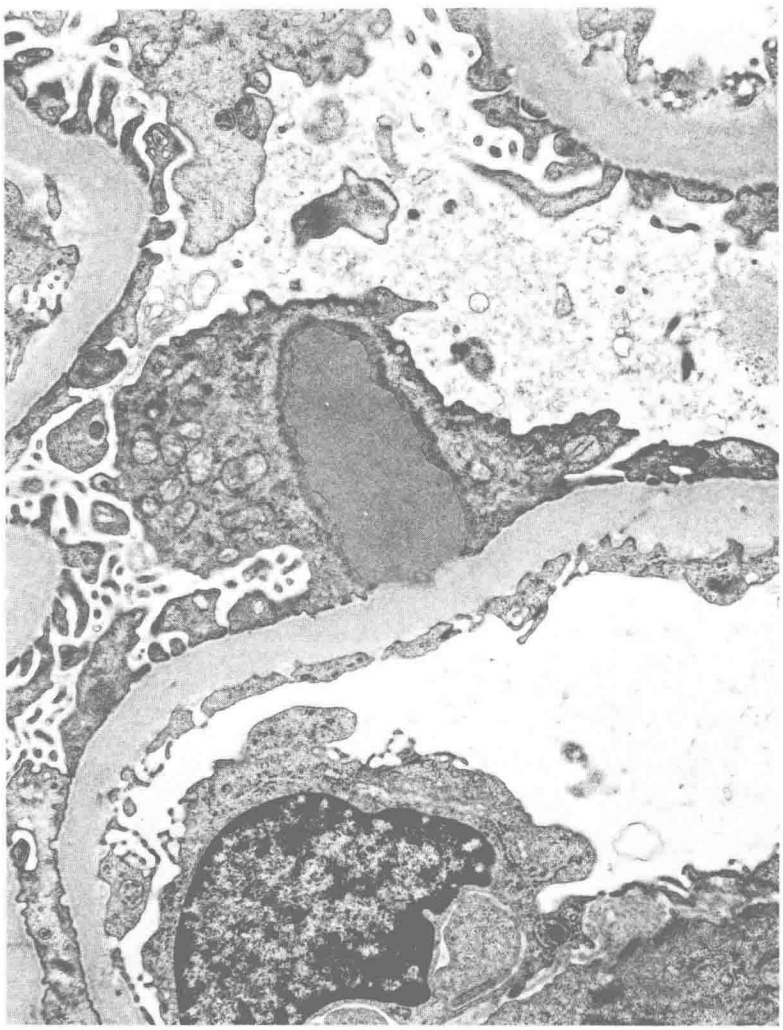


Figure 1-5 Endocarditis with large subepithelial deposits. Electron microscopy of renal tissue from a patient with culture-negative endocarditis showing extensive subendothelial and intramembranous deposits. Magnification × 10,000. (Reproduced with permission, R. A. Gutman, G. E. Striker, B. C. Gilliland et al., *Medicine* 51:1, 1972.)

noglobulins during the course of endocarditis has been clearly documented (56–58). It is apparent from the diversity of bacterial species that have now been described in association with IE that a vast array of thymus-dependent as well as independent antigens are probably being presented to the host at risk. Since the quality and intensity of the immune response may be genetically determined and directly governed by immune-response genes (59, 60), it is clear that this aspect as well may generate considerable variability in the individual immune response.

Another feature important to a clear understanding of the relation of immune complexes to disease manifestations in both IE and shunt nephritis is related to the emerging body of knowledge now accumulating on bacterial adherence. During recent years it has become increasingly apparent that the actual stickiness or adhesiveness of individual strains of bacteria may be related to their ability to cause infections. The most convincing evidence has been provided by studies of the relative adherence of various bacteria in the case of dental caries or in IE (61, 62). Individual strains of bacteria isolated from patients with endocarditis show increased adherence or stickiness when examined in parallel with similar strains not clinically implicated in a bacterial endocarditis situation. This aspect of the general problem will require increasing attention in the future.

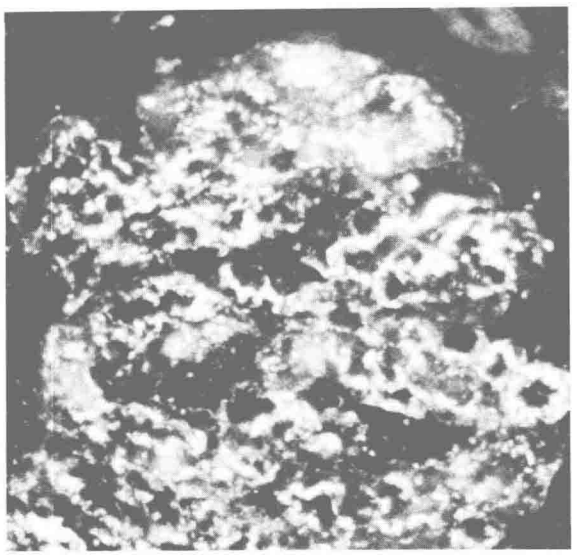


Figure 1-6 Diffuse granular deposition of properdin in the glomerulus of a patient with an infected subarachnoid-jugular shunt. Magnification × 210. (Photograph courtesy of A. F. Michael, Department of Pediatrics, University of Minnesota.)

Depending on the molecular lattice or combining ratios of antigen-antibody complexes, more or less of the potentially sticky bacterial surface or antigen might be exposed. In large complexes of Ag_2Ab_{10} or greater ratios, very little of the potentially adherent bacterial surface antigens would be available or exposed, whereas in complexes formed in low ratios of antigen to antibody (like Ag_2Ab), more potentially sticky bacterial surface antigens might be prominent. In the latter instance it is conceivable that the stickiness of antigen might then become partially responsible for the final peripheral biologic effects of such complexes.

With the availability of many parallel assay systems for the detection of antigen-antibody complexes, the original hypothesis raised concerning the presence of large quantities of circulating immune complexes in IE (37) has recently been confirmed. Reports by Bayer and associates (63) showed that 97 percent of a group of 29 patients with IE tested positive for the presence of complexes using the Raji-cell radioimmunoassay (64). Also of interest in this study were the findings of detectable elevations in circulating immune complexes in patients with right-sided IE, and decline in the quantitative levels of immune complexes in the course of successful treatment, including surgery. Notable also in this latter group of patients were extravalvular manifestations of IE —arthralgia and arthritis, splenomegaly, glomerulonephritis, and thrombocytopenia. Representative examples of serial determinations of immune complexes in patients with IE taken from the Bayer report (63) are given in Figure 1-7.

The whole question of whether peripheral manifestations of IE other than nephritis may be attributable to circulating complexes is one that has not yet been completely resolved. The early histological studies of Osler's nodes suggested intense perivascular infiltration by inflammatory cells, resembling what one might expect of an Arthus reaction where capillary or vessel wall is directly involved as the actual site of an acute antigen-antibody reaction (65, 66). More recently it has been demonstrated conclusively that etiologic bacteria often can be directly cultured or demonstrated in Gram's stains from characteristic Osler's node lesions (67, 68) where actual microabscesses in the papillary dermis may be present. Osler's nodes or emphemeral nodular lesions, usually in the skin of the hands and feet, may also be seen in typhoid fever, systemic lupus erythematosus, disseminated gonococcal infection, or marantic endocarditis (69).

This same problem of differential pathogenesis—bacterium alone or immune complex—is present in the peripheral manifestations of several important bacterial infections. In particular, one is reminded of the vasculitic skin lesions seen in some cases of gonococcal or pseudomonas sepsis. In the case of such lesions, which often resemble microinfarcts in the skin, bacteria can be demonstrated on Gram's stain; however, it is still not clear whether there are also immune complexes fixed in vivo in the lesions, which amplify the immune reaction through an acute Arthus-type reaction in small vessel walls. Most of the instances reported to date of actual microabscesses in association with Osler's node lesions have involved organisms such as *S. aureus* or candida, which are

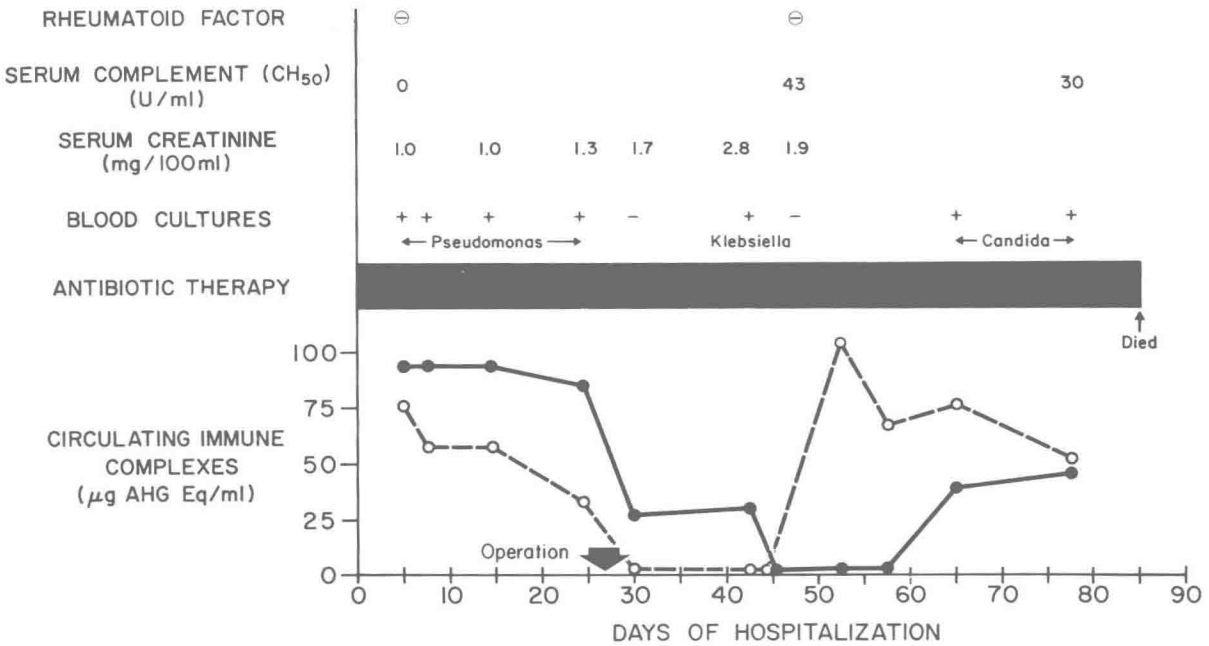


Figure 1-7 Serial studies of circulating immune complexes and other clinical parameters in a patient with infectious endocarditis. (Reproduced with permission, A. S. Bayer, A. N. Theofilopoulos, R. Eisenberg et al., *N. Engl. J. Med.* 295:1500, 1976.)

notorious for production of focal peripheral suppurative lesions in IE. Typical vasculitis lesions seen in such patients with gonococcal or pseudomonas sepsis are shown in Figures 1-8 and 1-9. The similarity of these skin lesions to those sometimes seen in association with the vasculitis of periarteritis or allergic angiitis is striking. A study of skin immunofluorescence during infective endocarditis (70) indicated that perivascular deposits of Ig and complement were often present in such patients in what appeared to be clinically normal skin, whereas control bacteremic patients without the prolonged course associated with endocarditis showed no such immune deposits. It seems clear from these and other similar observations that many of the peripheral clinical manifestations commonly associated with a variety of prolonged or particularly severe bacterial infections may be related at least in part to the local fixation of immune-complex deposits within certain tissues.

Patients with IE harbor a nidus or focus of infection, quite often with a relatively indolent and not particularly invasive or aggressive organism, and then appear to subject themselves to a subacute or chronic period of self-immunization with autologous complexes. Studies by Phair have shown that anti-γ-globulins or rheumatoid factors in sera from patients with IE often appear to show true autospecificity (71). Thus, they are best inhibited or absorbed out by autologous immune precipitates or immune complexes made from the patient's own gamma globulin and actual infecting bacterium. Recent studies by Carson and associates (72) using radioimmunoassay for both IgG and IgM rheumatoid factors have indicated that levels of these anti-γ-globulins seemed to peak later in the course of IE than did those of concurrently measured circulating complexes. The data again suggest that both IgG and IgM rheumatoid factors represent part of the host immune response to autostimulation by elevated levels of circulating immune complexes.

Since autoreactive rheumatoid factors are indeed often present and are specific or primarily directed at autologous complexes, inter-

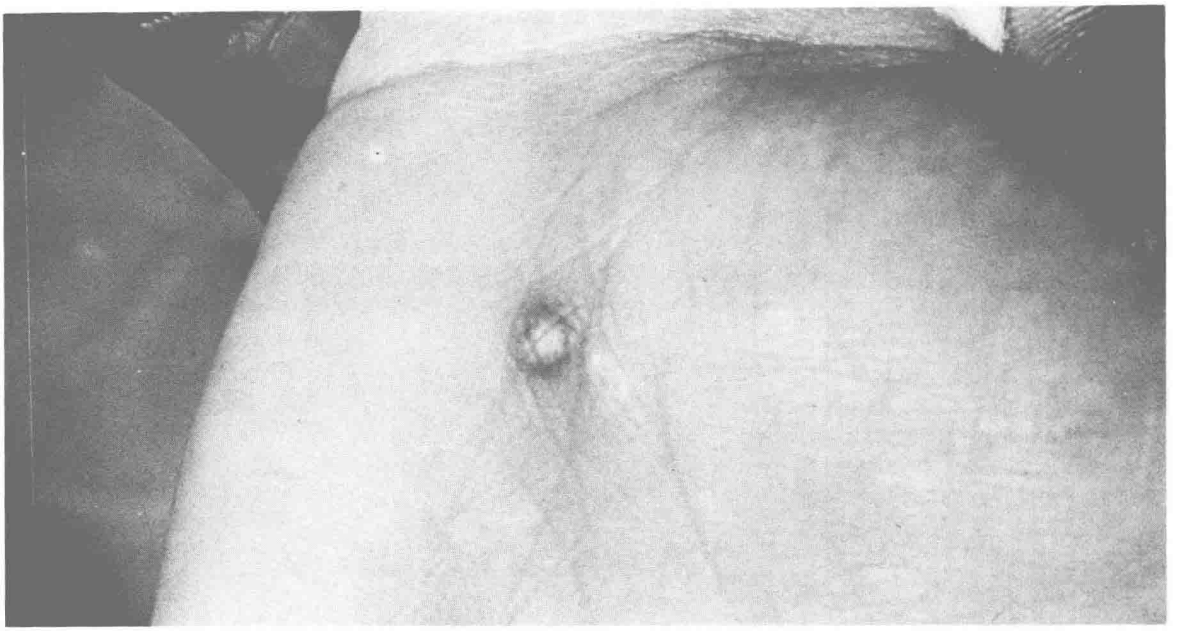


Figure 1-8 A typical circumscribed palmar lesion seen in association with gonococcal sepsis. The central purulent material in this patient yielded negative results on Gram's stain and culture.

est has centered on the possibility that they might have some physiological significance for the host. Early studies aimed at determining whether such anti-γ-globulins affected immune phagocytosis, for instance, indicated that in certain in vitro experimental systems such rheumatoid factors could block phagocytosis by interference with the binding of opsonic IgG antibody to the Fc receptor of the phagocytosing polymorph or monocyte (73). Other studies, however, appear to indicate enhancement of phagocytosis mediated by complement and rheumatoid factor (74). In the patients that I personally have studied, I have never obtained unequivocal evidence for potentiation of the immune-complex nephritis in IE by the presence of rheumatoid factor. However, in a recent large-scale survey of heterogeneous patients with a variety of renal diseases, Rossen and co-workers demonstrated what appeared to be a correlation between the degree of histological damage and the presence of tissue-bound anti-γ-globulins (75). It is not evident from the data in the Rossen study whether the method used for detecting tissue-bound rheumatoid factors was entirely comparable to methods generally in use for detection of serum anti-γ-globulin factors. Earlier experimental evidence presented by McCormick and co-workers (76) indicated accentuation of Masugi-type nephritis in rats by passive concurrent administration of human serum or γ-globulin preparations containing rheumatoid factor activity. Thus, it is conceivable that for microvascular insults seen in areas such as the renal glomerulus or skin in IE, rheumatoid factors may intensify the basic lesions.

Potentially important to the interpretation of immune mechanisms in IE is the occurrence of so-called autoantibodies in a substantial number of patients who have been carefully studied. In addition to the presence of rheumatoid factor and immunoconglutinin (37), antinuclear antibodies and anti–smooth-muscle antibodies have been recorded in some of my own patients. One of the patients reported by Beeler and colleagues (53) actually showed a positive LE cell test as well as a low hemolytic complement level, both of which disappeared completely after successful antimicrobial treatment. Reports by Bacon and associates (77) indicated the presence of smooth-muscle anti-