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Human Hypersensitivity Angiitis, An Immune Complex Disease

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Human hypersensitivity angiitis is an immune complex disease in which patients present with palpable purpuric lesions of the skin and may often have multiple organ involvement. The antigen may be derived from an infectious organism such as the hepatitis virus, streptococcus, or a drug, and complexes with antibody. Under circumstances of vascular turbulence or vessel wall dilatation this complex may become fixed, activating the complement sequence with elaboration of chemotactic factors for neutrophils. These cells release lysosomal enzymes resulting in vessel wall destruction. Red blood cells leak into the tissue producing purpura and the inflammatory infiltrate accounts for the palpability. Although many patients have skin lesions only, others may have involvement of joints, gastrointestinal tract, kidneys, and even the lungs.

The central question in the pathogenesis of this disease is why the immune complex is so selective in its site of deposition. Part of the reason must be related to the lattice formation of a particular complex, while other reasons are related to host factors of altered vascular permeability, integrity of clearance mechanisms or even a genetically determined defect of the phagocytic system.

Hypersensitivity angiitis is a term used to describe a well-recognized clinico-pathologic entity of palpable purpuric lesions of the skin seen clinically and small vessel wall destruction seen histologically. Confusion sometimes develops because of the variety of names used to describe the same disease and include: allergic vasculitis, leukocytoclastic vasculitis, necrotizing vasculitis, and Henoch-Schöenlein Purpura. Several clinical observations and experimental studies lend strong support to an immune complex mechanism for development of lesions. However, there are some critical unanswered questions. It is the purpose of this review to examine the evidence and explore the questions.

HYPERSENSITIVITY ANGIITIS AS A CLINICAL DISEASE

Patients usually present with the acute onset of palpable purpuric lesions on the lower legs (Fig 1). The presence of palpability immediately sets this process apart from the large group of conditions which are responsible for cutaneous purpura that is not elevated above the surface of the skin. The palpability implies an inflammatory process. As might be expected, lesions are not necessarily limited to the skin and may involve vessels in other organs, especially the kidneys, joints, gastrointestinal tract, and lungs. What is surprising, however, is that many patients may have lesions only in the skin and they may persist there recurrently for months or years without ever involving vessels in any other organ. Possible reasons for this will be considered later in this review. In other patients, identical clinical and pathologic lesions may occur in association with such diseases as systemic lupus erythematosus (LE), essential mixed cryoglobulinemia, and autoimmune hemolytic anemia. Also noteworthy, in light of the discussion to follow, is that similar histopathologic findings may be seen in specific larger vessels and organs leading to such entities as polyarteritis nodosa and Wegener's granulomatosus. As a full consideration of the clinical aspects of these diseases is beyond the intent of the present discussion the interested reader may wish to consult Price and Sams [1], Sams [2], or Fauci, Haynes, and Katz [3].

EVIDENCE FOR IMMUNE COMPLEXES IN THE PATHOGENESIS OF HUMAN VASCULITIS

The currently accepted hypothesis is that hypersensitivity angiitis is an immune complex disease [1–4] (Fig 2). The hypothesis states that circulating complexes composed of soluble antigen bound to antibody deposit within blood vessel walls, binding and activating complement. Complement chemotactic factors attract neutrophils which release lysosomal enzymes, causing compromised vessel function leading to hemorrhage. The observations and experimental evidence in humans to support the hypothesis are compelling and each will be discussed individually.

Neutrophilic Infiltrate

An inflammatory infiltrate composed of neutrophils is characteristic of immune complex diseases and is the dominant histopathologic feature in patients with hypersensitivity vasculitis [5] (Fig 3). These cells are found within and around the vessel walls and rapidly fragment-forming "nuclear dust" or leukocytoclasis. In addition, as the process advances there is loss of integrity of the vessel wall and deposition of fibrin. The sequences of this dynamic process will be discussed subsequently.

Granular Immunoreactants

Granular deposits of immunoglobulin and complement components are regularly observed in the vessel walls [6] (Fig 4), a characteristic of immune complex-mediated disease. Complement (particularly C3) may be the only immunoreactant demonstrable (possibly due to its greater sensitivity) and may be found even in clinically uninvolved skin [7]. This latter observation is particularly intriguing since it implies that either larger amounts of complement, or some other factors, are necessary before neutrophils are attracted.

Anticomplementary Activity of Sera

A number of years ago Cream [8] demonstrated that sera from some patients with vasculitis would prevent added complement from hemolysing sensitized sheep erythrocytes, implying that a substance, presumably an antigen-antibody complex, had bound complement so it was not available to react with the cells. Similar studies in larger groups of patients have confirmed these findings [9]. Similarly, presence of detectable levels of cryoglobulins has been thought to be presumptive evidence for presence of circulating immune complexes [9,10]. Obviously, findings such as these address neither the nature of the antigen nor antibody, or whether it is these same circulating complexes which become bound to tissue.

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Abbreviations:
LE: lupus erythematosus

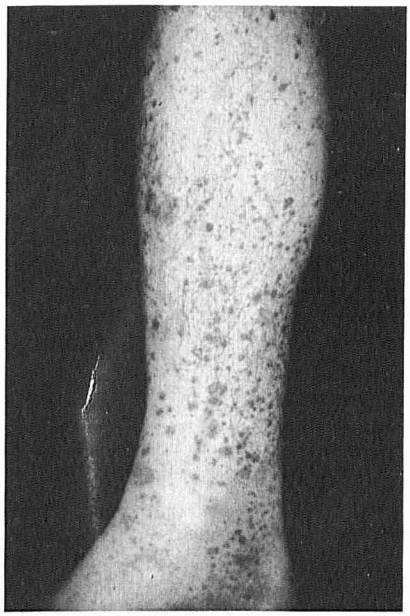

FIG 1. Palpable purpuric lesions as they commonly appear on the lower legs. The palpability implies an inflammatory process.

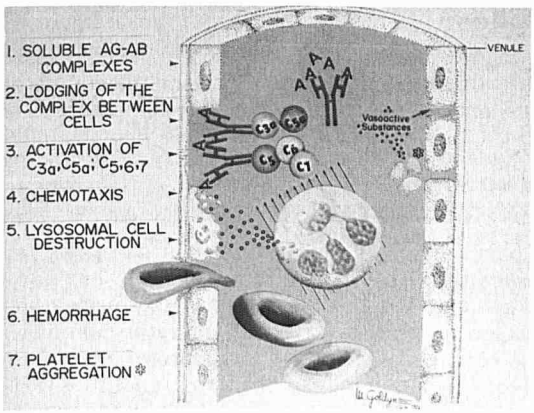

FIG 2. The immune complex pathogenesis of vasculitis (see text).

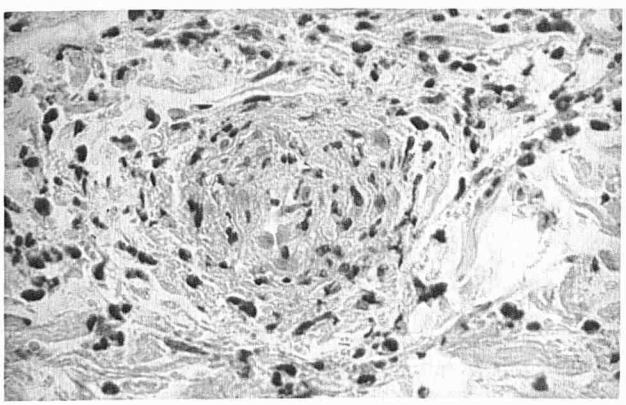

FIG 3. Histopathology reveals neutrophils within and around the vessel wall, thickening of the wall, fibrinoid deposition, and hemorrhage.

Presence of Hypocomplementemia

The presence of depressed serum complement levels usually suggests binding by immune complexes. In patients with cutaneous allergic vasculitis in association with a systemic disease such as LE or severe rheumatoid arthritis, the serum complement levels are frequently low [10]. However, patients with cutaneous allergic vasculitis without systemic disease usually, although not invariably, have normal serum complement levels [11,12]. This normal complement level should not be unexpected since it presumably reflects the relatively small number of vessels involved—too few to depress total serum complement.

Detection of Circulating Immune Complexes

The development of sensitive methods to measure circulating immune complexes provided further opportunity to consider cutaneous vasculitis an immune complex disease. One of the more commonly employed methods is the Clq binding assay in which Clq labelled with ^{125}I is added to test and control sera, incubated, polyethylene glycol added to separate free from bound Clq and radioactivity measured, thus providing a sensitive assay for detection of antigen-antibody complexes capable of binding complement.

Although most authors place great importance on the significance of such studies in relationship to the pathogenesis of the disease the critical observer will readily recognize that it is not complexes in the serum which causes disease—the complexes must first fix to tissue. It is further recognized that immune complexes form frequently in healthy individuals but are cleared rapidly. Nevertheless, unless complexes are first formed in the serum they cannot be deposited, with the exception of those which may occasionally form in situ. Thus, the demonstration of elevated levels of immune complexes in the serum of patients with active vasculitis is presumptive evidence that they may be playing a role in the pathogenesis of the disease [11,12].

It is also possible that immune complexes may deposit in the vessels so rapidly after formation that they do not reach detectable levels in the serum, which would help explain those patients with active vasculitis and normal immune complex levels.

Histamine Trap Test

Rationally it would seem that the most convincing experiments to corroborate an immune complex pathogenesis for vasculitis would be one in which complexes could be made to deposit on cue and the sequence of events leading to full lesion expression could be examined. Braverman and Yen [13] performed the first such experiments in which they injected histamine intradermally in 16 patients with active vasculitis and biopsied the site at 3–4 h post injection. Their electron microscopic observations of those sites revealed clumps of electron dense deposits between endothelial cells and pericytes within the basement membrane of postcapillary venules. Neutrophils

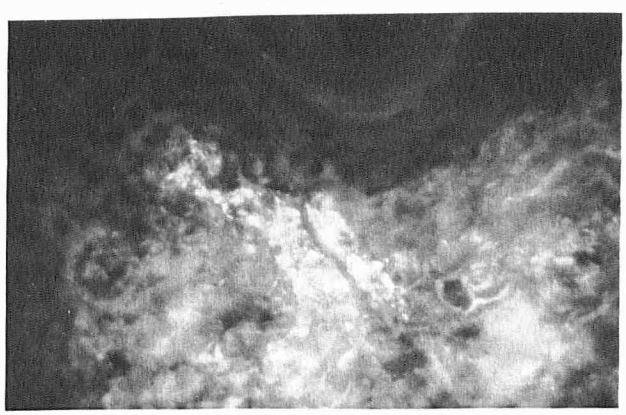

FIG 4. Immunofluorescence demonstrates granular deposition of immunoglobulins and complements within the vessel walls. Biopsy of an active lesion stained with fluorescein-conjugated anti-C3.

were also seen between endothelial cells and within the vascular wall. In 4 of 9 biopsies studied granular deposits of immunoglobulin and complement (C3) were found. A further suggestion that these immune complexes are pathogenic was that they found immunoreactants without neutrophils in clinically normal noninjected skin confirming the prior observation of Sams et al [7]. This implies that these deposits play a primary role and do not appear merely as a secondary event to prior tissue damage.

Gower et al [14] extended these studies doing sequential biopsies at 1, 4, 8, and 24 h after intradermal histamine injection in 5 patients with active vasculitis. Although the timing and sequence of monocytic and neutrophilic infiltration varied in the 5 patients, immunoreactants were consistently deposited in large amounts in the first hour (Figs 5, 6) accompanied by either no or very few inflammatory cells. Over the ensuing hours of the study immunoreactants decreased (Fig 7) in amount until at 24 h only those within phagocytic cells were visible. This is similar to the rapid removal of deposited complexes in animals described by Cochrane [15].

Thus, these two studies provide some of the most direct evidence for the role of immune complexes in the pathogenesis of cutaneous vasculitis.

Clearance of Complexes

As mentioned earlier, normal individuals form immune complexes and presumably clear them rapidly and, since it is possible that patients with vasculitis have a decreased ability to clear complexes, Dambuyant et al [16] elected to study the question. Erythrocytes from patients with vasculitis and controls were labeled with ^{51}Cr and disappearance rates determined as well as radioactive scans recorded over the liver and spleen. No patient demonstrated a decreased clearance. In contrast, Frank et al [17] describe a series of studies in which a decreased clearance rate of IgG coated radiolabeled autologous erythrocytes is found in such autoimmune diseases as systemic LE and mixed cryoglobulinemia. However, patients with isolated cutaneous vasculitis were not studied although some of their patients with mixed cryoglobulins had typical cutaneous vasculitis.

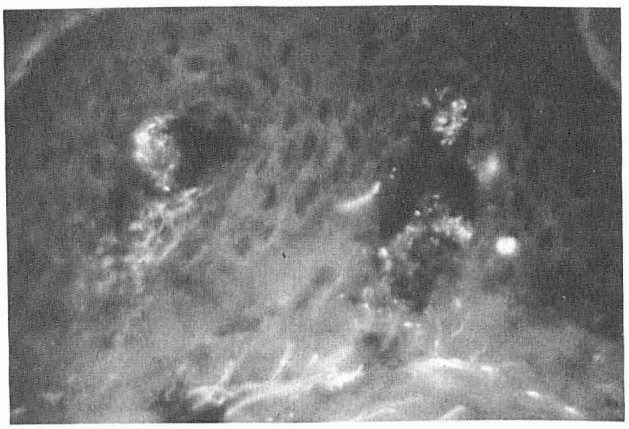

FIG 5. Histamine trap test. Biopsy of clinically normal control skin immediately after histamine injection. Note small amount of granular C3 staining.

FIG 6. Histamine trap test. Biopsy of clinically normal skin which had been injected with histamine 1 h previously. C3 is now deposited in huge amounts.

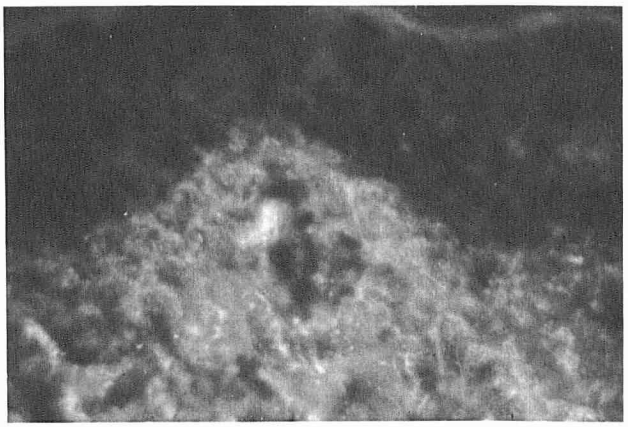

FIG 7. Histamine trap test. Biopsy of clinically normal skin which had been injected with histamine 8 h previously. Much of the deposited C3 has already been removed.

EXPERIMENTAL STUDIES IN ANIMALS

Quite obviously there are a number of questions raised by these observations that cannot be answered in humans so that investigators over the past 25 years have performed numerous critical experiments in a variety of laboratory animals. These studies up through 1972 are best summarized by Cochrane and Koffler [18]. They pointed out the importance of a vasodilator released from basophilic leukocytes, which, in the rabbit model, caused platelets to clump and to release vasoactive amines. The latter caused an increase in vascular permeability, immune complexes entered these areas and became entrapped along the vessel basement membrane. They noted that in complement-depleted animals glomerulitis would occur but arteritis would not unless complement was present to attract neutrophils. Only if the complex was larger than 19S in size would it deposit. They also noted that deposited complexes persist less than 24 h and that neutrophils in culture degrade complexes.

It was becoming abundantly clear that large complexes, and particularly those with extensive lattice formation, are removed rapidly from the circulation by the reticulo-endothelial (monocyte-macrophage) system, whereas $AgAb_2$, Ag_2Ab, and AgAb complexes may persist in circulation for a long time [18,19], and may then have more of an opportunity to initiate tissue damage.

Joselow and Mannik [20] have extended these studies by examining complex deposition in mouse skin. They found that complexes made at 5 times antigen excess with large lattices deposited, whereas those made at 50 times antigen excess, consisting of small-latticed complexes, did not localize in skin or other tissues. In addition, the deposits were patchy so that some vessels were spared while the lip showed a high frequency and intensity of deposition. This is analogous to the clinical discreteness of cutaneous lesions in humans and probably reflects individual vessel patency or permeability at the time of high levels of circulating complexes.

UNANSWERED QUESTIONS

From the foregoing discussion it becomes clear that the evidence strongly implicates an immune complex pathogenesis for allergic vasculitis. But there remain some central unanswered questions. One question relates to immunologic mechanisms other than immune complex deposition, another to the nature of the antigen and a third to the specific tissue localization of the complex.

Other Possible Immunologic Mechanisms

The observation that the infiltrate is lymphocytic and monocytic rather than neutrophilic in some biopsies of active lesions and that some patients have normal serum complement levels has led to speculation that cellular immune mechanisms may be involved in some patients [3,21]. It is proposed that sensitized lymphocytes, upon re-exposure to specific antigen, release lymphokines including migration inhibition factors. The latter results in migration into and accumulation of monocytes in a localized area. These cells are transformed into activated macrophages which release lysosomal enzymes capable of causing vascular damage similar to that seen with neutrophils. These activated macrophages might subsequently transform to epitheloid and multinucleated giant cells and develop the typical histologic appearance of granulomatous vasculitis seen in Wegener's granulomatosis and allergic granulomatous vasculitis.

Unfortunately, no well-developed experimental studies have directly addressed this possible pathomechanism so that no more than speculation can be offered at this time.

Nature of the Antigen

Although the list of proposed antigens is long [2], very few of these have been directly demonstrated. Probably the most widely accepted is the hepatitis B surface antigen, but even this association is based primarily on epidemiologic studies [22] and on groups of patients with both diseases simultaneously [23,23]. Many antigen associations are temporal where typical vasculitic lesions follow drug or infectious exposure. For instance, there are occasional reports, such as that by Lambert and colleagues [25], where a patient administered the same drug on two occasions developed allergic vasculitis. Experienced clinicians can relate anecdotes of patients who develop a flu-like illness each winter followed by vasculitis, or farmers repeatedly exposed to insecticides who develop typical lesions.

Nevertheless, this inability to clearly demonstrate the antigen in patients with spontaneous disease in no way detracts from the experimental animal studies of injection of preformed known complexes, or with the basic principles of immune complex deposition as the pathomechanism for vasculitis.

Specific Tissue Localization of the Complex

This is a more difficult question to address and one that requires some knowledge of the way in which immune complexes may be formed and the local factors that may cause deposition. A fundamental question is why, if both allergic vasculitis and polyarteritis nodosa are immune complex diseases, do the complexes in the former deposit in small postcapillary venules on the legs while, in the latter, complexes deposit in large muscular vessels such as the aorta and renal arteries?

IMMUNE COMPLEXES

To better understand the deposition of immune complexes it is first necessary to have an understanding of the nature of complexes, and factors affecting their deposition and clearance.

Immune Complex Formation

For a detailed discussion of immune complex formation the reader is referred to the lucid articles of Barnett et al [26] and Yancey and Lawley [27]. Briefly, the size of the final complex depends on both the valence of the respective antigen and antibody and on their relative concentrations (Fig 8). For instance, an antigen with only a single binding site (monovalent) can bind only one antibody. An antigen with 2–4 binding sites (oligovalent) can bind several antibodies to form small soluble complexes, while an antigen with multiple sites can cross-link with antibodies to form a latticework. The latter either precipitate or form large soluble complexes depending on the relative concentration of antigen and antibody (see below). Similarly the valence of the antibody may affect the latticework, as IgM has an effective valence of 5 while that of IgG is 2. The relative concentrations of antigen and antibody is of critical importance in determining the size of the resulting complex and may change rapidly depending on antigen exposure and antibody production. Antigen excess produces small complexes with limited opportunity for cross-linking because all reactive sites on the antibody are rapidly bound by antigen. At antigen-antibody equivalence the competition for available binding sites is minimal while the opportunity for cross-linking is maximal so that oligovalent antigens form large soluble complexes and multivalent antigens precipitate. At antibody excess oligovalent antigens form soluble complexes smaller than those formed at equivalence, while multivalent antigens precipitate. Thus, the complexes most likely to cause lesions are those with oligovalent antigens formed at or about antigen-antibody equivalence. That is, these are the largest complexes that remain soluble.

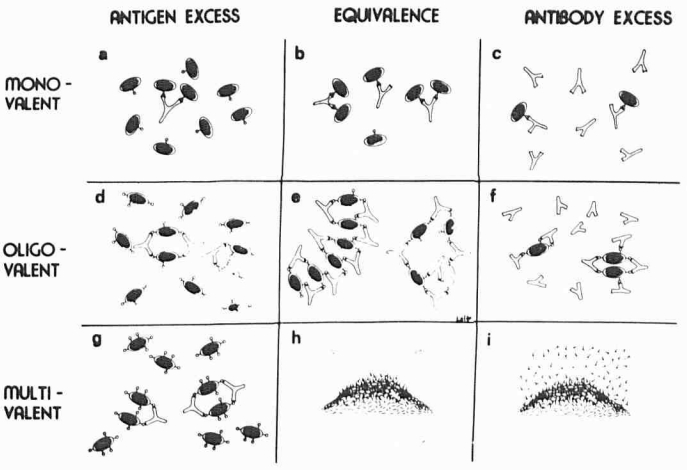

FIG 8. Schematic of the relative roles of valency and of antigen-antibody concentration on complex solubility and size. The complexes most likely to deposit in blood vessels are those with oligovalent antigens at or near antigen-antibody equivalence. See text for details. (Reproduced by permission from [26].)

Immune Complex Deposition

Of course, even a large and soluble complex may remain in the circulation unless something happens to the vessel wall to cause deposition. For instance, deposition may occur at sites of vessel bifurcation where the flow becomes turbulent, such as at the bifurcation of the renal artery and aorta in polyarteritis nodosa. Deposition may occur on the lower legs in allergic vasculitis because of the increased hydrodynamic pressure and sluggish flow, accentuated by the cooler temperature of the skin. Possibly this explains why lesions may occur recurrently on the legs without involvement of any internal organ.

An increase in vascular permeability appears likely to result in deposition of complexes and is likely due to vasoactive amines released from platelets and IgE triggered basophils [18,28]. Importantly, the histamine trap test discussed previously provides direct evidence that vasodilation, by whatever means, will likely cause circulating complexes to deposit.

Immune Complex Clearance

A third factor which would likely affect deposition of large soluble complexes is their rate of clearance. Obviously, a complex which circulates for some time has a greater chance to deposit than one that is cleared rapidly. Although this question has been addressed as discussed previously, those studies may not be quite applicable because the investigators examined clearance of labeled erythrocytes rather than immune complexes.

Another factor which may affect clearance is that the monocyte-phagocytic system may become saturated by an overwhelming amount of complexes and be physically unable to remove any more [29].

In summary, then, the specific tissue localization of a circulating immune complex is determined by a series of highly variable factors. That one of these factors is not the antigen itself is made clear by the wide qualitative and quantitative spectrum of disease expression in patients with hepatitis B antigenemia-associated vasculitis [30]. Much more likely is the nature of the individual complex and its interaction with an individual host response and its immunoregulatory mechanism, integrity of the monocyte-phagocytic clearing mechanisms, altered vascular permeability or even a genetically determined Fc receptor defect on phagocytes as proposed by Frank et al [17]. Sorting out the role of each of these in an individual patient will likely prove a formidable task.

REFERENCES

1. Price N, Sams WM Jr: Vasculitis. Dermatologic Clinics 1:475–491, 1983
2. Sams WM Jr: Necrotizing vasculitis. J Am Acad Dermatol 3:1–13, 1980
3. Fauci AS, Haynes BF, Katz P: The spectrum of vasculitis: clinical, pathologic, immunologic and therapeutic considerations. Ann Int Med 89:660–676, 1978
4. Soter NA, Sams WM Jr: Immune complexes and necrotizing vasculitis of the skin, Biochemistry and Physiology of the Skin, vol 2. Edited by LA Goldsmith. New York, Oxford University Press, 1982, pp 899–906
5. Cox AJ: Pathologic changes in hypersensitivity angiitis, The Skin. Edited by EB Helwig, FE Mostofi. Baltimore, Williams & Wilkins, 1971, pp 279–292
6. Schroeter AL, Copeman PWM, Jordon RE, Sam WM Jr, Winkelmann RK: Immunofluorescence of cutaneous vasculitis associated with systemic disease. Arch Dermatol 104:254–259, 1972
7. Sams WM Jr, Claman HN, Kohler PF, McIntosh RM, Small P, Mass MF: Human necrotizing vasculitis: immunoglobulins and complement in vessel walls of cutaneous lesions and normal skin. J Invest Dermatol 64:441–445, 1975
8. Cream JJ: Anticomplementary sera in cutaneous vasculitis. Br J Dermatol 89:555–559, 1973
9. Andrews BS, Cains G, McIntosh J, Petts V, Penny R: Circulating and tissue immune complexes in cutaneous vasculitis. J Clin Lab Immunol 1:311–320, 1979
10. Soter NA, Austen KF, Gigli I: The complement system in necrotizing angiitis of the skin. Analysis of complement component activities in serum of patients with concomitant collagen-vascular diseases. J Invest Dermatol 63:219–226, 1974
11. Kammer GM, Soter NA, Schur PH: Circulating immune complexes in patients with necrotizing vasculitis. Clin Immunol Immunopathol 15:658–672, 1980
12. Mackel SE, Tappeiner G, Brumfield H, Jordon RE: Circulating immune complexes in cutaneous vasculitis. Detection with Clq and monoclonal rheumatoid factor. J Clin Invest 64:1652–1660, 1979
13. Braverman IM, Yen A: Demonstration of immune complexes in spontaneous and histamine-induced lesions and in normal skin of patients with leukocytoclastic angiitis. J Invest Dermatol 64:105–112, 1975
14. Gower RG, Sams WM Jr, Thorne EG, Kohler PF, Claman HNC: Leukocytoclastic vasculitis: sequential appearance of immunoreactants and cellular changes in serial biopsies. J Invest Dermatol 69:477–484, 1977
15. Cochrane CG, Weigle WO, Dixon FJ: The role of polymorphonuclear leukocytes in the initiation and cessation of the Arthus vasculitis. J Exp Med 100:481–494, 1959
16. Dambuyant C, Thivolet J, Viala J-J, Ville D, Boyer J: Clearance mediated by splenic macrophage membrane receptors for immune complexes in cutaneous vasculitis. J Invest Dermatol 78:194–199, 1982
17. Frank MM, Lawley TJ, Hamburger MI, Brown EJ: Immunoglobulin G Fc receptor-mediated clearance in autoimmune diseases. Ann Intern Med 98:206–218, 1983
18. Cochrane CG, Koffler D: Immune complex disease in experimental animals and man. Adv Immunol 16:185–264, 1973
19. Mannik M, Arend WP: Fate of preformed immune complexes in rabbits and rhesus monkeys. J Exp Med 134:19–31, 1971
20. Joselow SA, Mannik M: Localization of preformed, circulating immune complexes in murine skin. J Invest Dermatol 82:335–340, 1984
21. Soter NA: Clinical presentations and mechanisms of necrotizing angiitis of the skin. J Invest Dermatol 67:354–359, 1976
22. McMahon BJ, Bender TR, Templin DW, Maynard JE, Barrett DH, Berquist KR, Lum MKW, Mann CC: Vasculitis in eskimos living in an area hyperendemic for hepatitis B. JAMA 244:2180–2181, 1980
23. Sergent JS, Lockshin MD, Christian CL, Gocke DJ: Vasculitis with hepatitis B antigenemia: long-term observations in nine patients. Medicine 55:1–18, 1976
24. Popp JW Jr, Harrist TJ, Dienstag JL, Bhan AK, Wands JR, LaMont JT, Mihm MC Jr: Cutaneous vasculitis associated with acute and chronic hepatitis. Arch Intern Med 141:623–629, 1981
25. Lambert WC, Kolber LR, Proper SA: Leukocytoclastic angiitis induced by clindamycin. Cutis 30:615–619, 1982
26. Barnett EV, Knutson DW, Abrass CK: Circulating immune complexes: their immunochemistry, detection, and importance. Ann Intern Med 91:430–440, 1979
27. Yancey KM, Lawley TJ: Circulating immune complexes: their immunochemistry, biology, and detection in selected dermatologic and systemic diseases. J Am Acad Dermatol 10:711–731, 1984
28. Henson PM: Interaction of cells with immune complexes: adherence, release of constituents and tissue injury. J Exp Med 134:114–135, 1971
29. Haakenstad AO, Mannik M: Saturation of the reticuloendothelial system with soluble immune complexes. J Immunol 112:1939–1948, 1974
30. Cochrane CG, Dixon FJ: Antigen-antibody complex induced disease, Testbook of Immunopathology. Edited by PA Meischer, HJ Muller-Eberhard. Grune & Stratton, 1976, p 137