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THE CUTANEOUS AND VISCERAL MANIFESTATIONS OF SYSTEMIC NECROTIZING VASCULITIS

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INTRODUCTION

Significant progress in the understanding of the mechanism of the various hypersensitivity reactions in man and experimental animals has been made in recent years (28). Immediate hypersensitivity reactions are initiated by the reaction of antigen with an appropriate antibody. This interaction modifies the antibody and leads to the exposure of new reactive sites, triggering a chain of secondary reactions which produce a particular biologic effect. The resultant tissue changes involve the generation and release of various mediator substances not structurally related to antibody. In the Type I, or anaphylatic reaction, mediators are derived from mast cells with IgE on their surface. In the Type III, or antigen-antibody complex reaction, they come from activation of the complement system. These complement-derived mediators focus an inflammatory response at the site of the immune reaction.

Necrotizing vasculitis is a pathologic designation reserved for those conditions with vessel wall necrosis and infiltration by polymorphonuclear leukocytes and nuclear fragments. The histologic criteria for necrotizing vasculitis are listed in Table I. (38) (87)

TABLE I

HISTOLOGIC CRITERIA FOR NECROTIZING VASCULITIS

I. PRIMARY CRITERIA (specific for necrotizing inflammation)

   a. Vessel wall necrosis with nuclear fragmentation (leukocytoclasis, "nuclear dust").

   b. Invasion of vessel wall with polymorphonuclear leukocytes.

   c. Fibrinoid deposits in or adjacent to the vessel wall.

II. SECONDARY CRITERIA (non-specific vessel injury)

   a. Thrombosis of the vessel.

   b. Perivascular hemorrhage.

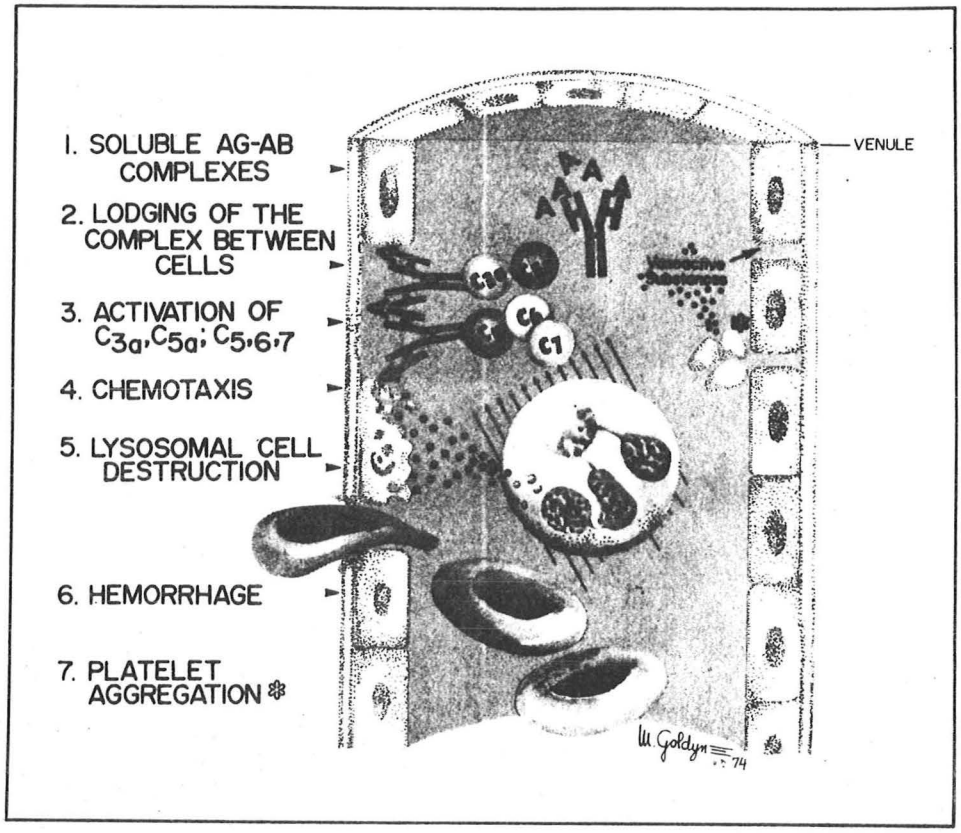
   c. Chronic granulomatous inflammation and fibrosis in perivascular areas.

The earliest and most direct light microscopic evidence of this type of vessel wall injury is the presence in vessel walls of fragmented nuclei, a change which is known as karyorrhexis or leukocytoclasis (16). This finding when associated with an accumulation of intact polymorphonuclear leukocytes in or about the affected vessels is a reliable sign of necrotizing inflammation (38). Since nuclear fragmentation, or leukocytoclasis, is a characteristic feature of this reaction in the skin, the term leukocytoclastic vasculitis has been used for cutaneous (small vessel) necrotizing vasculitis (175) (16). The cutaneous site that seems most vulnerable to this lesion is the post capillary venule (36), (160).

There is reasonable evidence that this inflammatory process is initiated by the subendothelial deposition of antigen-antibody complexes which are derived from the circulation (17) (27) (41) (152) (162). If these immune complexes are able to activate the complement system, then chemotactic complement factors will attract PMN leukocytes which, during phagocytosis release proteolytic enzymes and other inflammatory proteins, causing vascular necrosis (28) (154) (38). Thus, complement derived mediators mobilize and focus

this PMN leukocyte dependent inflammatory response in vessel walls, the site of immune complex deposition. Necrotizing vasculitis is an example of an immune-complex mediated disease or a Type III immediate hypersensitivity reaction. The details of this reaction are depicted schematically in Figure I. (154).

FIGURE 1



(taken from ref. 124)

Recent clinical and experimental data suggest that circulating soluble antigen-antibody complexes may cause little or no difficulty unless vascular permeability is altered (28-32). Cochrane and Koffler (28) have shown that IgE may be important in the deposition of circulating complexes by triggering mast cells to release vasoactive amines. In experimental serum sickness in the rabbit, these substances increase vascular permeability so that immune complexes can diffuse into the vessel wall. If these complexes are large (> 19S), they become lodged between the endothelial cell and the vascular basement membrane. Complement is then activated with the generation of leukotactic (C5 and C567) and vasoactive (C3a and C5a) factors. Polymorphonuclear leukocytes are attracted, begin to remove the complexes by phagocytosis and release their lysosomal enzymes. This leads to vessel wall necrosis, hemorrhage, platelet aggregation, coagulation with fibrin deposition, and in some instances thrombosis and ischemic necrosis.

Platelet aggregation also seems to be an important initiating event in this sequence since a vasoactive agent, possibly serotonin, is released from activated platelets. Platelet activation may occur secondary to hemodynamic forces, minor trauma, or a platelet activating factor released by the interaction of antigen with IgE on the surface of basophils (29). This may explain the observation that certain vasculitic lesions occur at sites of trauma, near vessel branch-points where irregularities in flow dynamics are encountered or on the lower extremities where hemodynamic forces are increased.

The main purpose of this review is to discuss the various forms of systemic necrotizing vasculitis, emphasizing those diseases most often associated with vasculitis in the skin.

CLASSIFICATION OF NECROTIZING VASCULITIS

Zeek (178) was the first to recognize that the anatomical distribution of necrotizing vascular lesions is related to the size of the blood vessels involved. Zeek's classification, shown in Table II, continues to be a valuable basis for the pathologic identification of the clinical syndromes within the spectrum of systemic vasculitis.

TABLE II

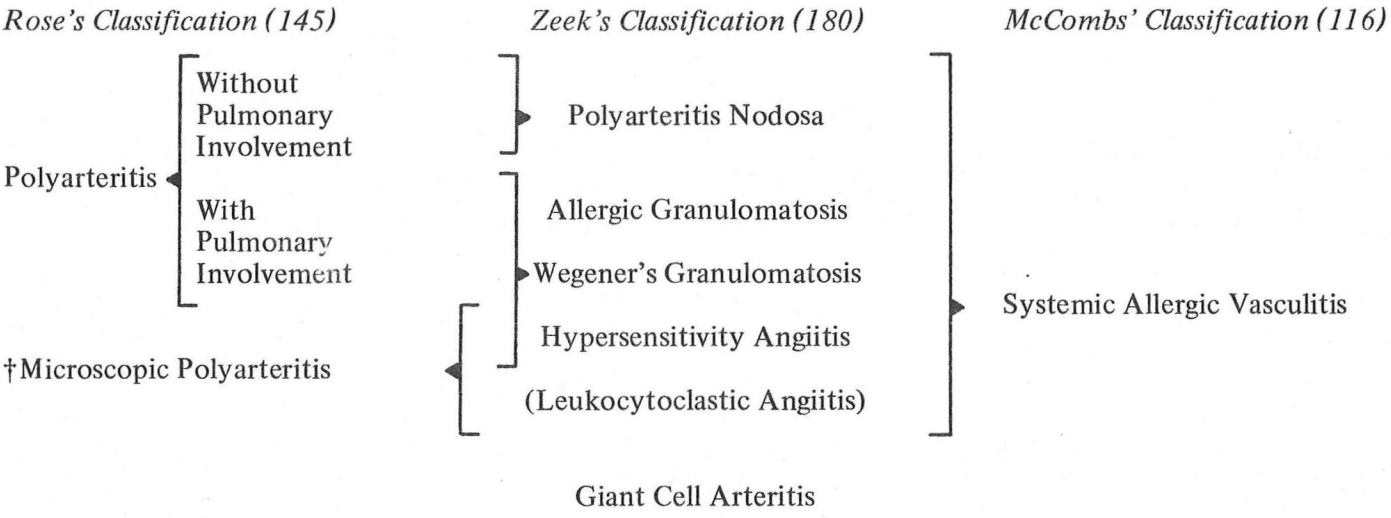
ZEEK'S CLASSIFICATION OF NECROTIZING VASCULITIS

I. Hypersensitivity Angiitis
II. Allergic Granulomatosis
III. Wegener's Granulomatosis
IV. Polyarteritis Nodosa
V. Giant Cell Arteritis

For several reasons, however, this classification has not been universally accepted. First, in clinical practice it is often difficult or impossible to obtain adequate tissue from visceral sites to classify the disease according to these pathologic criteria. In addition, distinct clinical subsets of these major categories have been recognized and given separate names. Also, vasculitides secondary to various rheumatic diseases are not included. Finally, other classifications based on certain constellations of clinical and laboratory features have been used, causing much overlap and duplication of terms. Table III illustrates this overlap in terminology (4) (75) (116) (117) (145) (180).

TABLE III

OVERLAP OF SCHEMA FOR THE CLASSIFICATION OF NECROTIZING ANGIITIS



Based on a review of the following studies:

Rose, GA. Natural History of Polyarteritis. *Brit. Med. J.* 2:1148, 1957 (ref 145).
Zeek, PM. *NEJM* 248:764, 1953 (ref 180).
McCombs. Systemic Allergic Vasculitis. *NEJM* 284:262, 1971 (ref 116).
† Goldberger. *Am. J. Cardiol.* 3:656, 1959 (ref 75)

Rose (145) divided cases of polyarteritis into two groups: (1) those without and (2) those with pulmonary involvement. In those without lung involvement, severe renal disease and hypertension were common. This group seems to coincide with the classic form of periarteritis nodosa, a disease of muscular arteries (100). Those with pulmonary involvement usually had a respiratory disorder at the onset, commonly

had eosinophilia and rarely had hypertension. In general, these patients had a disease involving small vessels similar to allergic granulomatosis of Churg and Strauss (25), Zeek's hypersensitivity angiitis (179) or Allen's allergic angiitis (4). Other patients in this group probably had Wegener's granulomatosis. Goldberger (75) used the term microscopic polyarteritis in reference to cases with small vessel disease which corresponded, for the most part, with Zeek's hypersensitivity angiitis. McCombs simply called all cases of necrotizing vasculitis, systemic allergic vasculitis (116).

For the purpose of this review, I have chosen a modification of Zeek's classification which was recently devised by Dr. Chester Fink (59). I believe this improves upon some of the above mentioned shortcomings. Table IV gives this classification.

TABLE IV
NECROTIZING VASCULITIDES

I. LEUKOCYTOCLASTIC VASCULITIS (Hypersensitivity angiitis or Allergic Vasculitis)
   - A. Schonlein-Henoch Purpura
   - B. Hypocomplementemic vasculitis
   - C. Essential mixed cryoglobulinemia
   - D. Other disease-related dermal vasculitides

II. RHEUMATIC VASCULITIS
   - A. Systemic lupus erythematosus
   - B. Rheumatoid vasculitis
   - C. Scleroderma
   - D. Dermatomyositis
   - E. Acute Rheumatic Fever

III. GRANULOMATOUS VASCULITIS
   - A. Churg and Strauss Allergic Granulomatous Angiitis
   - B. Wegener's granulomatosis
   - C. Limited Wegener's

IV. POLYARTERITIS NODOSA
   - A. Classic type
   - B. Limited type (skin and muscle)
   - C. Hepatitis B antigen associated vasculitis
   - D. Vasculitis in drug addicts
   - E. Vasculitis following serous otitis media

V. GIANT CELL ARTERITIS
   - A. Temporal arteritis
   - B. Polymyalgia rheumatica
   - C. Takayasu's disease

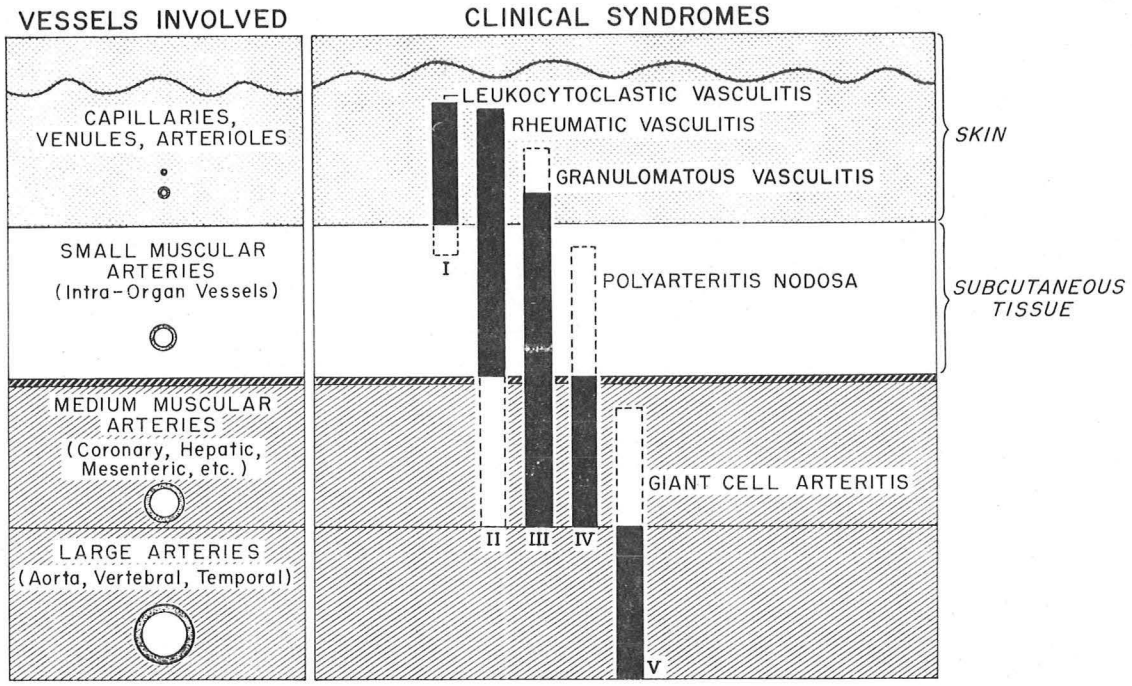
In this classification the term leukocytoclastic vasculitis is used for the small vessel disease which corresponds to hypersensitivity angiitis of Zeek. Allergic granulomatosis of Churg and Strauss and Wegener's granulomatosis have been listed together as subtypes of granulomatous angiitis and a new grouping, vasculitis associated with the rheumatic diseases, has been added.

DERMATOLOGIC MANIFESTATIONS OF NECROTIZING VASCULITIS

Most students of systemic vasculitis have been preoccupied with internal lesions and have neglected the skin lesions which characterize certain forms of vasculitis. Since changes in the skin are easily observable and biopsy is a simple procedure, the skin offers an ideal opportunity to obtain the pathological data needed to classify a given patient's disease. Figure 2 illustrates the different sizes of blood vessels affected by five types of systemic vasculitis and their location in the skin.

FIGURE 2

THE LEVEL OF CUTANEOUS INVOLVEMENT BY THE NECROTIZING VASCULITIDES



The solid vertical bars define the usual site of the primary cutaneous pathology for each type of vasculitis. The open bars indicate sites of occasional involvement. From inspection of this diagram several points are immediately obvious. First, giant cell arteritis never involves vessels of the skin or subcutaneous tissue; therefore, it will not be further discussed in this review of cutaneous manifestations of vasculitis. Polyarteritis nodosa (PAN) rarely involves the dermis, but may occasionally affect vessels in the subcutaneous tissue. The granulomatous vasculitides commonly involve the subcutaneous tissue and may produce dermal lesions as well. And finally, leukocytoclastic vasculitis is principally a dermal vasculitis. This simple scheme becomes clinically useful when one learns to predict the site of the primary vascular pathology by examining the gross morphology of the skin lesions. Table V lists the morphologic features of the most common skin lesions in these different vasculitis syndromes.

TABLE V

RELATIONSHIP BETWEEN THE VASCULITIS SYNDROMES AND THE MORPHOLOGY OF THE SKIN LESIONS

VASCULITIS SYNDROME	SKIN LESIONS
I, II Leukocytoclastic or dermal vasculitis	Purpuric papules, superficial erosions, hemorrhagic bullae, cutaneous infarcts
IIIa Allergic granulomatosis	Erythematous nodules, ulcerative nodules (deep ulcers), ecchymoses, plaques and purpuric papules
IIIb Wegener's granulomatosis	Ulcerative nodules, peripheral gangrene
IV. Polyarteritis nodosa	Subcutaneous nodules (occasionally pulsatile), livedo reticularis with nodules and ulceration, peripheral gangrene and large deep ecchymoses

The most distinctive clinical feature for diagnosis of cutaneous necrotizing (leukocytoclastic) vasculitis is the presence of purpuric papules on the distal part of the lower extremities (16) (27) (175). These purpuric lesions usually appear in crops and tend to evolve in tandem over the course of several days. Yellow-brown macules remain for some time after the active lesions disappear. When the process is more severe, hemorrhagic bullae, superficial erosions or depressed irregular cutaneous infarcts are present (175).

The skin lesions of the granulomatous forms of necrotizing vasculitis and polyarteritis are usually nodular (21) (149) (154) (158). Early lesions may resemble erythema nodosum or some other form of panniculitis. In granulomatous vasculitis these nodules often become necrotic and ulcerate, changes that do not occur in erythema nodosum. In addition to nodular lesions, dermal involvement characterized clinically by purpuric papules may also be present. Any combination of ulcerative nodules and purpuric papules suggests a granulomatous vasculitis. In general, vasculitides of larger and deeper vessels produce a greater variety of skin lesions. In contrast to leukocytoclastic vasculitis, the lesions of granulomatous vasculitis and polyarteritis are in all stages of development. Although fewer in number, the lesions are usually larger and more destructive. Ulceration is common in granulomatous vasculitis. Biopsies of these lesions show a granulomatous vascular pathology which is compatible with Wegener's or allergic granulomatosis (21) (24). The presence of large numbers of eosinophils is more characteristic of allergic granulomatosis (55). In PAN small and medium sized muscular arteries of the subcutaneous tissue are involved with sparing of the dermal blood vessels (38).

Palpable purpuric lesions are the hallmark of dermal inflammatory vascular disease (16). These purpuric lesions may be papules, pustules, hemorrhagic vesicles, bullae or cutaneous infarcts. In addition to immune complex deposition, septic processes can induce similar or identical vasculitic lesions, but differentiation on clinical grounds is usually possible. In general, the skin lesions of sepsis are often pustular, fewer in number, asymmetrically arranged and located on the distal aspects of upper as well as lower extremities. In contrast, the lesions of immune complex mediated dermal vasculitis are usually more numerous and appear in crops that are arranged in a symmetrical manner mainly on the lower extremities.

In addition to vasculitis, a list of the differential diagnostic possibilities for deep dermal or subcutaneous nodular lesions is shown in Table VI. A biopsy which includes ample subcutaneous tissue can be extremely helpful in making the diagnosis and should always be done.

TABLE VI

NON-VASCULITIC NODULAR SKIN LESIONS

Erythema nodosum	Sarcoidosis
Thrombophlebitis	Lymphoma
Subcutaneous abscess	Metastatic Cancer
Panniculitities Lupus profundus (Lupus panniculitis) Pancreatitis Weber-Christians' disease	Histiocytoma

DERMAL NECROTIZING (LEUKOCYTOCLASTIC)VASCULITIS

Dermal necrotizing vasculitis and leukocytoclastic angiitis are generic terms which imply small vessel necrotizing vasculitis (175). Hypersensitivity angiitis (179), allergic vasculitis or angiitis (4) (117) and cutaneous-systemic vasculitis (16) are other names which have been used for this purpose. In addition, a similar pathologic change is seen in the skin of patients with anaphylactoid or Schonlein-Henoch purpura, hypocomplementemic vasculitis (118) (159), essential mixed cryoglobulinemia (122) (168) and in some patients with benign hyperglobulinemic purpura (102).

Leukocytoclastic angiitis affects small cutaneous and visceral blood vessels, usually less than .1 mm in diameter (38). Skin involvement is very common and is often the only site where angiitis is recognized. Usually the skin lesions first appear on the lower extremities as flat or slightly elevated erythematosus to urticarial areas which progress to purpuric papules. As mentioned, the palpable quality of these lesions is an important feature since this distinguishes them from various non-inflammatory forms of purpura. The skin lesions are concentrated in areas of dependency. The disease may be limited to the skin or there may be systemic involvement of joints, kidneys, lungs and the gastrointestinal tract. Table VII gives the frequency of

organ involvement in 5 studies. The figures vary considerably from study to study; it is clear however, that the most common sites of involvement are skin, kidneys and joints. Notice that in the series collected at autopsy, renal involvement was 100%. These studies have given the false impression that this form of small vessel vasculitis is commonly associated with severe, often fatal, renal disease. That this is not the case is shown by the lower incidence of renal disease in patients studied during life.

TABLE VII

MANIFESTATIONS OF LEUKOCYTOCLASTIC ANGIITIS

Series	Knowles and Zeek† (100)	O'Duffy et al.† (132)	Winkelmann and Ditto* (175)	McCombs*(*) (116)	Wilkinson* (174)	Avg. (%)
Number of Patients	10	11	36	72	23	
Organ involvement (percent)						
Lungs	40	55	20	30	Δ	36
G.I. Tract	40	55	15	10	22	28
Nervous System	50	64	20	25	0	32
Skin	**40**	**45**	**100**	**50**	**100**	**67**
Joints	**20**	**45**	**50**	**50**	Δ	**41**
Kidneys	**100**	**100**	**60**	**30**	**38**	**66**
Heart	10	64	0	0	0	15

(Modified from Braverman, 1970)

†Autopsy study.
*Studied during life.
(*)Seventeen of seventy-two patients had periarteritis nodosa. Organ involvement in two varieties of angiitis not separated in paper.
ΔOrgans affected but frequency not stated.

Leukocytoclastic vasculitis may follow an upper respiratory infection or the administration of drugs, although the specific antigen which triggers the process is usually unidentifiable. Case I is an example of drug induced leukocytoclastic vasculitis.

> **CASE I: (L.S., PMH No. 35 69 80)** L.S., a 54 year old white woman was admitted to the medical services in November, 1970 with complaints of joint aches, fever and a "purple rash" on the lower extremities. These symptoms had begun a week before admission. She had not had any respiratory tract symptoms, abdominal pain or evidence of renal disease. Eighteen months previously atrial fibrillation and thyrotoxicosis were diagnosed and she was placed on propylthiouracil, Ismelin, phenobarbital, digitalis, Naqua and KC1.
>
> On admission to the hospital her temperature was 101.2°, blood pressure 154/60 and pulse 100 and irregular. A purpuric rash covered her buttocks and distal lower extremities. Both ankles were red, warm and painful. Her shoulders were tender on palpation.
>
> **Laboratory work** included a WBC of 4600 with a normal differential; a Hgb of 11.3 gm; an ESR of 50 mm/hr; a platelet count of 250,000/mm^3; a normal urinalysis on two occasions; a negative Latex and ANA test; a total hemolytic complement (CH50) of 40U (normal 60U); cryoglobulins were not present; the stool guaiac was repeatedly negative.
>
> The digitalis and Ismelin were continued but all other drugs were stopped and the patient had a striking improvement in her rash, arthritis and fever.

Schonlein-Henoch or anaphylactoid purpura is a special form of leukocytoclastic vasculitis that has become established as a distinct subtype. The frequency and site of internal involvement is similar to that seen in other varieties of leukocytoclastic vasculitis. Any age may be involved (9) (40) (161) but children are more likely to have anaphylactoid purpura with a peak incidence from 4 to 8 years of age (6). The disease most often occurs in the spring and it is frequently preceded by an upper respiratory tract infection. The usual duration of the illness is from 6 to 16 weeks. Between 5-10% of patients recover only to relapse weeks or

months later (66). Such patients with persistent or recurrent disease may develop significant renal impairment. Renal involvement undoubtedly poses the most serious threat to the patient; however, the disease is usually self-limited, requiring only supportive care. The prognosis is determined mainly by the presence or absence of glomerulonephritis. Renal involvement may be more severe in adults as suggested by the data in Table VIII (9).

TABLE VIII

ORGAN INVOLVEMENT BY VASCULITIS OF SCHONLEIN-HENOCH PURPURA AND PROGNOSIS OF THE RENAL LESION

SERIES	Cream et al (40)	Ballard et al (9)	Ansell, B.M. (6)
Number of patients	77 Adults	14 Adults	75 Children
Organ involvement (%)			
Lungs	7	–	–
G.I. Tract	45	50	61
Nervous System	–	–	3
Skin	**100**	**100**	**100**
Joints	**55**	**100**	**74**
Kidneys	**49**	**100**	**47**
Heart	–	43	–
Mortality			
With renal involvement	4	28	8
Overall incidence	4	28	4

The classical triad which occurs in up to 60% of cases of Schonlein-Henoch purpura includes purpura, arthritis and abdominal pain (40) (175). The arthritis is transient and usually affects the knees and ankles. Gastrointestinal lesions may cause severe cramping abdominal pain, intussusception, hemorrhage, protein-losing enteropathy, or rarely, perforation (60) (83) (161) (107).

The histological evidence of a generalized small vessel vasculitis with clinical features of polyarthritis and nephritis supports the current view that the Schonlein-Henoch Syndrome is an immune complex disease. Immunofluorescence studies have shown gammaglobulin and complement in cutaneous blood vessels and in the kidney (86) 181) although serum complement (C3) levels are characteristically normal.

Recent observations have provided a better understanding of the pathogenesis of this syndrome. By immunofluorescence, IgA is the most abundant and sometimes the only immunoglobulin in the skin and kidney (86) (53). In two cases of Schonlein-Henoch purpura congenital absence of the second complement component, C2, has been described (67) (163), indicating that the disease can occur without an essential early component of the classical complement pathway. IgA can only activate complement by the alternative complement pathway (81). Since complement activation is necessary for the chemotaxis of the PMN leukocytes which infiltrate these lesions, activation of the alternative pathway by IgA antibody-antigen complexes is probable. The reason that vascular deposits of IgA occur so commonly in the Schonlein-Henoch syndrome may be related to the fact that upper respiratory infections often precede this type of vasculitis and antigen entering by this route would be expected to encounter IgA antibody. Case II is a typical example of the Schonlein-Henoch Syndrome.

Case II (R.L.D. PMH No. 28 97 31) This 17 year old white man was in good health until 36 hours prior to admission when he developed a pruritic red rash on both ankles and the dorsal surface of his feet. On the day of admission he noticed pain and swelling of his elbows and pain with motion of the MCP and PIP joints of both hands. From the time of onset until admission, the rash gradually extended to above his knees. He experienced no abdominal pain or diarrhea. He denied dysuria, hematuria or uretheral discharge. He had not had a similar skin rash or joint symptoms previously.

Ten days prior to admission he had a sore throat with fever that lasted three to four days. During that time he took several "Listerine cold tablets" and aspirin for relief of symptoms.

The past medical history was unremarkable. There was no history of drug allergy or atopy. Other family members were in good health except for a sister with rheumatic heart disease.

On **physical examination** his blood pressure was 130/60, pulse 80 and regular and he was afebrile. The skin of his ankles, dorsal aspect of his feet and extensor surface of his legs to the mid-thigh were covered by numerous 2 to 10 mm elevated purpuric papules. There were no nodules, vesiculobullous or infarctive lesions. The oral and nasal mucous membranes appeared normal. There was no conjunctival or scleral inflammation. The heart, lungs and abdomen were normal. There was tenderness, swelling and limitation of motion of both elbows and knees. Neurological examination was normal.

Laboratory findings were as follows: WBC 14,200; ESR 35 mm/hr; streptococcal organisms were cultured from the throat. The following were normal or negative: Hgb, urinalysis, electrolytes, BUN, creatinine, stool guaiac, serum complement and LFT's. Skin biopsy revealed changes of a leukocytoclastic angiitis involving upper dermal blood vessels, findings typical of the Henoch-Schonlein Syndrome.

After an uneventful hospital course marked by progressive improvement in joint pain and resolution of the skin rash, he was discharged. Follow-up urinalysis before discharge was normal. Two days after discharge he was seen in the emergency room with cramping abdominal pain of 14 hours duration. Stool guaiac was negative and urinalysis was again normal. There was no recurrence of the skin rash. Following a period of observation he improved and was sent home. The abdominal pain subsided the next day and he has had no further symptoms.

Hypocomplementemic vasculitis, initially described by McDuffie and coworkers (118) in 1973, is a second variant of leukocytoclastic vasculitis. This form of cutaneous vasculitis is characterized by recurrent erythematous urticaria-like lesions, arthritis and marked hypocomplementemia. Biopsy of the skin shows leukocytoclastic vasculitis similar to the Schonlein-Henoch Syndrome although the skin lesions appear more urticarial (159).

Immunoglobulin and C3 are present in the blood vessels of samples taken from early lesions. Some patients have glomerular immunoglobulin deposits and a mild glomerulitis. Abdominal pain may be a major feature of this type of vasculitis. Facial and laryngeal edema similar to that seen in hereditary angioedema have been observed. The clinical course is prolonged and relatively benign. Hypocomplementemic vasculitis must be differentiated from hereditary angioedema, mixed cryoglobulinemia and systemic lupus erythematosus. Case III illustrates the clinical manifestations of hypocomplementemic vasculitis.

CASE III: (D.P. DMSC No. 06 82 61 7) D.P., a 17 year old high school student, developed a rash and intermittent swelling of the feet in March, 1974. He also noticed swelling of the hands, the first MCP and PIP joints and one wrist. He had transient and intermittent pain and swelling of elbows, knees and ankles. These attacks became recurrent, lasting 1 to 2 days, with 2-3 attacks per month. During these episodes he developed scattered urticarial-like lesions over the trunk and extremities and diffuse swelling of his hands and feet.

Pertinent findings on **physical examination** were as follows: His blood pressure was 128/50, pulse 65 and regular, respiratory rate 16 per minute. There were numerous 1-2 cm raised erythematous papules and plaques on the thighs and lower abdomen. Some of these showed areas of purpura. Several macular pigmented areas were present at sites where lesions had resolved.

Numerous laboratory tests were normal or negative. However, he had a persistently low serum complement (both CH50 and C3). Prednisone, 20 mg per day, and Periactin, 4 mg q6h has partially controlled his disease.

A third distinct form of leukocytoclastic vasculitis is the syndrome of purpura, arthralgia, weakness and *mixed cryoglobulinemia*, described first by LoSpalluto and associates (109) and later by Meltzer and coworkers (122). Patients with this syndrome generally have widespread vasculitis and often develop severe glomerulonephritis (122). Immune deposits containing complement have been demonstrated in vessel walls (39) (124) and along the glomerular basement membrane (76). Most mixed cryoglobulins contain IgG and IgM. The IgM component has anti-IgG, or rheumatoid factor activity (113). Patients with this syndrome have recurrent episodes of purpura, usually involving the lower extremities, with arthralgias and slight to moderate hepatosplenomegaly and lymphadenopathy. Many have rheumatoid factor against human IgG with a positive RA latex test. This antiglobulin antibody is often unreactive with rabbit IgG so that the SSCA test is negative. Moderate anemia, hyperglobulinemia, positive antinuclear antibody tests and hypocomplementemia are often present. Diffuse glomerulonephritis may lead to terminal renal failure. The clinical and histologic picture can be identical to the Schonlein-Henoch Syndrome. However, the cryoglobulinemia, positive rheumatoid factor test and low serum complement level make the distinction between these two possibilities relatively simple. Distinguishing this syndrome from SLE, however, may be more difficult. The absence of characteristic LE skin lesions and of antibodies to native DNA aids in making this distinction. Rheumatoid arthritis, lymphoma, Sjogren's syndrome, thyroiditis, cirrhosis, primary biliary cirrhosis and renal tubular acidosis have been associated with this syndrome and these must be excluded. Mixed cryoglobulinemia can also be seen in a

number of other chronic diseases. The relative frequency of this association is shown in Table IX. Case IV, is a patient seen at Parkland who had end-stage cirrhosis and symptoms from an associated mixed cryoglobulinemia.

TABLE IX

DISEASES ASSOCIATED WITH MIXED CRYOGLOBULINEMIA (169)

Diagnosis (120 cases)	Percent
Purpura-Arthralgia syndrome (Essential mixed cryoglobulinemia)	17
Systemic Lupus Erythematosus	18
Juvenile rheumatoid arthritis	10
Connective tissue diseases	9
False-positive serology	9
Syphilis	8
Infectious mononucleosis and CMV*	7
Bacterial infections	8
Other diseases: Lymphoma, thyroiditis, cirrhosis, primary biliary cirrhosis, renal tubular acidosis, Sjorgren's syndrome, glomerulonephritis	15

*cytomegalovirus infection

From Wagner, O. and J.A. Rasanen, 1970 (Ref. 169)

CASE IV: (M.S. PMH No. 49 44 01) M.A., a middle aged chronic alcoholic Mexican man, was admitted to the medical service in January, 1975 with the following problems: (1) A "wine-colored" rash on his ankles and feet for three weeks; (2) arthralgias for 3 weeks; (3) Yellow eyes and dark urine intermittently since May, 1974; and (4) Abdominal swelling and dependent edema for 3 to 4 months. He had a purpuric rash on his legs and feet, a markedly elevated sedimentation rate, abnormal liver chemistries, hematuria with granular cast, azotemia and anemia. Shortly after admission he developed hepatic encephalopathy. Blood cultures were positive for Klebsiella. He was given a number of antibiotics, IV fluids and lactulose and after several days regained consciousness. Additional laboratory work showed a negative RA latex; positive antinuclear; negative LE test; a cryoglobulin of 138 mg% which contained IgG, IgA and IgM; a low C3 (18 mg%); ESR 120 mm/hr; negative Coombs test; and a platelet count of 78,000.

A skin biopsy was diagnostic of a small vessel (leukocytoclastic) vasculitis. Immunofluorescent staining of the biopsy tissue revealed staining of dermal vessels for IgM and IgA.

The patient's condition stabilized and he was discharged to return to Mexico City.

In some of these diseases listed in Table IX, the pathologic significance of the cryoglobulin is unclear; it probably represents a circulating immune complex that may or at times may not be detrimental. The laboratory and clinical features of these secondary mixed cryoglobulinemias are usually distinctive enough to avoid confusion with the idiopathic forms of leukocytoclastic vasculitis.

Cutaneous leukocytoclastic vasculitis has also been reported in association with a heterogeneous group of systemic diseases in the absence of cryoglobulinemia (45-52). These are listed in Table X. Skin vasculitis is an uncommon feature of all these diseases, and if present, one should strongly consider that the vasculitis is due to drug hypersensitivity and not to the disease. However, a complete differential diagnosis should include

these possibilities in an evaluation of a patient with leukocytoclastic vasculitis. Case V is an example of cutaneous vasculitis associated with one of these diseases. In this case drug hypersensitivity seemed unlikely.

TABLE X

SYSTEMIC
DISEASES ASSOCIATED WITH LEUKOCYTOCLASTIC VASCULITIS

1. Subacute bacterial endocarditis (91)
2. Benign hyperglobulinemic purpura (79) (102)
3. Sjogren's Syndrome (173)
4. Chronic active hepatitis
5. Ulcerative colitis (see case V) (61)
6. Malignant lymphomas (153)
7. Retroperitoneal fibrosis (84) (88)
8. Primary biliary cirrhosis
9. Goodpasture's Syndrome (172)

CASE V: (R.R. PMH No. 08 79 77) R.R., a 19 year old black man, was admitted to the PMH surgery service for rectal bleeding on 5-6-72. Eight days before admission he developed a purpuric eruption on his lower extremities along with diarrhea and polyarthralgia. In August, 1971, he developed arthritis of the knees and ankles which was associated with chronic diarrhea and a urticarial rash. He was found to have ulcerative colitis and was treated with Azulfidine until December, 1971 when he voluntarily discontinued the drug.

The pertinent findings on **physical examination** were a temperature of 99°F, a papular (slightly palpable) purpuric eruption on his lower extremities and moderate generalized adenopathy. There was no evidence of frank arthritis. The abdomen was diffusely tender but there was no organomegaly.

Laboratory Findings: The following laboratory values were obtained: Hbg 10 gm%; WBC 13,500; platelets 40,000; stool guaiac 4+ positive; Coombs negative; C3 135 mg% (normal); cryoglobulins negative; amylase 640 units; gamma globulin 2.9 gm%. Urinalysis and tests of renal function were normal. The ANA test and LE preps were negative. A bone marrow revealed slight hyperplasia of all elements and normal numbers of megakaryocytes. Skin biopsy showed a small vessel (leukocytoclastic) vasculitis of the Henoch-Schonlein type.

Treatment and Course: He was given prednisone initially 100 mg/day, with resolution of his symptoms and return of the blood tests to normal. He was again placed on Azulfidine for control of his ulcerative colitis. However, in September, 1972 the Azulfidine was discontinued and two weeks later he again developed diarrhea, purpura, arthralgia and thrombocytopenia.

RHEUMATIC VASCULITIS

The necrotizing vasculitis that occurs in the rheumatic diseases can affect small capillaries, venules, larger veins and small to medium sized muscular arteries. This accounts for the wide range of clinical features attributed to this complication. It also explains why the diseases in this group tend to share many clinical features with both leukocytoclastic vasculitis and polyarteritis nodosa. Indeed, vasculitis is one of the factors linking this group of diseases by producing overlapping clinical findings. Dermal vasculitis involving small blood vessels, although seen in several of the rheumatic diseases, is most common in SLE and rheumatoid arthritis.

Ten to 20% of patients with SLE develop dermal vasculitis at some time during the course of their illness (51) (164). This is manifested clinically as cutaneous infarcts or small purpuric papules on the lateral aspect of the finger tips, around the ankles, feet, toes or elbows. These lesions often are linear, depressed, purple to black in color, and few in number. If present, they suggest widespread small vessel vasculitis and provide a bad prognostic sign since they are often accompanied by vasculitis in visceral areas (57) (123). These small vessel lesions tend to coexist with lesions of larger vessels so that a triad of purpuric digital infarcts, cutaneous ulcers

and distal gangrene may be found (133). Various vascular syndromes including cutaneous vasculitis, Raynaud's phenomenon, aseptic necrosis of bone, peripheral arterial occlusion, chronic leg ulcers, recurrent thrombophlebitis and livedo reticularis tend to occur either at different times or simultaneously during the course of the illness in the same patients (3) (99). An example of the striking clinical similarity between widely different multisystem diseases that have circulating immune complexes is provided by the splinter hemorrhages (62) and Osler's nodes (150) which may be seen in active SLE with vasculitis and polyarteritis (157) or in bacterial endocarditis and other chronic infections.

Chronic and/or recurrent leg ulcers are occasionally the principal manifestation of lupus vasculitis (8) (43) (80) (97). The ulcers are usually located over the pretibial and malleolar areas and are similar to those seen in rheumatoid arthritis. Other manifestations of vasculitis are usually present in these patients.

Peripheral gangrene is an infrequent but well documented manifestation of lupus vasculitis (23). The gangrene commonly has an insidious onset with symptoms of coldness and tenderness of the tips of the digits. This is followed by persistent cyanosis, more severe pain and dry gangrene. Histologic changes of a chronic necrotizing vasculitis of the digital arteries are found on microscopic examination of specimens that have been surgically removed.

Like the visceral manifestations, the dermatologic features of rheumatic vasculitis also overlap with both leukocytoclastic vasculitis and polyarteritis nodosa. In some SLE patients a clinical syndrome mimicking polyarteritis nodosa is seen (108) (155) while in others the picture is more like leukocytoclastic vasculitis (35) (40). Case VI demonstrates some of these clinical features.

CASE VI: (M.Z., PMH No. 49 50 63) M.Z., a 27 year old Latin American woman, was admitted to the Parkland medical services in January, 1975 for evaluation of the following problems: (1) active arthritis; (2) an enlarging ulcer on the left calf which appeared 6 months earlier; (3) increasing proteinuria; (4) dyspnea and (5) persistent pneumonitis. She gave a history of rheumatic fever at age 12 and for 12 years thereafter she had intermittent arthralgias. Three years before this admission she had an episode of severe polyarthritis with a recurrence two years later which was accompanied by a deep red rash on her legs. During the three months prior to admission she became dyspneic and orthopneic. One month before admission she was seen at another hospital for treatment of "pneumonia." Since she continued to do poorly following antibiotic treatment she was referred to Dr. Eric Hurd for further evaluation.

On **physical examination** she was pale and slightly dyspneic. Her temperature was 98.8; pulse 100 per min.; respirations 28 per min.; and blood pressure 120/70. There was dullness and rales at both lung bases, and signs of consolidation on the right. The PMI was diffuse in the sixth intercostal space at the anterior axillary line. There was a right ventricular lift; a III/VI mid-systolic murmur at the base and along the left sternal border, a non-radiating holosystolic regurgitant murmur and a low pitched diastolic murmur at the apex. There was a prominent S3 gallop. Leg edema was present bilaterally. All peripheral pulses were palpable. A large ulcer was present on the inner aspect of the left calf. Bilateral small, freely movable subcutaneous nodules were present just distal to the elbows. Several purpuric papules were scattered around the knees and ankles. The hands showed rheumatoid-like deformities.

Laboratory Findings: At the time of admission the chest x-ray showed marked cardiomegaly, with a right lower lobe infiltrate, fluid in the minor fissure and small bilateral pleural effusions. The ESR was 94 mm/hr.; the ANA test was 4+ positive at a titer of 1:2560 (speckled pattern); the RA latex was 3+ positive and the SSCA test was positive at 1:128. Three LE preps were positive and cryoglobulins were negative on two occasions. The total hemolytic complement was low (15 U, normal 60 U). The ENA antibody test was negative. A 24 hour urine contained 2.3 gm% of protein and the creatinine clearance was 64 ml/minute.

A percutaneous renal biopsy was attempted but insufficient tissue was obtained for evaluation. A skin biopsy was interpreted as showing a necrotizing vasculitis. Immunofluorescent staining of both lesional and normal skin showed IgM and C3 deposits in dermal vessels and at the dermal-epidermal junction.

The histological features of lupus vasculitis are characterized by prominent fibrinoid deposits in vessel walls. These lesions often differ from the typical lesions of leukocytoclastic vasculitis by the relative lack of cellular infiltration (38). As was observed in Case VI, immunofluorescent staining of biopsies from both lesional and nonlesional skin of patients with SLE vasculitis frequently shows immunoglobulin and C3 deposited in dermal blood vessel walls. This immunoglobulin in vessel walls in uninvolved skin correlated with both dermal and visceral vasculitis.

In contrast, immunoglobulin deposits at the dermal-epidermal junction of uninvolved SLE skin is not related to LE skin disease or vasculitis (70). Skin from areas of involvement also frequently has immune deposits in the vicinity of the dermal-epidermal junction (165); however the lymphocytic character of the infiltrate in these LE skin lesions, the absence of immune deposits in early lesions and the occurrence of deposits in otherwise normal skin make immune-complex mediated injury in such LE-specific skin lesions unlikely. In contrast, the histologic and immunopathologic features of the necrotizing vascular skin lesions,

which are not specific for SLE, suggest that they are probably a manifestation of vascular localization of toxic immune complexes.

Evidence for the mediation of SLE renal disease by circulating immune complexes containing DNA and antibody to DNA is well known. Recent data suggest that certain functional or physical properties of DNA antibodies of different immunoglobulin classes may be related to discrete manifestations of SLE (47) (68) (94) (137). The size of the immune aggregate as well as the complement fixing activity and/or affinity of the DNA antibody may also be important in this regard. For example, Johnson, Edmonds, and Holborrow found that precipitating antibodies to DNA correlated with cutaneous vasculitis, but not renal disease (94). Further clinical and immunological studies along these lines may explain why some immune complexes are nephrotoxic, others seem to cause vasculitis while still others play little if any pathogenic role.

GRANULOMATOUS VASCULITIS

Granulomatous vasculitis can be subdivided into three types: [1] Allergic granulomatous angiitis of Churg and Strauss (24) (25), [2] Wegener's granulomatosis (52) (55) and [3] a limited form of Wegener's granulomatosis (21) (22). These types of necrotizing vasculitis differ histologically from the leukocytoclastic and rheumatic varieties in two ways. First, they show histiocytic proliferation with the formation of both vascular and extravascular granulomata; and second, lesions of varying stages of development and healing are present simultaneously.

Allergic granulomatous angiitis was first described by Churg and Strauss (25). Their initial study included 13 patients with asthma, hay fever or sinusitis followed after an average of 3 years by fever, eosinophilia and evidence of widespread vasculitis. It is now recognized that in addition to the vascular lesions, extravascular necrotizing granulomas are present in the connective tissues of multiple organs. The lesions are composed of a central area of fibrinoid surrounded by histiocytes, epithelioid cells and eosinophils. Recurrent episodes of pneumonia may be observed and heart failure is a common cause of death. The mortality of allergic granulomatous angiitis is high. Steroid administration in large doses usually leads to improvement in some cases. Whether cytotoxic drugs would be more effective is at present unknown.

Wegener's granulomatosis is characterized by necrotizing granulomatous vasculitis of the upper and lower respiratory tracts, together with glomerulonephritis (52) (74). Before the introduction of effective therapy, death usually occurred from progressive renal failure within 5 months of the onset of renal involvement (170). The characteristic histologic features, the absence of tissue and blood eosinophilia and the absence of asthma warrant the separation of this entity from allergic granulomatosis as suggested by Churg (24).

Frequent presenting symptoms in patients with Wegener's granulomatosis are severe rhinorrhea, nasal mucosal ulceration or sinus pain and drainage. Pulmonary symptoms and signs such as cough, hemoptysis and pleuritic chest pain are common and x-ray changes are usually present. Alternatively, peripheral manifestations such as skin ulcerations, joint symptoms, eye and middle ear problems, fever and weight loss may first cause the patient to seek medical care. Table XI lists the signs and symptoms in order of frequency in 18 patients recently reported by Fauci and Wolff from the NIH (55).

TABLE XI

SIGNS AND SYMPTOMS ASSOCIATED WITH WEGENER'S GRANULOMATOSIS
(18 Patients)

	Number	Percent
Rhinorrhea and sinus pain	17	94
Fever	14	78
Not accountable for by detectable infection	7	39
Probably secondary to sinus infection	7	39
Anorexia and weight loss	14	78
Cough	11	61
Chest pain	10	56
Arthralgia	10	56
Skin lesions	8	44
Otitis media	7	39
Eye symptoms	7	39
Hemoptysis	4	22
Arthritis	4	22
Neurological symptoms	4	22

This data emphasizes the frequency of sinopulmonary disease. Respiratory tract involvement is a cardinal finding and **the diagnosis of Wegener's should not be made without the presence of either upper or lower respiratory tract disease.** The radiological manifestations of the pulmonary disease in Wegener's granulomatosis are numerous (5) (58) (101) (104) (112). The most common patterns are solitary or multiple nodular densities or infiltrates. These may be poorly defined (58) or sharply circumscribed (144). Cavitation is quite common, being either unilocular or multilocular with irregular walls (120) (58). The infiltrates may be extremely transient with one disappearing in one lung field while another is appearing in a different location (120). Mediastinal lymph node enlargement is very rare (101).

TABLE XII

SYSTEM INVOLVEMENT IN WEGENER'S GRANULOMATOSIS (55)

	Number	Percent
Respiratory tract	18	100
Renal	15	83
Joints	10	56
Skin or muscle	8	44
Eye	7	39
Middle Ear	7	39
Heart or pericardium	5	28
Nervous system	4	22

Table XII, from the same NIH study, gives the frequency of involvement in various organ systems in patients with Wegener's granulomatosis. Disease of the skin, muscles and joints occur commonly. Seventy-five percent of the patients with skin lesions in this series had vasculitis on biopsy and in half of these granulomata were found. These skin lesions were often early manifestations of the disease and they paralleled the general clinical course.

Anemia, leukocytosis (usually without eosinophilia), elevated erythrocyte sedimentation rate and hyperglobulinemia are characteristic findings in Wegener's (52). Antinuclear antibody, anti-DNA antibody and LE cells are generally absent. Cryoglobulins have not been found and complement levels and generally normal (55) (143). Several reports have documented elevated IgA and IgE levels in serum and secretions (54) (156) (34) and there is a high incidence of antiglobulin or rheumatoid factor activity (55) (176).

Prior to the use of immunosuppressive agents, Wegener's granulomatosis appeared to be a uniformly fatal disorder. During the 1960's the prognosis improved when selected patients were treated with a variety of cytotoxic agents. These drugs include chlorambucil (121) mechlorethamine (89) Azathioprine (14) (130) methotrexate (20) and cyclophosphamide (54) (136). Cyclophosphamide now appears to be the drug of choice in Wegener's granulomatosis (141). The long-term effectiveness of this drug suggests that it may even include permanent remissions in certain patients with this disease (141). Case VII is a patient who was seen at PMH that temporarily responded to Imuran and Prednisone.

CASE VII: (B.K. PMH No. 30 99 92) G.K., a 27 year old white man, was first admitted to the medical service in 1966 with a history of a telescoped urine and renal failure. Chest x-ray at that time showed multiple nodular densities. He had episcleritis, polyarthritis and polyneuritis. A pulmonary nodule was resected and a histologic diagnosis of necrotizing granuloma was made. A renal biopsy showed a focal glomerulonephritis with vasculitis, compatible with the diagnosis of Wegener's granulomatosis. He was given 60 mg of prednisone and Imuran, 200 mg per day. On this regime he improved steadily and was practically asymptomatic for 4 years. Two years after institution of this therapy he voluntarily discontinued the drugs. He remained asymptomatic until July, 1970. He then developed general malaise, fever and weight loss. In August, 1970, he was re-admitted to Parkland for evaluation.

On admission his blood pressure was 180/130, his fundi showed hypertensive changes and he had marked cardiomegaly.

The laboratory findings were as follows: Hgb 7.6 mg%; WBC 8200; ESR 96 mm/hr; urinalysis revealed proteinuria, numerous red cells, white cells, and cellular and hyaline casts; BUN 135 mg%; creatinine 15.6 mg%. The chest x-ray showed a new pulmonary nodule and a renal biopsy revealed active nephritis. Reinstitution of immunosuppressive drugs failed to improve his condition.

Limited Wegener's granulomatosis: A limited form of Wegener's granulomatosis has been described by Carrington and Liebow (21). Their initial report described 16 patients with pulmonary lesions identical to those of Wegener's granulomatosis, but with absent or limited lesions elsewhere and without evidence of glomerulonephritis. Clinically these were often confused with neoplastic diseases, infectious granulomas or lymphomas. Eight of these 16 patients died and six of the 8 deaths were disease related. The other 8 patients survived for long periods, some apparently recovered completely and are presumably free of disease. Steroid treatment seemed beneficial in some of these patients, although others did equally well without such therapy. In still others, steroids were ineffective in altering the progression of the illness. The following case emphasizes certain of these points.

CASE VIII: (J.S.H. SUH No. 28 30 80) J.S.H., a 26 year old white woman, was admitted to the Stanford University Hospital in December, 1968, with complaints of nodules of the eyes and lower legs. The patient first noted redness of both eyes in August, 1968. She went to an ophthalmologist in September who recommended topical steroids. At about this same time she developed several tender red lumps over the anterior surfaces of both legs. In November, 1968 she was told by her internist that she had erythema nodosum. These red nodular lesions subsequently ulcerated and further subcutaneous nodules developed over the posterior portions of her lower legs, the left wrist and upper eyelids. Except for some mild arthralgias she denied other symptoms such as fever, chills, night sweats, cough, chest pains, shortness of breath, myalgia, weight loss, etc.

She started taking C-Quens, (Mestranol and Mestranol plus Chlormadinone acetate) in August, 1968. In November, at the suggestion of her ophthalmologist she discontinued the drug, however, since new nodules continued after she stopped the C-Quens she assumed that the pills were not a fault and began taking them again in December. She continued on the drug while in the hospital until she finished her cycle early in January.

On admission she was afebrile, had a pulse of 80, respiratory rate 18 and blood pressure 120/80. There was a small ulcerative lesion on the nasal margin of the left upper eyelid. There was an erythematous scleral nodule lateral to the right iris. There was no adenopathy. The chest was clear and the heart and abdomen were unremarkable. There were multiple, erythematous, nodular lesions on the anterior tibial surfaces. Some were ulcerated and covered with an adherent black eschar. There were also some deeper subcutaneous nodules over the calves.

The following **laboratory values** were obtained: Hgb 11.6 gm%; WBC 3200 (normal diff.); platelets 243,000; ESR 44 mm/hr; urinalysis, SMA-12 quantitative urine protein, LE preps, VDRL, RA latex, DNA and ENA antibodies and serum complement were all normal or negative.

The chest x-ray at the time of admission revealed scattered nodular densities (up to 1 cm dia.) in both lung fields. There was no hilar adenopathy. Two skin biopsies were obtained from nodules on her leg. The first showed a granulomatous panniculitis without definite evidence of vasculitis. The diagnosis of Weber Christians disease was suggested. The second biopsy showed a necrotizing granulomatous vasculitis. An open lung biopsy was performed and the histological picture was diagnostic of Wegener's granulomatosis.

When it was discovered that the patient had continued taking the birth control pills, these were stopped. She was kept at complete bed rest and her nodular skin lesions showed progressive, spontaneous healing. Serial chest x-rays indicated that spontaneous resolution was also occurring in her pulmonary lesions. As she continued to improve clinically and since her disease seemed limited to skin, lungs and eyes, it was felt that systemic immunosuppressive or antiinflammatory agents were not indicated. She continued to improve over the next 6-8 months and eventually had complete recovery from her disease. She was never given steroids or cytotoxic drugs.

POLYARTERITIS NODOSA

In 1866 Kussmaul and Maier introduced the term periarteritis nodosa in delineating a multisystem disorder with nodules palpable along the course of medium-sized muscular arteries. Polyarteritis has now replaced periarteritis, since the histopathological lesions are not confined to the periphery or adventitia of the arteries but rather may involve any or all arterial layers. Polyarteritis occurs predominantly in adult middle-aged males but it affects all ages and both sexes. There have been over twenty cases in infants under 1 year of age; and instances of possible neonatal transmission have been reported (13) (127). One of the oldest patients reported in the literature was observed in the eighth decade of life (131).

Continued disease activity with attempts at repair lead to one or more of the following pathologic changes: (1) satisfactory healing; (2) excessive fibrosis with nodule formation; (3) intimal thickening with thrombosis; (4) aneurysmal dilatation and occasional rupture and (5) arterial dissection (158). This disease may manifest itself as an acute abdominal catastrophe, a myocardial infarction, polyneuritis, muscle pain, arthralgia, Raynauds or peripheral gangrene. Any organ may be involved, but the brain and lungs are usually

spared. Hypertension and renal failure usually dominate the course of the disease. Sixty to 80 percent of patients have significant hypertension. Contrary to earlier reports that hypertension always antedated the onset of polyarteritis and was therefore a possible etiological factor (100), the current view is that the hypertension is the consequence of healing or healed renal polyarteritis (145). **The possibility of polyarteritis nodosa should always be considered in undiagnosed cases of severe or rapidly advancing hypertension.**

The kidneys are involved in 80% of the cases of classic polyarteritis (7) (138) and renal insufficiency is the most frequent cause of death. Occasionally a renal aneurysm may rupture spontaneously (113) (119) (134). Due to this threat of massive hemorrhage some have suggested that angiography be performed before attempting a percutaneous renal biopsy if PAN is suspected. Of equal importance is the fact that the angiographic findings may be diagnostic of PAN (18) (19) (26) (48) (101) (108). Cardiac disease is also common (approximately 60%) either secondary to hypertension, coronary vasculitis or less often, acute pericarditis (90). Approximately one-half of the reported cases have neurologic involvement and in most of these it is ischemic peripheral neuropathy due to arteritis of the nutrient arteries of peripheral nerves (145) (82) (128) (129) (131). The gastrointestinal tract is often the locus of complaints and may be responsible for the initial manifestations of polyarteritis. Abdominal pain is the most common GI complaint. Acute abdominal catastrophes such as gastric or intestinal perforation and hemorrhage, appendicitis, pancreatitis, cholecystitis, or the interhepatic rupture of an aneurysm may occur (71) (50) (42). As mentioned, the classic form of polyarteritis nodosa rarely involves the lungs in contrast to the frequent occurrance of pulmonary lesions in patients with small vessel disease. Arthralgia or myalgia is present in a majority of PAN patients (111) (115) (63). Occasionally myositis may be sufficiently acute to suggest trichinosis or acute dermatomyositis (158).

Skin lesions are not common in the classic form of polyarteritis nodosa but skin involvement does occur in 5 to 15 percent of patients, and for almost a century nodules in either the skin or subcutaneous tissues have been recognized as important clinical findings. If they are detected, removed by biopsy and examined microscopically, the diagnosis is established. The skin manifestations of PAN are usually nodules on the distal extremities although they may occur anywhere. These nodules vary from 0.5 to 1.0 cm in diameter, are often tender and may pulsate. The skin over these lesions may appear normal, however there is usually some erythema and occasionally the overlying skin breaks down to form large irregular ulcers. Livedo reticularis and peripheral gangrene are also features of PAN. Livedo reticularis, a fixed, deep bluish-red, blotchy or reticulated vascular pattern, may involve the entire trunk or limb, or it may be scattered in discontinuous patches. This discoloration persists even after warming the skin, unlike the evanescent livedo pattern seen in infants and young children known as cutis mormorata. Livedo reticularis is a sign of impaired cutaneous circulation of multiple causes. When due to vasculitis, it is indicative of disease involving deep dermal or subcutaneous muscular arteries (37) (see Figs. 3, 4 and 5).

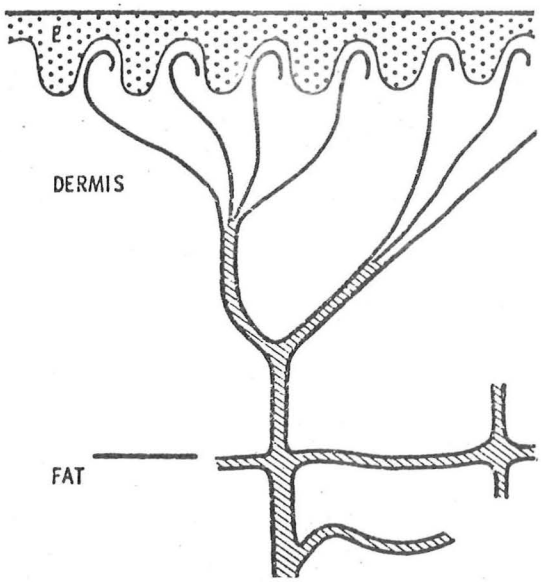


FIGURE 3

Anatomical arrangement of arteritis, arterioles and capillaries in the skin and subcutis. Muscular arteries in the subcutaneous fat branch into arterioles, each of which supplies a group of capillaries that form a loop in the dermal papillae (37).

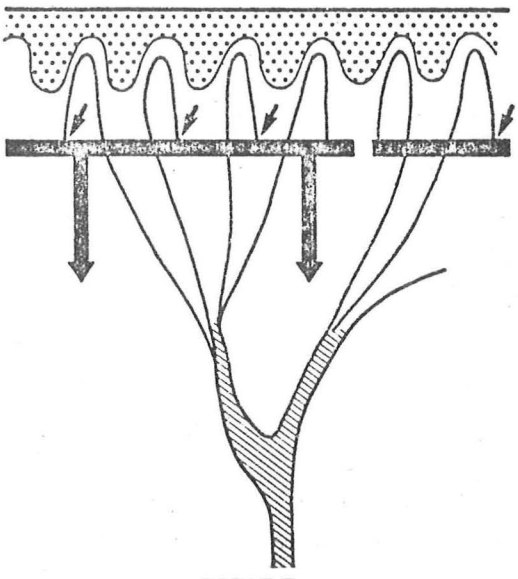


FIGURE 4

The papillary capillaries drain venous blood into the horizontally oriented subpapillary venous plexus (shown as a heavy line) (37).

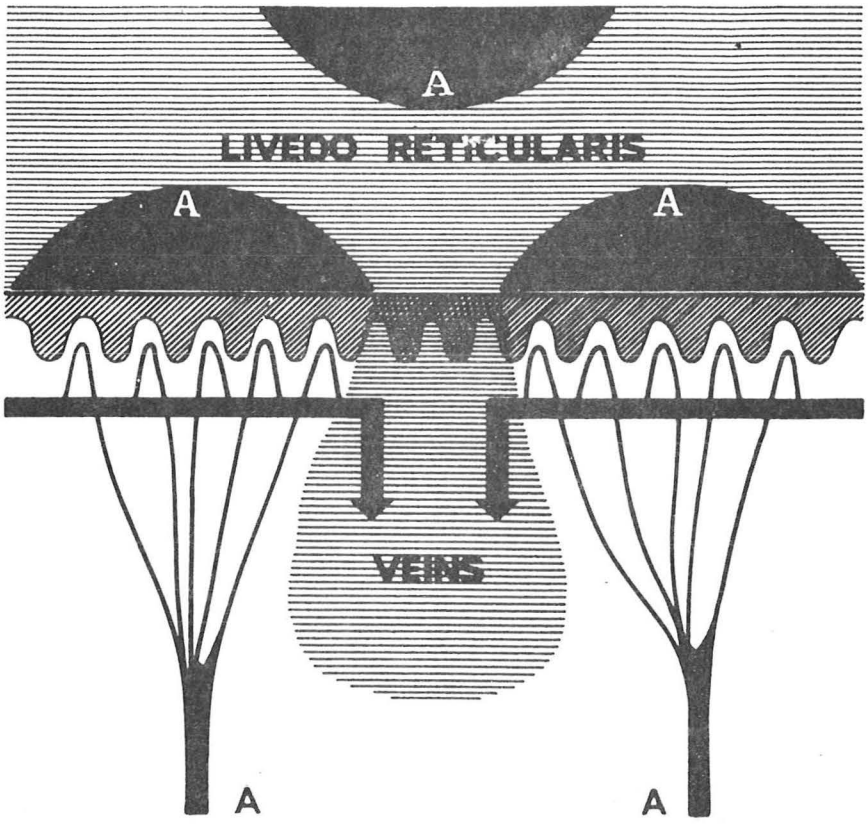


FIGURE 5

Each arteriole with its capillaries form a cone-like arrangement with a base (A) of 2-3 cm in diameter. The areas between these cones represents the peripheral zone of arteriolar blood supply. These peripheral areas are thus rich in venous blood. Any process that slows the blood flow in these vessels will result in an excentuation of the bluish net-like or livedo pattern. (taken from ref. 37)

This vascular pattern has been observed in patients with a number of different diseases. Some of the diseases associated with livedo reticularis are listed in Table XIII.

TABLE XIII

DISEASES ASSOCIATED WITH LIVEDO RETICULARIS

Polyarteritis nodosa
Systemic Lupus Erythematosus
Rheumatoid Arthritis
Cryoglobulinemia
Drug induced vasculitis
Thrombotic Thrombocytopenic purpura (TTP)
Disseminated intravascular coagulation
Polycythemia vera
Thrombocytosis
Pancreatitis

When livedo reticularis is associated with tender subcutaneous nodules, it is due to vasculitis. Biopsy of these nodules will show a necrotizing vasculitis of subcutaneous muscular arteries. Cutaneous infarction, ulceration and peripheral gangrene are also frequently associated features; however, these are not specific changes of vasculitis. Table XIV lists other causes of peripheral gangrene.

TABLE XIV

DISORDERS ASSOCIATED WITH MULTIPLE PERIPHERAL GANGRENE

I. CARDIOPULMONARY DISEASE
- Congestive heart failure
- Myocardial infarction
- Massive pulmonary embolism
- Mitral stenosis, with or without left aftrial ball thrombus

II. OVERWHELMING INFECTION
- Meningococcal Pneumococcal
- Rickettsial
- Viral (purpura fulminans)

III. EMBOLIZATION
- Atheromatous
- Infected
- Thromboemboli

IV. PRIMARY ARTERIAL DISEASE
- Polyarteritis nodosa
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Arteriosclerosis obliterans
- Thromboangiitis obliterans

V. PRIMARY VENOUS DISEASE

VI. VASOSPASTIC DISORDERS
- Ergotism'
- Raynaud's syndrome

VII. HEMATOLOGIC ABNORMALITIES
- Cold agglutinins
- Cryoglobulinemia
- Cryofibrinogenemia

VIII. MISCELLANEOUS
- Carbon monoxide poisoning
- Fibrin thrombi
- Cold injury
- Crutch pressure arteritis

(from: Laws, J.W. et al. ref. 103)

A special form of PAN, known as cutaneous polyarteritis, is clinically benign and primarily affects the skin and muscles (15) (45) (148). Although fever, arthralgia, and myalgia are frequently present, systemic disease involving the kidneys, heart or bowel is absent. In one series (45), 4 of 8 patients with this relatively

benign form of cutaneous PAN who had electromyography showed peripheral neuropathy and/or focal myositis. Woodward and Andreini (177) have recently described three patients with a similar condition who had the additional feature of periosteal new bone formation. Polyarteritic involvement of organs apart from the musculoskeletal system and skin was not apparent in any of these patients. This limited form of polyarteritis usually follows a long but relatively benign course. Case IX is an example of this polyarteritis variant that was recently seen in our clinic.

CASE IX (C.T. PMH No. 53 25 13) C.T., a 34 year old white man, was first seen in the Parkland Special Dermatology Clinic on March 24, 1976. His illness dated back to 1952 (age 10) when he developed tender nodular lesions over his extremities and trunk, myalgias, arthralgias and fever following a penicillin injection for a streptococcal sore throat. A clinical diagnosis of polyarteritis nodosa was made and corroborated by biopsy at the May Clinic in 1959. Treatment consisted of repeated courses of systemic steroids. There was never any evidence of renal involvement, hypertension, abdominal pain, weight loss or evidence of central or peripheral nervous system disease.

On examination deep tender nodules were present in the right arm. Livedo reticularis was present on the trunk and deep, polyangular ulcers formed a reticulated (livedo) pattern on the left pretibial area. Laboratory studies were all normal.

A second variant of polyarteritis has recently been described in 7 patients by Sergent and Christian (157). These patients developed widespread necrotizing vasculitis a few weeks to months following acute serous otitis media. Although otitis is recognized as a common feature of Wegener's granulomatosis, the absence of sinopulmonary disease, asthma and eosinophilia in these patients made the possibility of Wegener's or allergic granulomatosis unlikely. The clinical and laboratory findings in these patients are summarized in Table XV.

TABLE XV

CLINICAL AND LABORATORY FINDINGS IN PATIENTS WITH NECROTIZING VASCULITIS AFTER ACUTE SEROUS OTITIS MEDIA

Case	Interval Between Otitis and Vasculitis	Neurological Disease	Scleritis	Blood Pressure	Urinalysis	Creatine	Rheumatoid Factor	Serum Complement†	Hepatitis B Antigen
	months			*mm Hg*		*mg/100ml*		*CH_{50} units*	
1	6	Peripheral sensory neuropathy	Present	125/75	1+ protein, 100 erythrocytes, numerous casts	3.0-4.7	1:80	179	Negative
2	6	Mononeuritis multiplex	Present	124/80	Trace protein, 20 to 40 erythrocytes, 1 to 2 casts	1.6-2.1	1:1280	226	Negative
3	5	None	Present	125/85	1 to 3+ protein, 20 to 40 erythrocytes, rare casts	1.3	Negative	300	Negative
4	3	Seizure; intrapontine hemorrhage	None	130/70	0 protein, 1 to 3 erythrocytes, 1 to 3 leukocytes	1.0	1:1280	ND	ND
5	2 weeks	Mononeuritis multiplex; seizures, cerebral infarct	None	125/60	1+ protein, occasional erythrocytes, 2 to 5 casts	1.0	1:160	162	ND
6	2	Mononeuritis multiplex; peripheral sensory neuropathy	Present	145/90	2+ protein, 5 to 10 erythrocytes, 5 to 10 leukocytes	0.9-1.6	1:160	285	Negative
7	10	Mononeuritis multiplex	None	148/75	Normal	0.3	1:5120	200	Negative

*ND= not done.
†Normal, 150 to 250 CH_{50} units.

From Sergent and Christian (157).

Two of the seven died and one developed chronic renal insufficiency. Six of the seven were seen during an 8 month interval and they accounted for all but one of the new cases of necrotizing vasculitis seen during that

period. The epidemic character, suggesting an infectious etiology, and the established association between necrotizing vasculitis and certain viral infections (33) (72) (73) raised the possibility of a viral etiology in these patients. However, this could not be proven.

Polyarteritis, and other forms of necrotizing vasculitis have been repeatedly related to infection and hypersensitivity to drugs. Table XVI is a partial listing of the agents that have been postulated as etiologic factors in various forms of necrotizing vasculitis.

TABLE XVI

DRUGS OR NOXIOUS AGENTS IMPLICATED IN THE PATHOGENESIS OF NECROTIZING VASCULITIS

Streptomycin	Guanethidine	Quinidine
Chloramphenicol	Procaine Amide	Propylthiouracil
Penicillin	Phenylbutazone	Bacterial infections Streptococcal pharyngitis
Dilantin	Allopurinol	S B E
Poison oak and primrose	Gold Thiomalate	Viral infections Hepatitis B
Mercury	Vaccines	Insecticides
Arsenicals	Methamphetamine	Weed Killers
Thiourea	LSD	Birth control pills
Iodine	Heroin	
Thiazides	Barbiturates	
Sulfonamides	Chlorpromazine	
	Bismuth	

(Taken from the following references: (1) (12) (16) (26) (33) (44) (65) (69) (73) (85) (95) (96) (93) (105) (147) (151) (158) (163) (167))

Clearly, the practical value of such a list of causative factors is limited but it can alert the clinician to some of the many etiological possibilities so that his questioning and workup of patients may be directed toward these possible leads. Case X is an example of polyarteritis which was probably precipitated by phenylbutazone.

CASE X: (J.C. PMH No. 42 94 32) J.C., a 15 year old white girl, was admitted to the medical service in July, 1972 with fever, polyarthritis, mouth ulcers, bluish discoloration of a toe and a finger and scattered deep-set cutaneous and subcutaneous nodules. Her illness began 4 to 5 days after taking phenylbutazone for a backache.

On admission she had a temperature of 101°F. Her physical exam was normal except for the changes mentioned. Her white count was 28,700 per mm^3. Renal function and urinalysis were normal.

She was placed on high dose prednisone (100 mg per day) with gradual reduction over the next two months. She was maintained under partial control at doses above 40 mg/day. Her prednisone was finally discontinued in 1975 and she is now in complete remission.

SUMMARY

From the currently available immunopathologic data is seems reasonable to implicate the deposition of complement fixing antigen-antibody complexes in vessel walls as the inciting event in polyarteritis nodosa as well as in the other types of necrotizing vasculitis. All of these can be thought of as different expressions of immune complex disease. The contrasting clinical and histologic features of these diseases, as shown in Table XVII, emphasize the importance of determining the caliber of the vessels involved since this dictates, to a large degree, the overall nature of the disease process. The morphology of the skin lesions can be helpful in that determination.

TABLE XVII

A SUMMARY OF THE CLINICAL, HISTOLOGIC AND IMMUNOFLUORESCENT FINDINGS IN FIVE TYPES OF SYSTEMIC NECROTIZING ANGIITIS

	Hypersensitivity Angiitis	*Rheumatic Vasculitis*	*Wegener Granulomatosis*	*Granulomatous Angiitis*	*Periarteritis Nodosa*
CLINICAL FEATURES:					
Allergic history	Frequent	Occasional	Rare	Frequent	Occasional
Preceding bacterial infections	Occasional	Rare	Always	Occasional	Occasional
Initial events	Various: (arthralgia, purpura, albuminuria)	Purpura CNS and GI symptoms	Ulceration & necrosis in respiratory system	Asthma, respiratory infections	Various: (arthralgia, G.I. symptoms, renal failure)
Hypertension	Occasional	Occasional	Occasional	Occasional	Frequent
Eosinophilia	Occasional	Rare	Absent	Frequent	Rare
Response to Steroid	Frequent	Frequent	Rare	Frequent	Occasional
Common cause of death	Various	Various	Uremia	Cardiac failure, cerebral hemorrhage, uremia	Urema, congestive heart failure
HISTOLOGICAL FEATURES:					
Type of vessels involved	Venules, arterioles, small arteries	Veins, capillaries, small and medium arteries	Small arteries and veins	Veins, arterioles, capillaries, small arteries	Muscular arteries
Site of lesions	Skin, joints, kidney, lungs, CNS, GI tract	Skin, joints, kidney, GI tract, gallbladder, pancreas, adrenal CNS	Upper and lower respiratory tract, kidney and skin	Lungs, skin, cardiovascular system	Mesentery, G.I. tract, liver, gallbladder, kidney, pancreas, muscles, testis, peripheral nerves and skin
Stage of lesions	Acute and healing	Acute	Acute and healing	Acute or healing	Acute and healing
Inflammatory reaction	Neutrophils, eosinophils	Neutrophils	Neutrophils histiocytes	Neutrophils, eosinophils, histiocytes	Neutrophils
Renal glomerular involvement	Frequent	Various	Always	Frequent	Frequent
IMMUNOHISTOCHEMICAL LOCALIZATION IN VESSELS OF:					
Immunoglobulins	Frequent	Frequent	Occasional	Frequent	Frequent
Complement	Frequent	Frequent	Occasional	Frequent	Frequent
Fibrinogen	Occasional	Occasional	Frequent	Occasional	Frequent

The factors which are responsible for the production and persistence of circulating soluble immune complexes and for localization of these complexes to large versus small vessels are unknown. Certain properties of the antibody, the antigen and the host response must all be important in this regard. Since many different common antigens have been implicated as triggering these conditions it is somewhat surprising that these forms of immune complex disease are not extremely common. A complete understanding of these diverse immunologic diseases will not be possible until much more is known about the influence of numerous environmental and complex genetic factors on the immune response. Hopefully, with this understanding, early recognition and correction of these aberrant immune responses will ultimately control these devastating diseases.

REFERENCES

1. Adelson, L: Periarteritis nodosa in infancy: Report of a case following allergic reactions to penicillin. *J. Pediatr.* . 39:346, 1951.

2. Alarcon-Segovia, D. and A.L. Brown: Classification and etiologic aspects of necrotizing angiitides: an analytic approach to a confused subject with a critical review of the evidence for hypersensitivity in polyarteritis nodosa. *Mayo Clinic Proc.* 39:205, 1964.

3. Alarcon-Segovia, D. and P.J. Osmundson: Peripheral vascular syndromes associated with systemic lupus erythematosus. *Ann. Int. Med.* 62:907, 1965.

4. Allen, A.C.: *IN: The Kidney: medical and surgical diseases.* Grune and Stratton, New York, 1962.

5. Allen, A.R. and C.W. Moen: Wegener's granulomatosis. *J. Thorac. Cardiovasc. Surg.* 49:388, 1965.

6. Ansell, B.M.: Henoch-Schonlein purpura with particular reference to the prognosis of the renal lesion. *Brit. J. Dermatol.* 82:211, 1970.

7. Arkin, A.: A clinical and pathological study of periarteritis nodosa: A report of five cases, one histologically healed. *Am. J. Pathol.* 6:401, 1930.

8. Baker, L.P.: Disseminated lupus erythematosus with leg ulcers. *Arch. Dermatol. Syph.* 66:758, 1952.

9. Ballard, H.S.: Renal manifestations of the Henoch-Schonlein syndrome in adults. *Am. J. Med.* 49:328, 1970.

10. Bank, N.: The relation of malignant hypertension to periarteritis nodosa in humans. *J. Mount Sinai Hosp.* 22:290, 1955.

11. Beetham, Wm. P., Jr.: Evaluation of biopsy material in the diagnosis of systemic vasculitis. *Lahey Clinic Foundation Bul.* 20:33, 1971.

12. Bjornberg, A. and H. Gisslen: Thiazides and necrotizing vasculitis. *Lancet* 2:982, 1965.

13. Boren, R.J., and M.A. Everett: Cutaneous vasculitis in mother and infant. *Arch. Derm.* (Chicago) 92:568, 1965.

14. Bouroncle, B.A., E.J. Smith and F.E. Cuppage: Treatment of Wegener's granulomatosis with Imuran. *Am. J. Med.* 42:314, 1967.

15. Bradford, W.D., C.D. Cook and G.E. Vawter: Livedo reticularis: a form of allergic vasculitis. *J. Pediatrics* 60:266, 1962.

16. Braverman, I.M.: The Angiitides *In: Skin Signs of Systemic Disease*, pp 199-238, W.B. Saunders, Philadelphia, 1970.

17. Braverman, I.M. and A. Yen: Demonstration of immune complexes in spontaneous and histamine-induced lesions and in normal skin of patients with leukocytoclastic angiitis. *J. Invest. Dermatol.* 64:105, 1975.

18. Bron, K.M. and A. Gajaraj: Demonstration of hepatic aneurysms in polyarteritis nodosa by arteriography. *N. Eng. J. Med.* 282:1024, 1970.

19. Bron, K.M., C.A. Strott and A.P. Shapino: The diagnostic value of angiographic observations in polyarteritis nodosa. *Arch. Intern. Med.* 116:450, 1965.

20. Capizzi, R.L. and J.R. Bertino: Methotrexate therapy of Wegener's granulomatosis. *Ann. Intern. Med.* 74:74, 1971.

21. Carrington, C.B. and A. A. Liebow: Limited forms of angiitis and granulomatosis of Wegener's type. *Am. J. Med.* 41:497, 1966.

22. Casson, S.M., D.T. Coles and E.G. Harrison: The concept of limited forms of Wegener's granulomatosis. *Am. J. Med.* 49:366, 1970.

23. Cheah, J.D.: Systemic lupus erythematosus in a Chinese woman presenting with gangrene of the fingers. *Aust. N.Z. J. Med.* 3:197, 1973.

24. Churg, J.: Allergic granulomatosis and granulomatous-vascular syndromes. *Ann. Allerg.* 21:619, 1963.

25. Churg, J. and L. Strauss: Allergic granulomatosis, allergic angiitis, and periarteritis nodosa. *Amer. J. Pathol.* 27:277, 1951.

26. Citron, B.P., M. Halpern, M. McCarron et al: Necrotizing angiitis associated with drug abuse. *N. Eng. J. Med.* 283:1003, 1970.

27. Claman, H.N., R.M. Karr, P.F. Kohler, et al: Systemic (Allergic?) vasculitis. *J. Allergy & Clin. Immunol.* 54:54, 1974.

28. Cochrane, C.G. and D. Koffler: Immune complex disease in experimental animals and man. *Adv. Immunol.* 16:185, 1973.

29. Cochrane, C.G.: Mechanisms involved in the deposition of immune complexes in tissues. *J. Exp. Med.* 134:75, 1971.

30. Cochrane, C.G.: Studies on the localization of circulating antigen-antibody complexes and other macromolecules in Vessels I. *Structural studies. J. Exp. Med.* 118:489, 1963.

31. Cochrane, C.G.: Studies on the localization of circulating antigen-antibody complexes and other macromolecules in vessels: II. Pathogenetic and pharmacodynamic studies. *J. Exp. Med.* 118:503, 1963.

32. Cochrane, C.G. and D. Hawkins: Studies on circulating immune complexes. III. Factors governing the ability of circulating complexes to localize in blood vessels. *J. Exp. Med.* 127:137, 1968.

33. Combes, B., J. Shorey, A. Barrera et al: Glomerulonephritis with deposition of Australia antigen-antibody complexes in glomerular basement membrane. *Lancet* 11:234, 1971.

34. Conn, D.L., McDuffie, F.C., Holley, K.E. and Schroeter, A.L.: Immunologic mechanisms in systemic vasculitis. *Mayo Clin. Proc.* 51:511, 1976.

35. Copeman, P.W.M. and T.J. Ryan: The problems of classification of cutaneous angiitis with reference to histopathology and pathogenesis. *Brit. J. Dermatol.* 82:2, 1970.

36. Copeman, P.W.M.: Investigations into the pathogenesis of acute cutaneous angiitis. *Brit. J. Dermatol.* 82:51, 1970.

37. Copeman, P.W.M. and T.J. Ryan: Cutaneous Angiitis; patterns of rashes explained by (1) flow properties of blood; (2) anatomical disposition of vessels. *Brit. J. Dermatol.* 85:205, 1971.

38. Cox, A.J.: Pathologic changes in hypersensitivity angiitis. *IN: The Skin.* E.B. Helwig and F.K. Mostofi, Eds. Williams & Wilkins, pp. 279-292, 1971.

39. Cream, J.J.: Immunofluorescent studies of the skin in cryoglobulinemic vasculitis. *Brit. J. Dermatol.* 84:48, 1971.

40. Cream, J.J., J.M. Gumpel and R.D.G. Peachey: Schonlein-Henoch purpura in the adult. *Quart. J. Med.* 39:461, 1970.

41. Cream, J.J. and J. L. Turk: A review of the evidence for immune complex deposition as a cause of skin disease in man. *Clinical Allergy* 1:235, 1971.

42. Dawson, J.L.: Polyarteritis Nodosa presenting as an acute abdomen. *Proc. Roy. Soc. Med.* 55:195, 1962.

43. Desser, K.B., G.P. Sartiano and J.L. Cooper: Lupus livedo and cutaneous infarction. *Angiology* 20:261, 1969.

44. Dewar, H.A. and M.J.T. Peaston: Guanethidine toxicity in hypertension. *Brit. Med. J.* 2:609, 1964.

45. Diaz-Perez, J.C. and R.K. Winkelmann: Cutaneous periarteritis nodosa. *Arch. Dermatol.* 110:407, 1974.

46. Diaz-Rivera, R.S. and A.J. Miller: Periarteritis nodosa: A clinicopathological analysis of seven cases. *Ann Intern. Med.* 24:420, 1946.

47. Dines, D.E., Polyarteritis nodosa. Report of a patient receiving long-term anticoagulant therapy. *J.A.M.A.* 189:156, 1964.

48. Dornfeld, L., J.W.Lecky and J.B. Peter: Polyarteritis and intrarenal renal artery aneurysms. *J.A.M.A.* 215:1948, 1971.

49. Dorsch, C. and E.V. Barnett: The occurrence and nature of precipitating antibodies in anti-DNA sera. *Clin. Immunol. & Immunopath.* 2:310, 1974.

50. Dzwonczyk, J., Jr., O. Serlin and P.V. Skerrett: Spontaneous rupture of the liver: report of a case secondary to polyarteritis nodosa. *Ann. Surg.* 150:327, 1959.

51. Estes, D. and C.L. Christian: The natural history of systemic lupus erythematosus by prospective analysis. *Medicine* 50:85, 1971.

52. Fahey, J., E. Leonard, J. Churg, and G. Goodman: Wegener's granulomatosis. *Amer. J. Med.* 17:168, 1954.

53. Faille-Kuyper, E.H. de la, L. Kater, C.J. Koviker and E.J. Mees Dorhout: IgA-deposits in cutaneous blood vessel walls and mesangium in Henoch-Schonlein syndrome. *Lancet* 1:892, 1973.

54. Fauci, A.S., S.M. Wolff and J.S. Johnson: Effect of cyclophosphamide upon the immune response in Wegener's granulomatosis. *N. Eng. J. Med.* 285:1493, 1971.

55. Fauci, A.S. and S.M. Wolff: Wegener's granulomatosis: studies in eighteen patients and a review of the literature. *Medicine* 52:535, 1973.

56. Fauci, A.S., S.M. Wolff: Immunological features of Wegener's granulomatosis. *Lancet* 1:688, 1974.

57. Feinglass, E.J., F.C. Arnett, C.A. Dorsch, T.M. Zizic and M.B. Stevens: Neuropsychiatric manifestations of systemic lupus erythematosus: diagnosis, clinical spectrum and relationship to other features of the disease. *Medicine* 55:323, 1976.

58. Felson, B.: Less familiar roentgen patterns of pulmonary granulomatosis. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* 81:211, 1959.

59. Fink, C.W.: Polyarteritis and other diseases with necrotizing vasculitis in childhood. *Arth. Rheum.* (In press)

60. Fitzsimmons, J.S.: Uncommon complication (testicular pain) of anaphylactoid purpura. *Brit. Med. J.* 4:431, 1968.

61. Forrest, J.A.H. and D.J.C. Shearman: Pulmonary vasculitis and ulcerative colitis. *Amer. J. Digest. Dis.* 20:482, 1975.

62. Fraga, A. and G. Mentz: Splinter hemorrhages in SLE. *Arth. Rheum.* 9:648, 1966.

63. Freedman, P., J.H. Peters and R.M. Kark: Localization of gammaglobulin in the diseased kidney. *Arch. Intern. Med.* 105:524, 1960.

64. French, G.: Polyarteritis nodosa presenting as acute diabetes mellitus. *Brit. Med. J.* 1:1262, 1953.

65. Friedenthal, M. and R.N. Cagan: Periarteritis nodosa associated with the use of a proprietary mercurial preparation (a case with serial electrophoretic patterns). *Amer. Pract.* 3:218, 1952.

66. Gary, N.E., J.T. Mazzara and L. Holfelder: The Schonlein-Henoch syndrome: report of two patients with recurrent impairment of renal function. *Ann. Int. Med.* 72:229, 1970.

67. Gelfand, E.W., J.E. Clarkson and J.O. Minta: Selective deficiency of the second component of complement in a patient with anaphylactoid purpura. *Clin. Immunol. & Immunopath.* 4:269, 1975.

68. Gershwin, M.D. and A.D. Steinberg: Qualitative characteristics of anti-DNA antibodies in lupus nephritis. *Arth. Rheum.* 17:947, 1974.

69. Gibson, P.C. and J.T. Quinlan: Periarteritis nodosa in thiourea therapy. *Lancet* 2:108, 1945.

70. Gilliam, J.N., D.E. Cheatum, E.R. Hurd, P. Stastny and M. Ziff: Immunoglobulins in clinically uninvolved skin in systemic lupus erythematosus. *J. Clin. Invest.* 53:1434, 1974.

71. Glassman, E. and P.V. Skerrett: Rupture of an intrahepatic aneurysm due to polyarteritis nodosa. *Am. J. Med.* 28:143, 1960.

72. Gocke, D.J.: Extrahepatic manifestations of viral hepatitis. *Amer. J. of Med. Sci.* 270:49, 1975.

73. Gocke, D.J., C. Morgan, M. Lockshin, K. Hsu, S. Bombardieri and C.L. Christian: Association between polyarteritis and Australia antigen. *Lancet* 2:1149, 1970.

74. Godman, G.C., Churg, J.: Wegener's granulomatosis. Pathology and review of the literature. *Arch. Pathol.* 58:533, 1954.

75. Goldberger, E.: Etiology and pathogeneses of syndromes associated with periarteritis nodosa lesions. A unified theory. *Am. J. Cardiol.* 3:656, 1959.

76. Golde, D. and W. Epstein: Mixed cryoglobulins and glomerulonephritis. *Ann. Int. Med.* 69:1221, 1968.

77. Golden, R.L.: Livedo reticularis in systemic lupus erythematosus. *Arch. Dermatol.* 87:67, 1963.

78. Golding, D.N.: Polyarteritis presenting with leg pains. *Brit. Med. J.* 1:277, 1970.

79. Goltz, R.W. and R.A. Good: Benign hyperglobulinemic purpura. Relation to Mikulicz's disease, sicca syndrome and epidermolysis bullosa dystrophica. *AMA Arch. Dermatol.* 83:26, 1961.

80. Goltz, R.W. and N.G. Smith: Recurrent lower leg ulcers in lupus erythematosus. *Minn. Med.* 41:348, 1958.

81. Gotz, O. and H.J. Muller-Eberhard: The C activator system: an alternate pathway of complement activation. *J. Exp. Med.* 134:905, 1971.

82. Griffith, C.G. and I.L. Vural: Polyarteritis nodosa: a correlation of clinical and postmortem findings in seventeen cases. *Circulation* 3:481, 1951.

83. Grossman, H., W.E. Berdon and D.H. Baker: Abdominal pain in Schonlein-Henoch syndrome: its correlation with small bowel barium roentgen study. *Amer. J. Dis. Child.* 108:67, 1964.

84. Hache, L., D.C. Utz and L.B. Woolner: Idiopathic fibrous retroperitonitis. *Surg. Gyn. and Obst.* 115:737, 1962.

85. Halpern, M. and B.P. Citron: Necrotizing angiitis associated with drug abuse. *Am. J. Roent. Rad. Ther. and Nucl. Med.* 111:663, 1971. Also see *New Eng. J. Med.* 283:1003, 1970.

86. Harrington, J.T.: Acute oliguric renal failure with IgA glomerular deposits (Henoch-Schonlein purpura) CPC. *New Engl. J. Med.* 290:1365, 1974.

87. Harris, D.R.: Cutaneous Expression of Hypersensitivity Angiitis, *Present Concepts* 3:631, 1970.

88. Hellstrom, H.R. and E.C. Perez-Stable: Retroperitoneal fibrosis with disseminated vasculitis and intrahepatic sclerosing cholangitis. *Amer. J. Med.* 40:184, 1966.

89. Hollander, D. and R.T. Manning: The use of alkylating agents in the treatment of Wegener's granulomatosis. *Ann. Intern. Med.* 67:393, 1967.

90. Holsinger, D.R., P.J. Osmundson and J.E. Edwards: The heart in periarteritis nodosa. *Circulation* 25:610, 1962.

91. Horwitz, L.D. and R. Silber: Subacute bacterial endocarditis presenting as purpura. *Arch. Int. Med.* 120:483, 1967.

92. Howell, S.B. and W.V. Epstein: Circulating immunoglobulin complexes in Wegener's granulomatosis. *Amer. J. Med.* 60:259, 1976.

93. Israel, H.L. and Patchefsky, A.S.: Wegener's granulomatosis of lung. Experience with 12 cases. *Ann. Intern. Med.* 74:881, 1971.

94. Johnson, G.D., J.P. Edmonds and E.J. Holborrow: Precipitating antibody to DNA detected by two-stage electroimmunodiffusion. Study in SLE and in rheumatoid arthritis. *Lancet* 2:883, 1973.

95. Johnson, T.E.: Angiitis in drug abusers. *New Engl. J. of Med.* 284:504, 1971.

96. Kaufman, D.B. and R. McIntosh: The pathogenesis of the renal lesion in a patient with streptococcal disease, infected ventricutoatrial shunt, cryoglobulinemia and nephritis. *Am. J. of Med.* 50:262, 1971.

97. Kirsner, A.B., J.G. Diller and R.P. Sheon: Systemic lupus erythematosus with cutaneous ulceration. *J.A.M.A.* 217:821, 1971.

98. Kjellbo, H., H. Stakeberg and J. Mellgren: Possibly thiazide-induced renal necrotizing vasculitis. *Lancet* 1:1034, 1965.

99. Klipper, A.R., M.B. Stevens, T.M. Zizic and D.S. Hungerford: Ischemic necrosis of bone in systemic lupus erythematosus. *Medicine* 55:251, 1976.

100. Knowles, H.C., P.M. Zeek and M.A. Blenkenhorn: Studies on necrotizing angiitis, periarteritis and hypersensitivity angiitis. *Arch. Intern. Med.* (Chicago) 92:789, 1953.

101. Kornblum, D. and R. Fienberg: Roentgen manifestations of necrotizing granulomatosis and angiitis of lungs. *Amer. J. Roentgenol. Radium Ther. Nucl. Med.* 74:587, 1955.

102. Kyle, R.A., G.J. Gleich, E.D. Bayrd and J.H. Vaughan: Benign hypergammaglobulinemic purpura of Waldenstrom. *Medicine* 50:113, 1971.

103. Laws, J.W., H.L. Fred, J.T. Sharp and E.R. Rabin: Multiple peripheral gangrene. *Arch. Intern. Med.* 115:547, 1965.

104. Levin, D.C.: Pulmonary abnormalities in the necrotizing vasculitides and their rapid response to steroids. *Radiology* 97:521, 1970.

105. Lichtenstein, L. and L.J. Fox: Necrotizing arterial lesions resembling those of periarteritis nodosa and focal visceral necrosis following administration of sulfathiazole; report of a case. *Amer. J. Pathol.* 22:665, 1946.

106. Liebow, A.A. and C.B. Carrington: The lymphomatoid variant of "limited Wegener's granulomatosis." *Amer. J. Pathol.* 55:78a, 1969.

107. Lindenauer, S.M. and E.S. Tank: Surgical aspects of Henoch-Schonlein purpura. *Surgery* 59:982, 1966.

108 Longstreth, P.L., M. Korobkin and A.J. Palubinskas: Renal microaneurysms in a patient with systemic lupus erythematosus. *Radiology* 113:65, 1974.

109. LoSpalluto, J., B. Dorward, W.Miller, Jr. and M. Ziff: Cyroglobulinemia based on interaction between a gamma macroglobulin and 7S gamma globulin. *Amer. J. Med.* 32:142, 1962.

110. Lovshin, L.L. and J.W. Kernohan: Peripheral neuritis in periarteritis nodosa: a clinicopathologic study. *Arch. Intern. Med.* 82:321, 1948.

111. Lowman, E.W.: Joint and neuromuscular manifestations of periarteritis nodosa. *Ann. Rheum. Dis.* 11:146, 1952.

112. Lynch, E.C., H.L. Fred and S.D. Greenberg: Pulmonary cavitation in Wegener's granulomatosis. *Amer. J. Roentgenol. Radium Ther. Nucl. Med.* 92:521, 1964.

113. Mandelbaum, I. and L.R. Radigan: Spontaneous hemorrhagic rupture of the kidney associated with periarteritis nodosa. *Surgery* 45:787, 1959.

114. MacKenzie, M.R., L.S. Goldberg, E.V. Barrett et al: Serological heterogenerity of the IgM components of mixed (monoclonal IgM-polyclonal IgG) cyroglobulins. *Clin. Exp. Immunol.* 3:931, 1968.

115. McCall, M. and J.W. Pennock: Periarteritis nodosa: our present knowledge of the disease. *Ann. Intern. Med.* 21:628, 1944.

116. McCombs, R.P.: Systemic allergic vasculitis. *J.A.M.A.* 194:1059, 1965.

117. McCombs, R.P.: Systemic allergic vasculitis. *New Engl. J. Med.* 284:262, 1971.

118. McDuffie, F.C., W.M. Sams, J.E. Maldonado et al: Hypocomplementemia with cutaneous vasculitis and arthritis: Possible immune complex syndrome. *Mayo Clin. Proc.* 48:340, 1973.

119. McGrae, J.D., Jr.: Perirenal hematoma secondary to polyarteritis nodosa: report of a case and review of the literature. *AMA Arch. Int. Med.* 104:421, 1959.

120. McGregor, M.B. and G. Sandler: Wegener's granulomatosis. A clinical and radiological survey. *Brit. J. Radiol.* 37:430, 1964.

121. McIlvanie, S.K.: Wegener's granulomatosis. Successful treatment with chlorambucil. *J.A.M.A.* 197:90, 1966.

122. Meltzer, M., E.C. Franklin, K. Ellias, R.T. McCluskey and N. Cooper: Cryoglobulinemia – a clinical and laboratory study. II. Cryoglobulins with rheumatoid factor activity. *Amer. J. Med.* 40:837, 1966.

123. Mentz, G. and A. Fraga: Arteritis in systemic lupus erythematosus. *Arch. Int. Med.* 116:55, 1965.

124. Miescher, P.A., F. Paronetto and D. Koffler: Immunofluorescent studies in human vasculitis. *IN: IVth International Symposium on Immunopathology.* P. Gruber and P.A. Miescher, Eds. B. Schwabe & Basel, pg. 446, 1965.

125. Miller, G., J.C. Hoyt and B.E. Pollack: Bilateral renal vein thrombosis and the nephrotic syndrome, associated with lesions of polyarteritis nodosa. *Amer. J. Med.* 17:856, 1954.

126. Miller, H.G. and M.G. Nelson: Periarteritis developing during antibiotic therapy with arsenicals: case report. *Lancet* 2:200, 1945.

127. Miller, J.J. and J.F. Fries: Simultaneous vasculitis in a mother and newborn infant. *J. of Pediatrics* 87:443, 1975.

128. Moskowitz, R.W.: The histopathological classification of periarteritis nodosa: a study of 56 cases. *Thesis, Graduate School, University of Minnesota*, 1960.

129. Mowrey, F.H. and E.A. Lundberg: The clinical manifestations of essential polyangiitis (periarteritis nodosa), with emphasis on the hepatic manifestations. *Ann. Int. Med.* 40:1145, 1954.

130. Norton, W.L., W. Suki and S. Strunk: Combined corticosteroid and azatioprine therapy: in two patients with Wegener's granulomatosis. *Arch. Intern. Med.* 121:554, 1968.

131. Nuzum, J.W., Jr., and J.W. Nuzum, Sr.: Polyarteritis nodosa: statistical review of one hundred seventy-five cases from the literature and report of a "typical" case. *Arch. Intern. Med.* 94:942, 1954.

132. O'Duffy, J.D., A.L. Scherbel, H.E. Rerdbord and L.J. McCormack: Necrotizing angiitis. I. A clinical review of twenty-seven autopsied cases. *Cleveland Clin. Quart.* 32:87, 1965.

133. O'Quinn, S.E., C.D. Kennedy and D.T. Baker: Peripheral vascular lesions in rheumatoid arthritis. *Arch. Dermatol.* 92:489, 1965.

134. Ostrum, B.J. and P.D. Soder: Periarteritis nodosa complicated by spontaneous perinephric hematoma: roentgenographic findings in three cases and a review of the literature. *Amer. J. Roentgenol.* 84:849, 1960.

135. Paronetto, F. and L. Strauss: Immunocytochemical observations in periarteritis nodosa. *Ann. Intern. Med.* 56:289, 1962.

136. Pearson, C.M. and S.N. Novack: Successful treatment of four cases of Wegener's granulomatosis with cyclophosphamide. *Arth. Rheum.* 14:408, 1971.

137. Pennybaker, J.B., J.N. Gilliam and M. Ziff: Significance of anti-nDNA classes in serum and skin in prognosis of systemic lupus erythematosus (SLE). *Arth. Rheum.* 19:815, 1976.

138. Ralston, D.E. and W.F. Kvale: The renal lesions of periarteritis nodosa. *Proc. Staff Meet., Mayo Clin.* 24:18, 1949.

139. Reed, W.B. and R. Anderson: Atheromatous embolism (with cutaneous manifestations resembling polyarteritis nodosa). *Cutis* 16:264, 1975.

140. Reza, M.J., L. Dornfeld, L.S. Goldberg, R. Bluestone and C.M. Pearson: Wegener's granulomatosis. *Arth. Rheum.* 18:501, 1975.

141. Reza, M.J., B.E. Roth, M.A. Pops and L.S. Goldberg: Intestinal vasculitis in essential, mixed cryoglobulinemia. *Ann. of Int. Med.* 81:632, 1974.

142. Rich, A.R.: Hypersensitivity to iodine as a cuase of periarteritis nodosa. *Bull. J. Hopkins Hopsital.* 77:43, 1945.

143. Roback, S.A., R.D. Herdman, J. Hoyer and R.A. Good: Wegener's granulomatosis in a child. *Amer. J. Dis. Child.* 118:608, 1969.

144. Rogers, J.V., Jr. and A.E. Roberto: Circumscribed pulmonary lesions in periarteritis nodosa and Wegener's granulomatosis. *Amer. J. Roentgenol.* 76:88, 1957.

145. Rose, G.A.: Natural history of polyarteritis. *Brit. Med. J.* 2:1148, 1957.

146. Rose, G.A. and H. Spenser: Polyarteritis nodosa. *Quart. J. Med.* 26:43, 1957.

147. Rosin, J.M.: Vasculitis following procaine amide therapy. *Amer. J. Med.* 42:625, 1967.

148. Rotstein, J., and R.A. Good: Periarteritis nodosa, limited to skin and muscle: report of a case with a discussion of the practical and theoretical implications. *Arth. Rheum.* 1:462, 1958.

149. Robenstein, M. and S.M. Wolff: Penile nodules as a major manifestation of subacute angiitis. *Archives of Int. Med.* 114:449, 1964.

150. RuDusky, B.M.: Recurrent Osler's nodes in systemic lupus erythematosus. *Angiology* 20:33, 1969.

151. Rytand, D.A., W.K. DeBurnham and A.J. Cox: Periarteritis nodosa following the dermatitis of poison oak and of primrose. *Stanford M. Bull.* 6:319, 1948.

152. Sams, W.M., H.N. Claman, P.F. Kohler, R.M. McIntosh, P. Small and M.F. Mass: Human necrotizing vasculitis: immunoglobulins and complement in vessel wells of cutaneous lesions and normal skin. *J. Invest. Dermatol.* 64:441, 1975.

153. Sams, W.M., D.D. Harville and R.K. Winkleman: Necrotizing vasculitis associated with lethal reticuloendothelial diseases. *Brit. J. Dermatol.* 80:555, 1968.

154. Sams, W.M., E.G. Thorne, P. Small, M.F. Mass, et al: Leukocytoclastic vasculitis. *Arch. Dermatol.* 112:219, 1976.

155. Schmid, F.R., N.S. Cooper, M. Ziff and C. McEwen: Arteritis in rheumatoid arthritis. *Amer. J. Med.* 30:56, 1961.

156. Shillitoe, E.J. and T. Lehner: Immunological features of Wegener's granulomatosis. *Lancet* 1:281, 1974.

157. Sergent, J.S. and C.L. Christian: Necrotizing vasculitis after serous Otitis Media. *Ann. Int. Med.* 81:195, 1974.

158. Shulman, L.E.: Polyarteritis nodosa. *IN: Immunological Diseases.* M. Samter, Ed. pp. 1029-1038, Little Brown & Co., Boston, 1971.

159. Soter, N.A., K.F., Austin and I. Gigli: Urticaria and arthralgias as manifestations of necrotizing angiitis (vasculitis). *J. Invest. Dermatol.* 63:485, 1974.

160. Soter, N.A., M.C. Mihn, I. Gigli, H.F. Dvorak and K.F. Austen: Two distinct cellular patterns in cutaneous necrotizing angiitis. *J. Invest. Dermatol.* 66:344, 1976.

161. Stremple, J.F., M.A. Placek and E.H. Ellison: The acute non-surgical abdomen of Henoch-Schonlein in the elderly patient. *Amer. J. Surg.* 115:870, 1968.

162. Stringa, S.G., C. Bianchi, A.M. Casala and O. Bianchi: Allergic vasculitis. Gourgerot-Ruiter syndrome. Immunofluorescent study. *Arch. Derm.* 95:23, 1967.

163. Sussman, M., J.H. Jones, J.D. Almedia and P. Lachmann: Deficiency of the second component of complement associated with anaphylactoid purpura and presence of mycoplasma in the serum. *J. Clin. Exp. Immunol.* 14:531, 1973.

164. Tay, C.H.: Cutaneous manifestations of systemic lupus erythematosus. *Aust. J. Dermatol.* 11:30, 1970.

165. Tuffanelli, D.L.: Lupus erythematosus. *Arch. Dermatol.* 106:533, 1972.

166. Tuffanelli, D.L. and D.M. Kay: Morphological and immunological studies of necrotizing vasculitis in systemic lupus erythematosus (SLE). *Clin Res.* 17:278, 1969.

167. Van Wyk, J.J., C.R. Hoffman: Periarteritis nodosa: A case of fatal exfoliative dermatitis resulting from "dilantin sodium" sensitization. *Arch. Intern. Med.* 81:605, 1948.

168. Wager, O., K.K. Mustakallio and J.A. Rasanen: Mixed IgA-IgG cryoglobulinemia. *Amer. J. Med.* 44:179, 1968.

169. Wager, O. and J.A. Rasanen: Mixed cryoimmunoglobulinemia in relation to autoimmune aberrations. *IN: Immune Complex Diseases.* L. Bonomo and J.L. Turk, Eds. Rockefeller Univ. Press. pg. 140, 1970.

170. Walton, E.W.: Giant-cell granuloma of the respiratory tract (Wegener's granulomatosis). *Brit. Med. J.* 2:265, 1958.

171. Walton, E.W.: Giant-cell granuloma of the respiratory tract (Wegener's granulomatosis). *Brit. Med. J.* 5:267, 1958.

172. Weeks, R.E., P.E. Bernatz and K.E. Holley: Clinicopathologic conference on Goodpasture's Syndrome. *Mayo Clin. Proc.* 43:449, 1968.

173. Whitehouse, A.C., C.E. Buckley, H. Nagaya and J. McCarter: Macroglobulinemia and Sjogren's Syndrome. *Amer. J. Med.* 43:609, 1967.

174. Wilkinson, D.S.: Some clinical manifestations and associations of "allergic" vasculitis. *Brit. J. Dermatol.* 77:186, 1965.

175. Winklemann, R.K. and W.B. Ditto: Cutaneous and visceral syndromes of necrotizing or "allergic" angiitis: a study of 38 cases. *Medicine* 43:59, 1964.

176. Wolff, S.M., A.S. Fauci, R.G. Horn, D.C. Dale: Wegener's granulomatosis. *Ann. Intern. Med.* 81:513, 1974.

177. Woodward, A.H. and P.H. Andreini: Periosteal new bone formation in polyarteritis nodosa. A syndrome involving the lower extremities. *Arth. Rheum.* 17:1017, 1974.

178. Zeek, P.M.: Periarteritis nodosa: a critical review. *Amer. J. Clin. Path.* 22:777, 1952.

179. Zeek, P.M., C.C. Smith and J.E. Weeter: Studies on periarteritis nodosa. III. The differentiation between the vascular lesions of periarteritis nodosa and hypersensitivity. *Amer. J. Path.* 24:889, 1948.

180. Zeek, P.M.: Periarteritis nodosa and other forms of necrotizing angiitis. *New Engl. J. Med.* 248:764, 1953.