Parkland Memorial Hospital
Medical Grand Rounds

November 4, 1971

SYSTEMIC ALLERGIC VASCULITIS

Inflammation and necrosis of blood vessels characterize a wide variety of disease processes and represent a general mechanism of reaction to injury. However, the distribution of vascular lesions in cutaneous or visceral areas, the size and type of vessel involvement, and the predominant character of the perivascular cellular infiltrate permit a classification of vasculitis syndromes which has important diagnostic, therapeutic and prognostic implications.

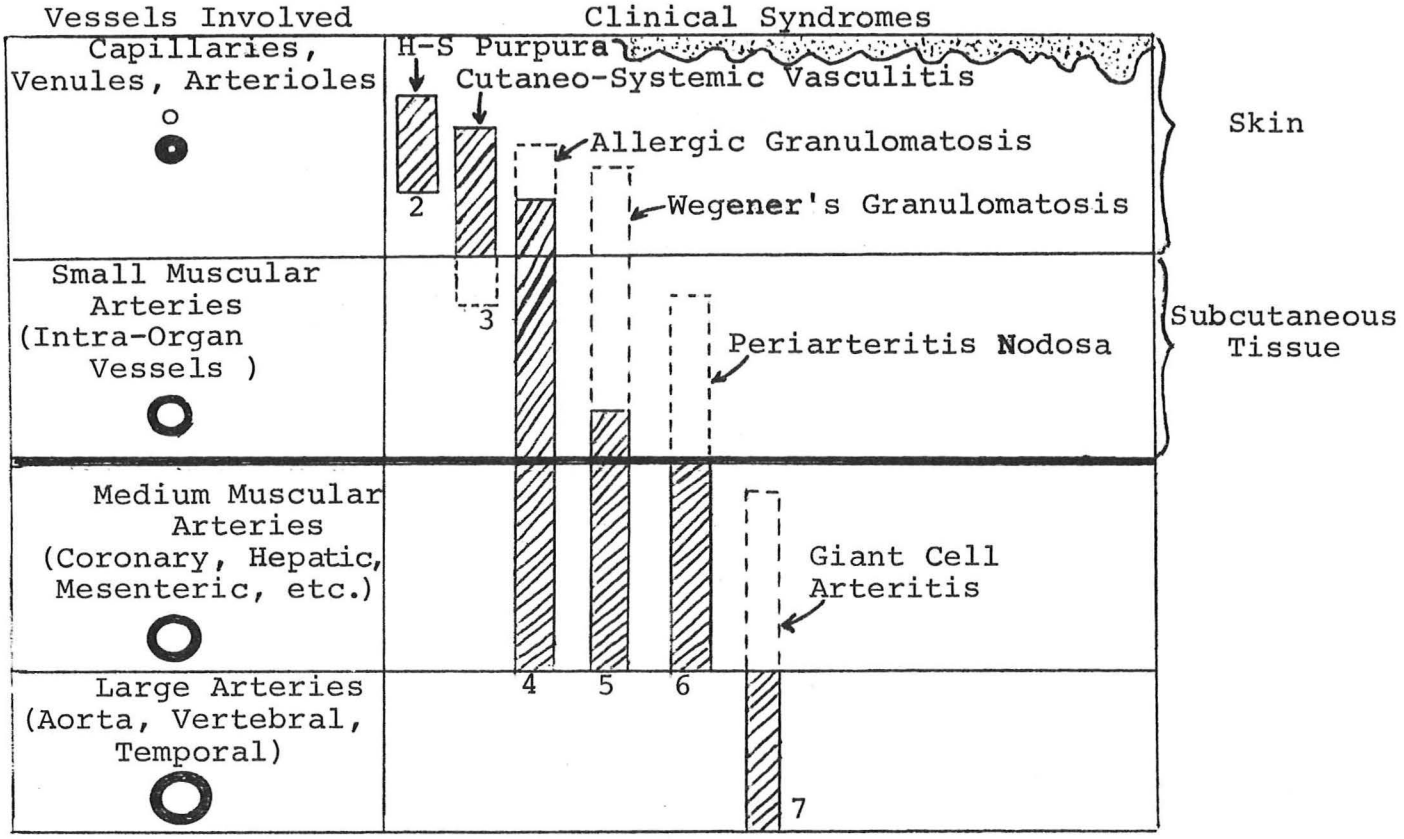
Table I. Classification (Ref. 1,2,3,4)

I. Small blood vessel inflammation
   A. Polymorphonuclear (necrotizing angiitis--venules and capillaries)
      *1. Henoch-Schönlein anaphylactoid purpura
      2. Hypersensitivity angiitis (Zeek, ref. 2)
   B. Lymphocytic
      Steven's-Johnson erythema multiforme
   C. Granulomatous (macrophages and lymphocytes)
      *1. Wegener's granulomatosis
      2. Allergic granulomatosis (Churg and Strauss, ref. 3)
      3. Lethal midline granuloma
      4. Eosinophilic granuloma of the lung (Loeffler's)

II. Medium and large blood vessel inflammation
   A. Polymorphonuclear
      *1. Polyarteritis nodosa
      2. Migratory thrombophlebitis (Behçet's and neoplasms)
   B. Lymphocytic
      1. Erythema nodosum
      2. SLE
   C. Granulomatous (macrophages and lymphocytes)
      1. Nodular vasculitis (Weber-Christian)
      *2. Giant cell arteritis-polymyalgia rheumatica

This classification suffers three significant defects. First, within each vasculitis syndrome listed above, some overlap occurs in the involvement of blood vessels of different sizes as is illustrated in Fig. 1. In addition, the character of the perivascular infiltrate may also overlap two or more cell types, making the disease encountered in some patients difficult to classify. And, third, vasculitis secondary to other systemic autoimmune diseases (other than SLE) are not included in the classification, although these other diseases may be responsible for more than half of thepatients with vasculitis observed clinically (Ref. 1).

Fig. 1. Clinical syndromes of cutaneous vasculitis illustrating variations produced by involvement of blood vessels of different sizes



Patient I. Henoch-Schönlein Anaphylactoid Purpura. [redacted], [redacted]. This 54 year-old WF was admitted on [redacted]-70, because of a purpuric rash on both legs, fever, chills and arthritis for 2 days prior to admission. She had developed atrial fibrillation and diffuse thyroid enlargement 20 months earlier, and had been diagnosed as having Graves' disease based on weight loss, PBI = 18 µg% and increased T3 and T4. She was begun on 400 mg of propylthiouracil/day, guanethidine, phenobarbital, digoxin, trichlormethiazide (Naqua^{R}) and KCl. She gained 14 lbs., felt better, but because of persistent hyperthyroidism, the propylthiouracil was increased to 1.0 g/day. Trichlormethiazide was stopped.

After 19 months, she noticed a transient erythematous rash on her legs and stopped taking all her medications. However, when seen in Clinic, she was instructed to restart propylthiouracil at a dose of 1.2 g/day, and trichlormethiazide, guanethidine and digoxin again given. Three weeks later, a splotchy, painless rash appeared on her right forearm followed soon afterward by fever, chills, arthritis of both ankles and both shoulders. She denied abdominal pain, headaches or urinary symptoms.

Findings at the time of her admission included T = 101.2^{o}, BP = 154/60, P = 100 with a few premature ventricular contractions. The skin rash was maculopapular, erythematous and composed of many superficial

petechiae, some with necrotic centers, over the buttocks, and lower legs. The thyroid was diffusely enlarged. A bruit was heard over the left carotid artery. A grade ii/vi systolic murmur was heard along the left sternal border. A striking arthritis was present in both ankles with pain on motion, warmth, redness and periarticular edema. Slight tenderness to palpation was present in both shoulders.

Laboratory: WBC = 4,600, 64% polys. Hgb = 11.3 gm%, Rbc indices confirmed microcytic hypochromic anemia. ESR = 50, platelet count = normal. Urinalysis: 0-8 Rbc's/hpf, 5-10 WBC's/hpf and 0-4 hyaline casts. Total serum complement = 45 $C'H_{50}$ units. The following tests were within normal limits: VDRL, R.A. latex fixation, antinuclear antibody, ASO, serum cryoglobulin, serum protein electrophoresis, Coombs, SGOT, alkaline phosphatase, bilirubin, EKG, urine culture.

Course: Propylthiouracil and trichlormethiazide were discontinued and she was continued on digoxin and guanethidine. Over the next 5 days, the rash faded rapidly leaving brownish discoloration of the skin. The arthritis, fever and microscopic hematuria also cleared and she was discharged for follow-up in the Endocrine Clinic.

Table II. Organ involvement by vasculitis of Henoch-Schönlein purpura and prognosis of the renal lesion (Ref. 5,6,7)

Series	Cream et al Q. J. Med. (1970)	Ballard et al Am. J. Med. (1970)	Ansell, B.M. B.J.D. (1970)
Number of pts.	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

Any age may be involved (Ref. 6, 7, 8), but children are more likely to have Henoch-Schönlein purpura than adults with a peak incidence from 4 to 8 years of age (Ref. 5). The usual duration of the illness is from 6 to 16 weeks. In addition to the findings mentioned in Table II above, leukocytosis with occasional eosinophilia, elevated ASO titer and hypertension are common. Less frequently cerebral involvement and gastrointestinal hemorrhage may occur.

Gastrointestinal involvement. Although much has been written about the "non-surgical" abdomen in Henoch-Schönlein purpura (Ref. 8) and the usefulness of bowel x-rays or other studies to avoid surgery (Ref. 9, 10), true surgical emergencies occur. Lindenauer

(Ref. 11) describes surgery in 7 patients out of 50 with abdominal symptoms in Henoch-Schönlein. Retroperitoneal or mesenteric hemorrhage produced intussusception in 3 patients requiring small bowel resection. The other 4 subjected to surgery showed no obvious abnormality and recovered from their disease without complications.

Renal involvement. Between 5 and 10% of patients recover from Henoch-Schönlein purpura only to relapse weeks to years later (Ref. 12). Focal mesangial cell proliferation and subendothelial deposits in glomerular capillaries (Ref. 13) (much like the renal lesions of acute post-streptococcal glomerulonephritis) constitute the pathological findings noted in the rare patient subjected to renal biopsy. The significant functional renal impairment during the acute phase of the disease returns to normal in more than 90% of patients. The small fraction (2 to 10%) of patients dying of their disease usually have renal involvement which is severe and may have produced permanent damage (Ref. 5).

Etiology. The offending antigen in Henoch-Schönlein purpura is often difficult to identify. In adults, drugs (as with our patient I) are probably the most frequent antigens involved. Insect bites (Ref. 14) have been implicated. In children, infections, especially with streptococci and staphylococci, may be the most frequent sources of sensitizing antigens (Ref. 15).

Treatment. Withdrawal of offending drugs and conservative management without steroids suffice for most patients. However, patients with quite severe diffuse changes frequently respond to high dosage corticosteroid therapy and to immunosuppressive drugs (Ref. 5).

Patient II. Wegener's Granulomatosis. [redacted]. This 27 year-old WM was admitted on [redacted]-70, with a 4-year history of Wegener's granulomatosis. He began his illness with cough, hemoptysis, nose bleeds and was found to have uremia and nodules in the left lung. Soon afterward, he developed polyneuritis, polyarthritis and episcleritis and was referred to Parkland where a lung biopsy showed "necrotizing granulomas compatible with Wegener's." Initially he was treated with 80 mg/day of prednisolone without benefit. On this dosage he became severely hypertensive and had a grand mal seizure. He was then given azathioprine (Imuran^{R}) 200 mg/day and the prednisolone reduced to 60 mg/day. He improved steadily and was able to return home and to work for the next 2 years. At this time, while on azathioprine, his wife delivered a full-term infant with multiple congenital anomalies, and soon afterward, the patient developed disseminated varicella (chickenpox) and azathioprine was discontinued. He recovered and did not have symptomatic return of his Wegener's for almost 2 more years. Then one month prior to his [redacted]-70 admission, he began to have generalized malaise and weight loss, and returned for re-evaluation.

Significant findings included B.P. = 180/130, Hgb = 7.6 gm%, WBC = 8,200, ESR = 96 mm/hr, urinalysis: 300+ mg% protein, many

Rbc's, WBC's and casts of all types, BUN = 135, creatinine = 15.6, creatinine clearance = less than 20 ml/min, K = 3.6 meq, CO_2 = 16 meq, calcium = 7.2 mg%, phosphorous 11 mg%, paper electrophoresis = normal, alkaline phosphatase = 25 K.A. units; L.E. prep, R.A. latex fixation test = both negative. The x-ray of chest showed a new pulmonary nodule in the left upper lobe.

He was restarted on a combination of 60 mg of prednisolone and 200 mg of azathioprine with improvement and was discharged for followup to the Arthritis Clinic.

Table III. Symptoms and signs in 56 patients with Wegener's granulomatosis (Ref. 16)

Symptoms and Signs	%	
Upper air passages	89.3	
Rhinorrhea and/or sinusitis		60.7
Nasal obstruction without rhinorrhea		7.1
Epistaxis		32.1
Saddle nose		8.9
Gum pain or ulcer		12.5
Hoarseness		15.3
Dysphagia		5.4
Otorrhea and/or deafness		32.1
Eyes	41.1	
Conjunctivitis		30.4
Proptosis		8.9
Dimness of vision		5.4
Scleritis		10.7
Lungs	48.2	
Cough		39.3
Hemoptysis		10.7
Pleural pain		19.6
Urinary tract	25.0	
Oliguria		17.9
Hematuria		7.1
Skin rash	46.4	
Polyarthritis	33.9	
Peripheral neuritis	28.6	

Pulmonary Lesions - Nodular areas of necrotic pulmonary parenchyma are bordered by polymorphonuclears surrounded by a granulomatous infiltrate of epitheloid cells and multinucleate giant cells. Other areas show focal fibrosis and eosinophilic infiltration. Small and medium-sized arteries and capillaries are conspicuously infiltrated by giant cells and polymorphonuclear cells without fibrinoid necrosis or involvement of veins or bronchi (Ref. 22).

Renal Lesions - A focal glomerulitis characterized by mesangial hypercellularity and polymorphonuclear infiltrate is found. These lesions are followed by destruction of the glomerular tuft and scarring. Conspicuously absent are the capillary subendothelial cell deposits characteristic of post-streptococcal glomerulonephritis, SLE or Henoch-Schönlein's syndrome (Ref. 22).

Table IV. X-ray and laboratory findings in 56 patients with Wegener's granulomatosis (Ref. 16)

Clinical Investigation	% Abnormal
Radiography	
Skull: sinus opacities	85.7
Lung shadows	95.0
Round and discrete	57.5
Bronchopneumonic infiltration	25.0
Hematology	
Microcytic anemia	97.0
Leukocytosis	67.9
Eosinophil leukocytosis	45.9
Urine	
Albumin	88.0
Erythrocytes	81.0
Leukocytes	50.0
Casts	66.7
Biochemistry	
Uremia	83.2
Hyperglobulinemia	80.0
High blood pressure	24.2

Prognosis and therapy. Patients developing Wegener's granulomatosis in the past had an average survival of only 5 months after the initial onset of their illness, most often dying from uremia (Ref. 17). Steroid therapy alone proved of limited value. However, beginning with a case report (Ref. 18) using chlorambucil in 1966, several immunosuppressive drugs used alone or with steroids have been evaluated in the therapy of isolated patients with Wegener's. Azathioprine (Ref. 19, 20, 21, 22), chlorambucil (Ref. 18, 23, 24), methotrexate (Ref. 25) and cyclophosphamide (Ref. 26) have all proven successful agents when compared to the otherwise bleak prognosis on steroids alone.

Limited Wegener's granulomatosis without significant glomerulonephritis has been described (Ref. 26, 27), but it seems to be a slightly more benign (~50% fatal) variant of the more extensive disease.

Closely related vasculitis syndromes include: (1) allergic granulomatosis which is usually associated with asthmatic symptoms, eosinophilia, greater restriction to the lungs and a good response to high dosage of corticosteroids (Ref. 29) although central nervous system involvement has been described (Ref. 30); and (2) lethal midline granuloma which is usually limited to the upper respiratory tract (Ref. 31). Like Wegener's lethal midline granuloma has been shown to respond to antimetabolite (methotrexate and 5-fluorouracil) therapy (Ref. 32).

Patient III. Polyarteritis Nodosa Associated With Australian Antigen Positive Hepatitis. [redacted] [redacted]. This 38 year-old WF was admitted on [redacted]-65, with a 5-month history of edema of the hands, joint swelling, arthralgias, fever and peripheral neuropathy. Personality changes compatible with organic brain disease had also been noted. An extensive work-up by her private physician had established the presence of cholecystitis, slight elevation of bilirubin, alkaline phosphatase = 8 to 17 Bodansky units, BSP = 30% retention in 45 min., SGOT = 78. A muscle and liver biopsy taken previously were reviewed after her admission to PMH and a diagnosis of "polyarteritis nodosa" made on both tissues.

Findings on P.E. after admission included B.P. = 130/90, T = 101° F., marked weakness, splenomegaly and hepatomegaly, RUQ tenderness, muscle atrophy of the quadriceps and gastrocnemius bilaterally, bilateral lower leg edema and bilateral wrist and ankle drop. Patchy sensory deficit was also present over the left arm and hand. Deep tendon reflexes were normal and Babinskis absent. No jaundice or skin rash was present.

Laboratory evaluation showed WBC = 10,200, urinalysis normal, ESR = 32, aldolase = nl, creatine phosphokinase = nl, EKG showed nonspecific ST and T-wave changes, and EMG and nerve conduction studies were consistent with a peripheral neuropathy.

She was begun on 60 mg of prednisolone daily and discharged after 8 days to return to her physician in New Mexico. No details of her subsequent course are available. In 1970, evaluation of her serum showed it to be positive for Australian antigen.

Table V. Symptoms and signs of periarteritis nodosa with frequency of occurrence in 300 cases (Ref. 33)

	%		%
Fever	85	Jaundice	10
Abdominal pain	65	Convulsions	10
Hypertension	60	Eruptions	10
Edema	50	Diarrhea	10
Neuritis	50	Muscle soreness	10
Weakness	45	Leukocytosis	80
Weight loss	45	Albuminuria	60
Cough and dyspnea	40	Hematuria	40
Vomiting	30	Eosinophilia	25
Headache	30	Uremia	15
Precordial pain	25		

Diagnosis of polyarteritis nodosa is more certain than some of the other types of vasculitis because of the characteristic distribution of involvement in small and medium-sized muscular arteries particularly at points of bifurcation or branching (Ref. 2). However, selection of an appropriate site for biopsy is essential for the highest yield of positive results. Table VI summarizes the actual distribution of vascular lesions present in a large group of autopsied patients dying of polyarteritis nodosa.

Table VI. Incidence of polyarteritis nodosa lesions in various organs at necropsy in 114 patients (Ref. 34, 35)

Organ	% Positive
Kidney (arteritis)	67
Liver	58
Heart	43
Gallbladder	40
Small intestine	39
Adrenals	39
Spleen	35
Testes, ovaries	17
Muscle	17
Skin	13
Peripheral nerves	7
Brain	4

From the above, it is obvious that kidney and liver biopsies would be more productive than the more frequently obtained skin and muscle. However, the nature of the vascular lesions and the frequent association of hypertension and uremia with very ill patients introduces both morbidity and mortality into biopsies of liver or kidney in these patients (Ref. 36).

Selective visceral angiography as a superior method for the diagnosis of polyarteritis nodosa. New techniques by which a percutaneous intra-aortic catheter may be placed in front of the renal, mesenteric or hepatic arterial orifices, and radiopaque contrast medium delivered to a particular aortic branch has allowed selective visceral angiography. This has demonstrated multiple aneurysm formation in the peripheral branches of the renal and mesenteric arteries now considered diagnostic of polyarteritis nodosa (Ref. 37-43). This technique allows a more widespread survey of abdominal viscera, perhaps with greater safety than renal or hepatic biopsy. Even in patients treated with steroids who recover from the disease, persistence of these aneurysms may produce intra-abdominal or perirenal hemorrhage years afterward (Ref. 36).

Table VII. Association of different drugs with subsequent polyarteritis nodosa (Ref. 34, 44-49)

Drug Implicated as Antigen
Sulfonamides
Penicillin
Gold thiomalate
Vaccines
Thiazide diuretics
Guanethidine
Methamphetamine
LSD
Heroin
Procaine amide

Etiology of polyarteritis nodosa. Until recently, the disease in about 25% of patients with polyarteritis nodosa could be attributed to drug sensitization (Table VII), and another 25% of patients were shown to have had preceding infections (Ref. 34, 50, 51). The remaining 50% of patients showed no identifiable association with a specific exogenous antigen. However, in 1970, Gocke and his coworkers (Ref. 52) and Trepo and his colleagues (Ref. 53, 54) showed that some of these remaining patients were positive for the Australian antigen. In Trepo's series (Ref. 53), 6 out of 7 patients studied were positive. Our own collection of polyarteritis patients here at PMH would suggest about 25% to be positive compared to an expected frequency of 0.5 to 1% in the general population.

The demonstration of a transferable serum factor in sera of patients with polyarteritis which is cytotoxic raises the possibility of circulating viral-antibody complexes (Ref. 55). Indeed, Williams (Ref. 56) has shown that such antigen-antibody complexes may be responsible for some of the cytotoxic properties of sera from patients with S.L.E.

The relationship of treatment to the long-term prognosis of PAN. Often the damage to small muscular arteries is extensive before a diagnosis is made and steroid therapy begun, and renal changes may have occurred which are irreversible. However, the lesions tend to come in waves and survival is enhanced by steroid therapy as is shown below.

Table VIII. Expected survivorships* in patients with polyarteritis nodosa (Ref. 57)

	Patients				Treated Patients			
	$\bar{c}$ Steroid		$\bar{s}$ Steroid		$\bar{c}$ HBP		$\bar{c}$ Renal Dis.	
Yrs. $\bar{p}$ Dx.	No.	Cumul. % Surviving	No.	Cumul. % Surviving	No.	Cumul. % Surviving	No.	Cumul. % Surviving
0	110	100.0	20	100.0	26	100.0	34	100.0
1/4	73	70.2	10	50.0	14	53.8	18	57.6
1/2	71	68.3	7	35.0	13	50.0	17	54.4
1	64	62.9	7	35.0	12	46.1	16	51.2
2	57	57.9	5	29.6	12	46.1	15	48.0
3	48	51.7	4	29.6	11	42.3	14	44.8
4	43	50.5	1	12.7	9	38.3	13	41.6
5	35	48.0	1	12.7	7	33.8	10	34.9
6	30	48.0						
7	27	46.8						
8	23	44.5						
9	19	42.4						
10	16	42.4						

*Calculated by the life-table method of Merrell and Shulman.

Steroid therapy accelerates healing of the vascular lesions, but aneurysms (Ref. 36) and residual renal glomerular damage remain. They occasionally cause severe worsening of hypertension or hypercalciuria with additional renal impairment (Ref. 58).

Both anticoagulant therapy (Ref. 59) and chlorambucil (Ref. 60) have been reported (in isolated patients) to have been beneficial in patients with polyarteritis nodosa not helped by steroid therapy.

Patient IV. Polymyalgia Rheumatica-Giant Cell Arteritis. [redacted]. This 44 year-old WF was referred by the Neurosurgery Dept. on [redacted]-70, because of progressive loss of vision in the right eye over the preceding 11 months. Her illness began 5 years earlier when she noted intermittent loss of balance with falling to the right, sometimes even while sitting in a chair, and heard brief bursts of high pitched whistling noises. Four years PTA, she began to notice flashing lights and circles of light in the right eye, and others observed that both pupils would dilate. Her private physician began her on a motion sickness pill, and skull x-ray showed old left mastoid injury from a fall age 12, but no other objective findings were observed. Mild right-sided headaches were relieved by aspirin, but if untreated, would last all day and recur once or twice each month. In addition, she had muscle stiffness and myalgias.

In 1967, she had a "nervous breakdown" and was seen once by a psychiatrist who treated her with Librium, later switching to doxepin (Sinequan). In 1968, she had a urethral dilatation, and while in the hospital developed an acute surgical abdomen. Laparotomy revealed no objective findings, however.

In [redacted], 1969, she consulted an ophthalmologist who found a blind spot in the right eye. Two months later, she had an episode of severe RUQ pain and was hospitalized for cholecystitis, but no surgery was done. During the past 5 years, she has lost 38 lbs. in weight with no effort at dieting, and has had unexplained episodes of fever about once each week as high as 101°F. In addition, she has had mild arthritis of the PIP joints of the right hand and has experienced classical Raynaud's phenomenon after cold exposure.

She denied pleurisy, peripheral neuropathy or other arthritis. However, she has experienced allergic skin rashes to sulfonamides (1954), Novocaine (1963) and penicillin (1965).

P.E.: Vital signs were normal. A right visual field was grossly abnormal with loss of all of her central vision. The left eye was normal. The pupils were round, regular and equal and both reacted to light and accommodation. The right shoulder joint was slightly tender to pressure, and there was pain to deep pressure in the RUQ. Tenderness over the right temporal artery was present, but no redness or nodularity. Some muscle soreness was noted.

Laboratory: WBC, Hgb and urinalysis were normal. ESR = 103 mm/hr (Westergren), serum protein electrophoresis showed elevated alpha-2 globulin, but normal gamma globulin. Carotid arteriography showed a 20% narrowing of the right internal carotid (?arteriosclerotic change), LE prep, RA latex fixation were both negative; cholesterol = 192, triglycerides = 116 mg%.

Course: The patient was diagnosed as having temporal arteritis and a temporal artery biopsy recommended on the right in the area of tenderness. This was done on [redacted]-70, and showed normal histology. She continued to complain of generalized muscle aches and low-grade fever, and was begun on 10 mg of prednisolone per day with dramatic improvement. She was able to taper the drug to 7.5 mg/day, and has continued to show improvement.

Manifestations of systemic giant-cell arteritis (Ref. 61). The clinical and laboratory features of 18 patients with the syndrome of polymyalgia rheumatica seen in an 18-month period showed the average age of the patients to be 68 years; 17 were women. All had proximal muscle pain and tenderness and high erythrocyte sedimentation rate (mean of 102 mm/hr). Fever, anemia and malaise were common. All these findings were rapidly reversed by corticosteroid therapy. A small maintenance dose was frequently needed for continued suppression of the illness. No patient had rheumatoid factor, antinuclear factors, or elevated muscle enzymes in the serum; none have developed arthritis, malignancy, or other disease after observation of at least one year. The temporal artery was biopsied in 12 patients and showed arteritis in 3.

Other studies (Ref. 62, 63, 64) have shown the disease in patients as young as 19 and as old as 83 years old. Skin involvement is very rare, but one patient had ulcerations of the scalp due to temporal artery occlusion (Ref. 65). Muscle wasting and peripheral neuropathy may be prominent features of the disease (Ref. 66). Recurrent blanching of the tongue is a highly suggestive symptom of this diagnosis (Ref. 67).

Diagnosis. As was true in our patient IV, even when tenderness is present, biopsy of the artery may show normal histology (Ref. 68) although biopsy and angiography (Ref. 69) are indicated diagnostic procedures in giant-cell arteritis.

Major complication of giant-cell arteritis is blindness. Once complete, this blindness is usually irreversible. Biopsy of the temporal artery may release a stimulus for vascular spasm and have therapeutic as well as diagnostic value (Ref. 70). One report of retrobulbar injection of steroid is said to have restored vision (Ref. 71).

Etiology of giant-cell arteritis is unknown in most patients. However, a few clearly related to drug therapy have been described (Ref. 72, 73). The self-limited aspects of the disease suggests some exogenous antigen in most patients (Ref. 62).

Therapy with corticosteroids is usually so effective that

it is almost diagnostic of the disorder, and low maintenance doses in the range of 5 to 7.5 mg of prednisolone/day are effective in maintaining remission in most patients for the 6-24 month course of the disorder (Ref. 62).

Variants of giant-cell arteritis include Takayashu's Disease (Pulseless disease) which affects larger vessels, younger persons and has fewer muscle and joint symptoms. It is quite rare in the United States (Ref. 74).

General Immunological Mechanisms of Vasculitis

Fig. 2. Manner in which complexes alter vascular function.

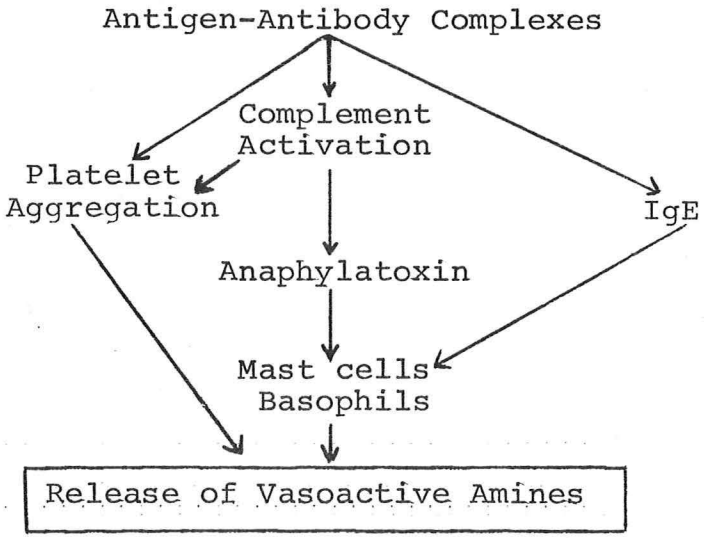


Table IX. Variables in antigen-antibody complexes which could alter the clinical manifestations of complex-induced vasculitis

1. Quantity
2. Size
3. Solubility
4. Ratio of Antigen to Antibody
5. Number of Antigenic Sites per Antigen Molecule
6. Character of the Antibody (IgE, IgG, IgM, etc.)

Arthus and Schwartzmann reactions have been suggested by some to explain many of the pathological features of systemic vasculitis (Ref. 75).

Fig. 3 AMPLIFICATION OF SUBSEQUENT ALLERGIC VASCULITIS BY PRIOR ENTRAPMENT OF ANTIGEN

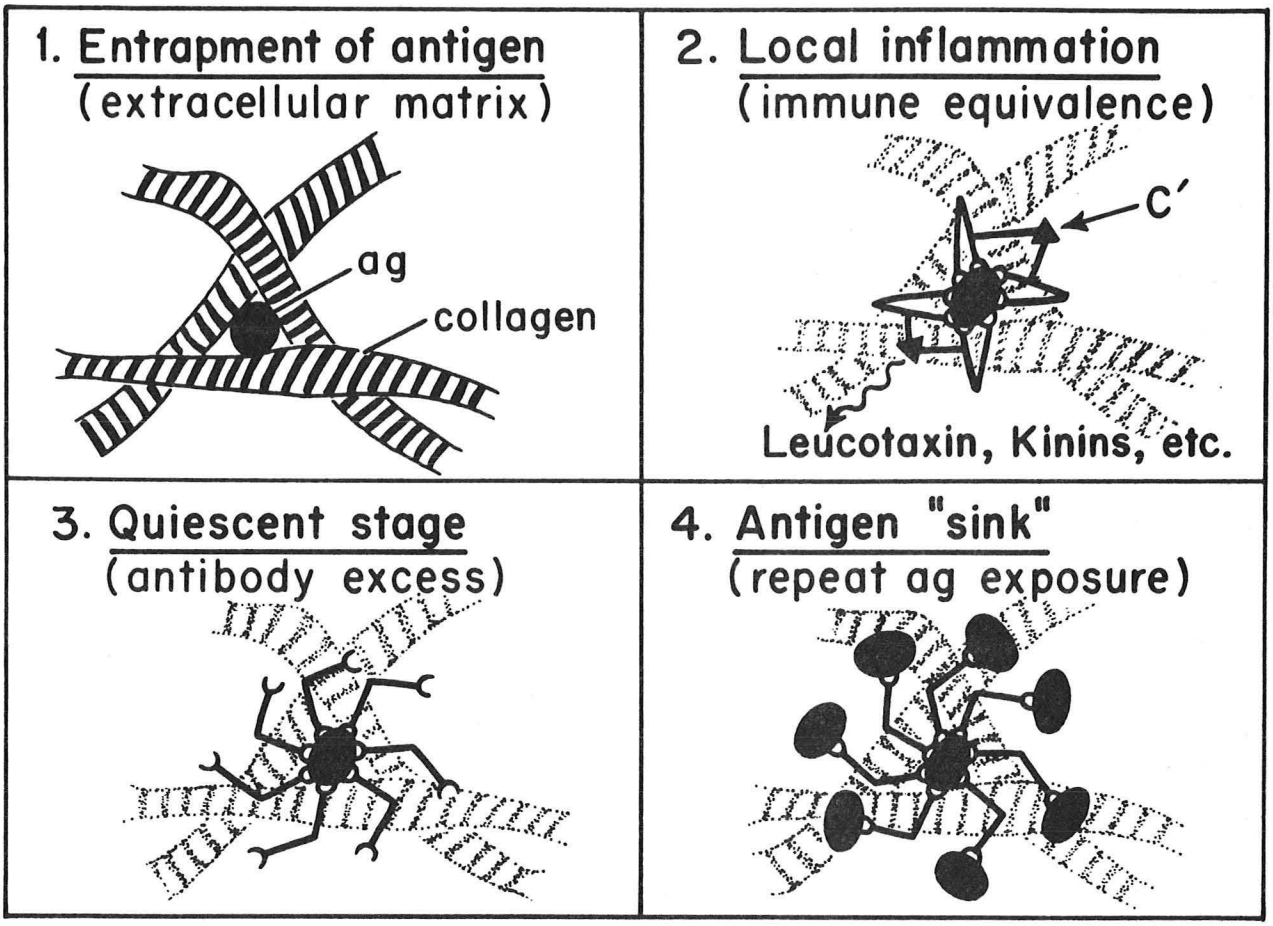
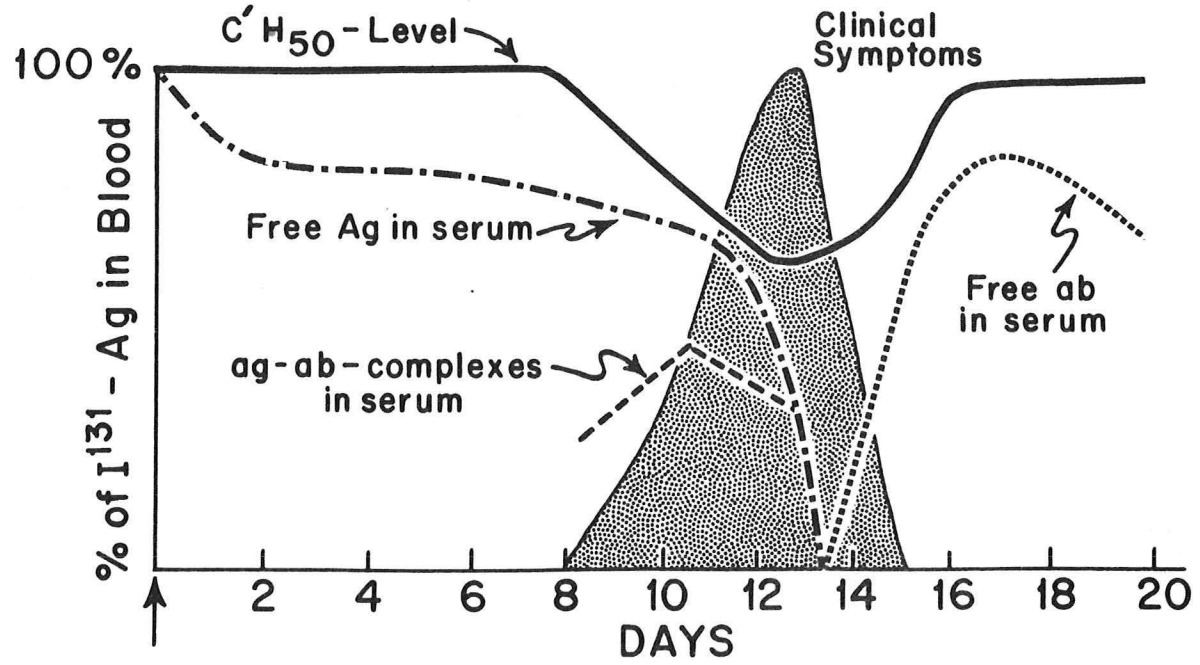


Fig. 4 ONE SHOT, ANTIGEN-INDUCED SERUM SICKNESS



Antigen localization in the connective tissue matrix of blood vessel walls and other extracellular areas. Recent studies by Sery and Nagy (Ref. 76) with the avascular rabbit cornea have shown entrapment of antigen on the injected side which persists for long periods and can be demonstrated by repeat injection of the rabbit at a distant site with the specific antigen. Similar findings have been noted by Jasin and Cooke (Ref. 77, 78) and by Webb et al (Ref. 79) in experimental antigen-induced arthritis in the rabbit. Jasin and Cooke (Ref. 78) have shown more than 67% of retained antigen to be trapped after more than two months in ligaments, tendons and cartilage of injected joints, and less than 1% retained by the metabolically active synovium.

Antigens (radioactively tagged) have been shown to persist for long periods in the extracellular space in the germinal centers of lymph nodes of immunized animals (Ref. 80, 81, 82), and the dendritic processes of lymphocytes have been shown to be in intimate contact with the reticulin fibers (collagen and polysaccharide) of the germinal center in such stimulated lymph nodes (Ref. 83).

A similar explanation could be used to explain the localization of antigen-antibody complexes which may be seen in or near the vascular basement membrane in chronic glomerulonephritis, SLE and the different varieties of systemic allergic vasculitis.

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