NECROTIZING ANGIITIS:
I. A CLINICAL REVIEW OF TWENTY-SEVEN AUTOPSIED CASES

JOHN D. O'DUFFY, M.B., ARTHUR L. SCHERBEL, M.D.,
Department of Rheumatic Disease

HOWARD E. REIDBORD, M.D.,* and LAWRENCE J. McCORMACK, M.D.
Division of Pathology

SINCE its description by Kussmaul and Maier[1] in 1866, polyarteritis nodosa has been variously classified, and yet its precise etiology is still unknown. In the first quarter of this century, numerous unsuccessful attempts were made to indict infection as an etiologic factor. Ever since 1925, when Gruber[2] suggested that a systemic hyperallergic reaction to various infections and toxic agents might be incriminated, there has been much speculation concerning the possible role of hypersensitivity. In 1952, Zeek[3] suggested that hypertension might play an important role in the precipitation of what she called 'necrotizing angiitis.' The term necrotizing angiitis includes all vascular lesions showing inflammation and necrosis; this term was designated by Zeek to include the entire spectrum of entities which had come to be known as polyarteritis nodosa. Zeek[3] sought to differentiate between the two entities, polyarteritis nodosa and hypersensitivity angiitis; the distinctive pathologic features of these two entities were outlined as follows:

(1) Involvement of large arteries in polyarteritis nodosa; involvement of small arteries, venules, and arterioles in hypersensitivity angiitis.

(2) Acute and healing lesions in polyarteritis nodosa; all lesions tending to be of the same age in what was considered to be the more lethal entity, hypersensitivity angiitis.

The concept that hypersensitivity angiitis of the type defined by Zeek[3] can be clinically differentiated from polyarteritis nodosa described by Kussmaul and Maier[1] has been challenged. Recently Austen and Fitzpatrick suggested that a unifying concept is needed in approaching this group of diseases, and that a classification based on clinicopathologic correlations is lacking.[4]

The purposes of this study are: (1) to determine whether or not clinical differences exist between patients with polyarteritis nodosa and those with hypersensitivity angiitis, and (2) to highlight certain clinical features that have not received sufficient attention.

Material

The series comprises 27 cases of necrotizing angiitis in which autopsies were performed at the Cleveland Clinic between January 1, 1942, and December 31, 1963.

**Formerly Fellow in the Division of Pathology; present address: Armed Forces Institute of Pathology, Washington, D.C. 20305.*

There were 18 male and 9 female patients, ranging in age from 6 to 79 years. Zeek's[3] classification was used to distinguish cases of polyarteritis nodosa from those of hypersensitivity angiitis. The pathologic diagnoses (*Table 1*) were as follows: polyarteritis nodosa in 12; hypersensitivity angiitis in 11; and Wegener's granulomatosis in 4. Hypertensive patients in whom the vascular lesions were predominantly those of that disorder even though vascular necrosis was present, and those whose renal disease was primarily chronic glomerulonephitis were excluded from this series. In 13 cases excluded for this latter reason, necrotizing lesions were found in only a few organs, pancreas, spleen, and intestine; and the acute vascular disease played little part in the cause of death.

Table 1.—*Clinical findings in 27 cases of necrotizing angiitis*

Factor	Number of cases				Percent
	Hypersensitivity angiitis (11 cases)	Polyarteritis nodosa (12 cases)	Wegener's granulomatosis (4 cases)	Total (27 cases)	
Sex					
Male	8	9	1	18	67
Female	3	3	3	9	33
History of allergy	4	1	1	6	22
Fever	9	9	4	22	81
Trauma	4	3	—	7	26
Edema	8	5	2	15	55
Purpura	5	—	1	6	22
Arthralgia	5	5	1	11	41
Pulmonary manifestations	6	2	4	12	44
Dermatologic abnormalities	5	4	3	12	44
Muscle	4	8	2	14	52
Neurologic abnormalities	7	6	2	15	56
Ocular abnormalities	2	3	3	8	30
Gastrointestinal tract dysfunction	6	7	3	16*	60
Anemia	7	9	4	20	74
Elevated sedimentation rate	6 of 6	4 of 5	1 of 2	11 of 13	85
Abnormal urine	11	8	3 of 3†	22 of 26	85
Associated malignancy	—	2	—	2	7
Cardiac abnormalities	7	6	—	13	48
Leukocytosis	7	10	4	21	78
Eosinophilia	3 of 10	3 of 12	2	8 of 24	33
Hypertension	8	6 of 11†	—	14 of 26	54

*Five of 15 showed abnormal liver function tests.
†Number of cases available.

Observations and Discussion

The male to female ratio of 2:1 is comparable to that reported in a previous large series.[5] It is interesting that the sex ratio in this connective tissue disease differs strikingly from that in systemic lupus erythematosus, in rheumatoid arthritis, and in scleroderma, all predominantly diseases of women.

The remarkable similarity between the systemic involvement in the 11 cases of hypersensitivity angiitis and that in the 12 cases of polyarteritis nodosa is depicted in *Table 1*. However, differences in the frequency of systemic involvement are: (1) Only 8 of 12 patients with polyarteritis nodosa had abnormal urine at some time during the course of illness, but all 11 patients with hypersensitivity angiitis had abnormal urine. (2) The patients with the large-vessel type of angiitis were less likely to have pulmonary changes observable on chest roentgenograms or to have a recent history of drug allergy. (3) No patient with polyarteritis nodosa had purpuric lesions, but 5 of 11 with hypersensitivity angiitis had purpura.

Therefore, although there is a great similarity between the systemic involvements in both entities, there are certain features that may help to distinguish them clinically. In a patient with angiitis the combination of renal involvement, purpura, a history of recent drug allergy, and pulmonary infiltrate favors a diagnosis of hypersensitivity angiitis rather than polyarteritis nodosa. However, since the mean duration of illness was 5.5 months in the patients with polyarteritis nodosa and 3.7 months in those with hypersensitivity angiitis, and since it is not known whether treatment is more effective in one type than in the other, it is at present merely of academic interest to be able to distinguish these two entities in the patient. The variety of reasons for which the patients were referred is depicted in *Table 2*.

Table 2.—*Main reason for referral in 27 cases of necrotizing angiitis*

Manifestations	Number of cases
Renal failure	8
Arthralgia	3
Fever of unknown origin	3
Abdominal pain	2
Cough	2
Myalgia	2
Anorexia	1
Asthma	1
Coma	1
Episcleritis	1
Nodular skin lesions	1
Otalgia	1
Sinusitis	1
Total	27

Renal involvement. Eight of the 27 patients were referred to the hospital primarily for hemodialysis because of renal failure. In a few of these patients angiitis was unexpected and diagnosed only at autopsy. The commonest terminal clinical picture was one of uremia and left ventricular failure. Eighty-five percent of the patients had abnormaliurine at some stage of the illness.

The high incidence of renal involvement may be contrasted with an incidence of 37 percent n the 37 cases diagnosed at biopsy reported by McCombs, Patterson, and MacMahon.[6] In their series the mortality rate was 50 percent and the authors concluded that the presence of renal involvement in necrotizing angiitis was an ominous finding.

Hypertension. Of the 14 patients in our series who had hypertension at some time during the course of illness, only one patient had a long history of high blood pressure. This patient died from fulminating vasculitis of the mesenteric vessels one week after undergoing resection of an aortic coarctation. This sequence of events has previously been reported,[7] and may be related to the vascular changes in experimental hypertension in the Sprague-Dawley rat; i.e., a sudden increase in blood pressure in the affected area caused vasculitis.

Pulmonary involvement. Pulmonary symptoms or signs, excluding those attributable to cardiac failure or uremia, were present in 12 patients. Fever (in 22 of 27 cases) often in the range of 102 to 103 F., was especially prominent in patients with outstanding pulmonary signs. Whereas nonspecific pulmonary infiltrates were seen in the roentgenograms of 6 of 11 cases of hypersensitivity angiitis, in each patient with Wegener's granulomatosis nodular densities were seen in the lungs.

Wegener's granulomatosis is characterized by necrotic and destructive granulomatous lesions of the upper and lower respiratory tracts, glomerulopathy, and a widespread arteritis.[8] Although Wegener's granulomatosis is generally considered to be a variant of polyarteritis nodosa, several authorities[8,9] classify it separately. Clinically, the diagnosis of Wegener's granulomatosis is usually grossly evident, inasmuch as purulent pansinusitis with or without oral or ophthalmologic involvement is present in about 90 percent of the cases in addition to the gross pulmonary lesions.

Rose and Spencer[10] found that the presence of pulmonary involvement in polyarteritis nodosa served as a useful guide in devising a classification of the disease. However, they stated that all of their patients with pulmonary involvement had had a previous respiratory infection. Their study was compiled from several different sources and the close association between prior infection and necrotizing angiitis has not been reported in any other series. Less clear is the status of the entity allergic granulomatous angiitis described by Churg and Strauss.[11] This condition is characterized by prominent allergic manifestations, particularly asthma, as well as extravascular granulomas, pronounced eosinophilia, and a diffuse vasculitis. It probably runs a more benign course than Wegener's granulomatosis or hypersensitivity angiitis.

Cardiac involvement. Cardiac involvement, manifested by cardiac enlargement or arrhythmia, was present in 13 of the 27 cases of necrotizing angiitis. In only two instances in our series was angina pectoris recorded, and one patient incurred a myocardial infarction. The findings on electrocardiograms of 18 of 22 patients were abnormal (*Table 3*). In several instances, the electrocardiograms changed from

Table 3.—*Electrocardiographic findings in 13 cases of necrotizing angiitis*

Findings	Number of cases
Nonspecific myocardial changes or left ventricular hypertrophy	10
Arrhythmia	3
Cardiac conduction defect	3
Myocardial infarction	1
Pericarditis	1
Total	13

normal at the onset, to grossly abnormal later in the course of the disease, presumably because of hypertension and renal disease. First-degree atrioventricular block was recorded twice; right bundle-branch block once. The arrhythmias consisted of two cases of atrial fibrillation and one of supraventricular tachycardia. At autopsy, in the patient who had the myocardial infarction, healed vasculitis of the coronary vessels was found. Therefore, in only one case was myocardial infarction directly related to the acute vascular disease.

Logue and Mullins[12] found a high incidence of coronary insufficiency in their review of cases of polyarteritis nodosa, but myocardial infarction occurred rarely. A frequent cause of death in the present series was myocardial failure after prolonged hypertension and renal failure.

Dermatologic involvement. The coexistence of purpura and hypersensitivity angiitis has already been stressed. In this series (*Table 4*) three of the four patients who had Wegener's granulomatosis had nodular ulcerating lesions of the skin. Biopsy of these lesions in two cases was the basis of the diagnosis of necrotizing angiitis. Whereas Raynaud's phenomenon is the rule in systemic sclerosis, and is common in systemic lupus erythematosus, it was present in only one patient in this series.

The skin lesions of necrotizing angiitis are microinfarcts resulting from arteriolar occlusion. In previously reported series,[13] the incidence of skin lesions has usually ranged from 20 to 35 percent. In general, the skin manifestations have been clinically nonspecific and are not distinctive enough to be helpful in making the clinical diagnosis. Few modern observers record palpable nodulations in the walls of medium-sized arteries as described by Kussmaul and Maier.[1] The common dermatologic lesions previously reported were disseminated papular and necrotic

Table 4.—*Skin lesions in 12 cases of necrotizing angiitis*

Lesion	Number of cases
Purpura	6
Nodulations	4
Macular erythema	2
Macular papular erythema	2
Urticaria	1
Raynaud's phenomenon (also purpura)	1

eruptions, purpura, erythema multiforme, and macular erythematous lesions. We suggest that skin biopsy can aid in a definite diagnosis if the skin lesions are large enough, and particularly if nodules exist. Furthermore, purpura of the dependent parts of a patient with a puzzling disease should raise suspicions of necrotizing angiitis.

Neurologic involvement. Fifteen (56 percent) of the 27 patients had neurologic symptoms; of these, 12 had involvement of the central nervous system, frequently in association with uremia or hypertensive encephalopathy. In one patient the signs of central nervous system disorder were so prominent that bilateral cranial trephinings were performed in search of an expanding intracranial hematoma. Only three of the patients had a distinct peripheral neuropathy; it was confined to the lower extremities and was mainly of the sensorimotor type.

There is a precedent for cranial trephining in hypersensitivity angiitis.[14] In other series[5,15] the incidence of peripheral neuropathy was from 20 to 35 percent.

Gastrointestinal manifestations. Prominent among the gastrointestinal symptoms of the 27 patients were abdominal pain, nausea, and vomiting. Nausea and vomiting were often related to uremia. One patient had a history of abdominal angina. One patient who was under treatment with corticosteroid drugs died during operation for a perforated appendix. Although mild abnormalities of hepatic function were found in 5 of the 10 patients tested, in no case was jaundice detected, despite the fact that the liver was so often pathologically involved.

Mowrey and Lundberg[16] reported the incidence of abdominal pain to be 40 percent in their series of 607 cases. Griffith and Vural[17] found that the liver was the most commonly affected organ in patients having polyarteritis nodosa. In a review of 607 cases of polyarteritis nodosa, Mowrey and Lundberg[16] found abnormal liver function tests in only 6 percent and that jaundice occurred rarely. They assumed that the dual hepatic blood supply rendered the organ much less susceptible to infarction.

Musculoskeletal involvement. Myalgia occurred in 14 of the 27 patients in this series and arthralgias in 11; the latter had often led to an erroneous diagnosis of

rheumatoid arthritis. In no case were the typical clinical changes of rheumatoid arthritis present, so that this series does not contain any instance in which polyarteritis nodosa was a complication of rheumatoid arthritis. One patient with rheumatoid arthritis who had angiitis proved by muscle biopsy was found to be free of angiitis when he died of *Proteus* peritonitis; this case was excluded from our study.

A necrotizing angiitis complicating rheumatoid arthritis has recently received emphasis, and its relation to previous administration of steroids has been questioned.[18, 19] Muscle tenderness is a useful sign of necrotizing angiitis, and, if possible, an area of such tenderness should be chosen for biopsy. The biopsy is much more likely to be positive when taken from a tender area.

Ocular manifestations. Excluding hypertensive retinopathy and conjunctival hemorrhage, there were eight cases of acute ocular manifestations in this series (*Table 5*). The two patients with episcleritis and the one patient with conjunctivitis

Table 5.—*Ocular lesions in eight cases of necrotizing angiitis*

Lesion	Number of cases
Blindness (optic neuritis or optic atrophy)	3
Episcleritis	2
Conjunctivitis	1
Conjunctival and retinal hemorrhage	1
Raised macular lesion	1
Total	8

had Wegener's granulomatosis. Inasmuch as the cornea, vitreous humor, sclera, uvea, and orbit are mesenchymal in origin, they are rich in polysaccharides and would therefore be expected to be involved in a disease of connective tissue.

All ocular structures have been reported[20-23] to be affected except the lens. Cytoid bodies, that is, cotton-wool exudates, have been described as typical manifestations of the connective tissue diseases and have been particularly associated with systemic lupus erythematosus. In necrotizing angiitis, a nongranulomatous iritis is uncommon, and retinal vasculitis with occlusion of the central retinal artery is better known.[22] Additional ophthalmologic changes reported have been episcleritis and nodular scleritis. In temporal arteritis, ocular involvement eventually occurs in about 40 percent of the cases, according to Bruce[23] and Parsons-Smith.[24] In necrotizing angiitis, angiospastic exudative retinopathy with partial or total occlusion of the retinal arterioles resulting in cotton-wool patches, hemorrhages, retinal or subretinal edema with or without retinal detachment and optic neuritis, is common according to Godtfredsen.[22]

Laboratory data. The high incidence (11 of 13 cases) of an elevated sedimenta-

tion rate in this series parallels that reported by Nuzum and Nuzum[5] who found an elevated sedimentation rate in 98 percent of 175 case reports that they reviewed from the literature.

The unusually high incidence of anemia, 20 cases (74 percent), in the present series is no doubt related to the high incidence of uremia. The incidence of eosinophilia (5 percent or more eosinophils) was 33 percent (eight cases), and is comparable to the 19 percent incidence reported by Nuzum and Nuzum.[5] Leukocyte counts of more than 10,000 per cubic millimeter were recorded for 21 of our cases, and in some cases there were leukemoid reactions with white blood cell counts of up to 50,000 per cubic millimeter.

The results of serum protein electrophoresis in seven cases of necrotizing angiitis are presented in *Table 6*. Hypoalbuminemia and an increase in α-2-globulin

Table 6.—*Results of serum protein electrophoresis in seven cases of necrotizing angiitis*

Case no.	Protein electrophoresis, gm./100 ml.				
	$\alpha 1$	$\alpha 2$	β	γ	Albumin
1	0.6	0.6	1.2	1.8	1.7
2	0.7	1.3	1.4	—	1.8
3	0.4	0.6	0.8	2.3	3.0
4	0.6	1.1	0.7	1.8	1.4
5	0.4	0.9	0.8	1.7	1.6
6	0.3	0.5	0.7	1.2	3.6
7	0.3	0.8	0.8	1.4	3.4
Average	0.47	0.83	0.91	1.45	2.35
Normal	0.23 ± 0.07	0.48 ± 0.10	0.64 ± 0.14	0.95 ± 0.20	4.73 ± 0.41

and γ-globulin occur characteristically. This protein distribution is similar to that found in patients having active rheumatoid arthritis or systemic lupus erythematosus. The presence of hypergammaglobulinemia lends some support to the theory that necrotizing angiitis is another of the so-called autoimmune diseases. However, Mackay and Burnet[25] admitted that the evidence for autoimmune processes playing a role in polyarteritis nodosa, scleroderma, and dermatomyositis is weaker than it is for systemic lupus erythematosus. They believed, however, that the hypergammaglobulinemia and the response to corticosteroids favored the existence of an autoimmune process in this group of diseases. Mellors and Ortega[26] detected fluorescent anti γ-globulin antibody in the arteries of a patient with polyarteritis nodosa. However, the reaction occurring against the γ-globulin component is nonspecific, because antialbumin and antifibrinogen antibodies can also be detected by immunofluorescence.[27] Fialkow, Fudenberg, and Epstein[28] reported the case of a patient with multiple immunologic abnormalities whose sibling died from polyarteritis nodosa. At present, however, there is no convincing evidence that necrotizing angiitis is an autoimmune process.

Pathogenesis. Four patients had clinically or bacteriologically proved preexisting infection. Although six patients had a history of previous allergy especially to penicillin and the sulfonamides, it was not possible to relate it to a specific drug in the pathogenesis. Two patients with polyarteritis nodosa had coexisting carcinoma, one prostatic and the other gastric. It is believed that the malignant neoplasms were coincidental and unrelated to the angiitis.

In reviewing this group of 27 cases, it was discovered that there was an unusually high incidence of preexisting trauma. The types of trauma and the lapses of time between the traumatic event and the onset of the illness are outlined in *Table* 7. In

Table 7.—*Types of trauma and lapses of time between traumatic events and onset of necrotizing angiitis in seven cases*

	Necrotizing angiitis		
Case no.	Type of trauma	Disease	Time lapse between trauma and onset of disease, wk.
1	Nasal polypectomy	Hypersensitivity angiitis	12
2	Fracture of hip and pelvis	Hypersensitivity angiitis	20
3	Severe hematoma of shin	Polyarteritis nodosa	4
4	Head injury	Hypersensitivity angiitis	1
5	"Sprain" of trunk	Hypersensitivity angiitis	12
6	Abdominoperineal resection for carcinoma of rectum	Polyarteritis nodosa	12
7	Resected coarctation of aorta	Hypersensitivity angiitis	1

three patients, the trauma resulted from surgical procedures, and in four, from accidents. In some instances the time lapse between the trauma and the onset of disease was so short that the patients presumed that their illness resulted from the accident. To our knowledge, trauma has not previously been considered an etiologic factor in necrotizing angiitis. In this series the incidence (26 percent) of recent significant trauma is as high as the incidence of recent infection, and is higher than the incidence of recent allergic drug reaction, which was surprisingly low. It can be argued that an allergen was used at the time of the onset of trauma and was responsible for the ensuing angiitis. In this regard, agents that come to mind include tetanus toxoid or a general anesthetic.

It is of interest that Mackay and Burnet[25] also pointed to the role that local tissue damage seemed to play in two obscure disorders, namely, the postcommissurotomy syndrome and the postinfarction syndrome. With regard to the role of previous streptococcal infections stressed by Rose and Spencer[10] in the possible etiology of polyarteritis nodosa, Mackay and Burnet[25] speculated that this could favor the establishment of forbidden clones by causing local tissue damage, particularly in certain predestined patients who had "... a weakness of immunologic homeostasis."

Knowles, Zeek, and Blankenhorn[29] considered that all their cases of polyarteritis nodosa were triggered by hypertension, and that hypersensitivity angiitis was related to a preexisting allergic mechanism.

It is our belief that necrotizing angiitis can be triggered in a variety of ways. In fact, after 40 years we are back to the original concept of Gruber[2] who stated that this disease might represent a reaction evoked by various infectious, allergic, or toxic agents. To this list in the last 25 years two further mechanisms have been added, namely, drug ingestion[30] and hypertension.[3] To complicate matters still further it is suggested that trauma might be yet another precipitating factor. In this regard there is much evidence that external stimuli can trigger vascular or intravascular disease: exposure to sunlight can be followed by a flare-up in systemic lupus erythematosus; exposure to cold may precipitate gangrene in cryoglobulinemia. Gardner and Diamond[31] described a syndrome occurring in women in which apparent autosensitization to red blood cells developed after mild trauma and ecchymosis formation.

Evidence that amines can damage the walls of blood vessels is afforded by the carcinoid syndrome in which high circulating concentrations of serotonin are associated with fibrotic lesions on the valvular and endocardial surfaces of the heart. However, evidence for a massive release of low molecular tissue substances, such as potent amines from tissue cells, after a traumatic episode cannot explain the self-perpetuation of the lesion in necrotizing angiitis. On the other hand, the self-perpetuating nature of the disease is held to be a major incentive for applying the forbidden-clone hypothesis to polyarteritis nodosa. Furthermore, no specific noxious chemical agent has so far been identified in the blood in this condition. A unifying concept explaining the diverse etiologies would be that any of the above-mentioned stimuli could induce a protein alteration in the vessel wall. The resultant altered protein might in turn be antigenic and could therefore evoke a strong antigen-antibody reaction. This in turn would be manifested by a vasculitis, since the attacked cells are in the vessel walls.

Summary

The autopsy findings in 27 cases of necrotizing angiitis are reviewed. By the pathologic criteria of Zeek[3] there were 12 cases of polyarteritis nodosa and 11 cases of hypersensitivity angiitis; four patients had Wegener's granulomatosis. In an effort to distinguish these three entities from one another clinically the comparative frequency of the clinical involvement of organ systems by each pathologic entity was examined. Wegener's granulomatosis emerged as a distinct clinical syndrome, but polyarteritis nodosa and hypersensitivity angiitis could not be so readily differentiated on clinical grounds. However, it was found that the presence of purpura or a history of drug allergy suggested a diagnosis of hypersensitivity angiitis. It does not seem that rigid clinical separation of the two entities is impor-

tant since there is no striking difference in the prognosis, in the choice of treatment, or in the response to treatment of these two entities. The commonest clinical picture at the terminal stage of these disorders was uremia and left ventricular failure. All four patients with Wegener's granulomatosis had nodular densities on chest roentgenograms, and three of these had nodular ulcerating lesions of the skin.

Although electrocardiographic abnormalities were present in 18 of 22 cases, only in one case did coronary arteritis lead to myocardial infarction.

A peripheral neuropathy of sensorimotor type was present in three patients, and prominent musculoskeletal symptoms were recorded in half the cases. Three patients became blind due to optic neuritis or optic atrophy.

The electrophoretic protein distribution revealed an elevation in the α-globulin and γ-globulin portions of the serum.

A high incidence of recent trauma was noted and the implications of this finding are discussed.

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