NECROTIZING ANGIITIS: III. CORRELATION OF CLINICAL FINDINGS WITH BIOPSY EVIDENCE IN THIRTY-ONE PATIENTS

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THE presence of vasculitis in biopsy specimens can be of great help in the diagnosis of obscure clinical problems. The difficulty in obtaining a diagnostic biopsy is reflected in the paucity of published antemortem tissue diagnoses of generalized necrotizing angiitis. Patalano and Sommers[1] reported 30 autopsied cases of polyarteritis nodosa, yet in only one had there been an antemortem diagnosis. In another study[2] it was found that only one of 15 antemortem biopsies was positive in patients proved to have necrotizing angiitis at autopsy. Maxeiner, McDonald, and Kirklin[3] found that 92 percent of biopsy specimens of muscle taken at random were negative, and the presence of a nodule was suggestive but no guarantee that a lesion would be found. The difficulties are compounded by the focal nature of the lesion in the vessel and by the limitations apparently inherent in biopsy methods.[4]

It is clear that necrotizing angiitis can be a rapidly fatal disease in many instances. In regard to the series of 30 patients with "allergic vasculitis," reported by McCombs, Patterson, and MacMahon,[5] four died of anal failure. Winkelmann and Ditto[6] evaluated 38 cases of cutaneous vasculitis and found that vascular disease caused four deaths. An even more ruinous diagnosis than necrotizing angiitis or vasculitis is that of 'periarteritis nodosa': death occurred within a few years in the majority of patients.[5]

On the other hand, severe disease may be evident in a vessel involved in oral inflammatory processes or may be limited to vessels of one organ with one systemic involvement.[7] The maximum diagnostic value that can be obtained from a biopsy specimen demonstrating vasculitis can be determined only by correlating the clinical picture and the morphologic alterations. It was therefore believed that a review of our series of cases of necrotizing angiitis, with correlation of the pathologic and the clinical findings, might be of aid to other physicians in their efforts to resolve some of their different clinical problems.

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MATERIALS AND METHODS

All surgical reports since 1950 were reviewed and the cases in which there was inflammation of vessels were selected. The histologic slide were reviewed and when arteritis was present the morphologic change were tabulated; small arteries ranged from 0.1 to 0.5 mm. in diameter medium, from 0.5 to 1 mm.; and large, more than 1 mm. Cases with no involvement of muscular arteries larger than arterioles were rejected in order to exclude the patients with anaphylactoid reactions and other cutaneous lesions characterized by arteriolar and venular inflammation.

Clinical histories were then examined in detail. If the patient had a disease process that is known to be associated with vasculitis, such as rheumatoid arthritis, disseminated lupus erythematosus, dermatomyositis, or malignant hypertension, the case was omitted. So-called secondary angiitis was thereby excluded. There remained 27 cases of apparently 'idiopathic or primary' angiitis involving muscular arteries with inflammation and often mural necrosis. Four biopsied cases of Wegener's granulomatosis were included because most authors and we consider this entity to be a variant of necrotizing angiitis, and extrapulmonary vascular lesions are commonly present.

RESULTS

For the purposes of discussion the series was divided into four groups according to the biopsy sites: muscle, skin, miscellaneous, and lungs (Wegener's granulomatosis).

MUSCLE BIOPSIES

Clinical features. Fifteen muscle biopsies demonstrating necrotizing vasculitis were accepted (*Fig. 1*). There were nine men and six women whose ages ranged from 21 to 77 years. In the 15 cases the following symptoms were recorded: pain in muscles (four patients); pain in joints (four patients); weakness (four patients); temperature elevation (three patients) upper respiratory infection (two patients); swelling of joints (one patient) and rash (one patient). The duration of the symptoms ranged from two months to nine years. Two patients had long histories of asthma.

Pathologic features. The microscopic changes in vessels in the muscle biopsies varied considerably. The largest arteries involved were more than 1.0 mm. in diameter in two cases, medium sized (0.5 to 1.0 mm.) in nine cases, and small (less than 0.5 mm.) in four cases. The lesions showed predominantly polymorphonuclear infiltrate in eight patients, predominantly lymphocytic in three patients, and fibrous vasculitis of a healtype with collagen deposition in four patients. Of the 15 biopsy specimens there was extensive necrosis in eight, slight necrosis in three, and

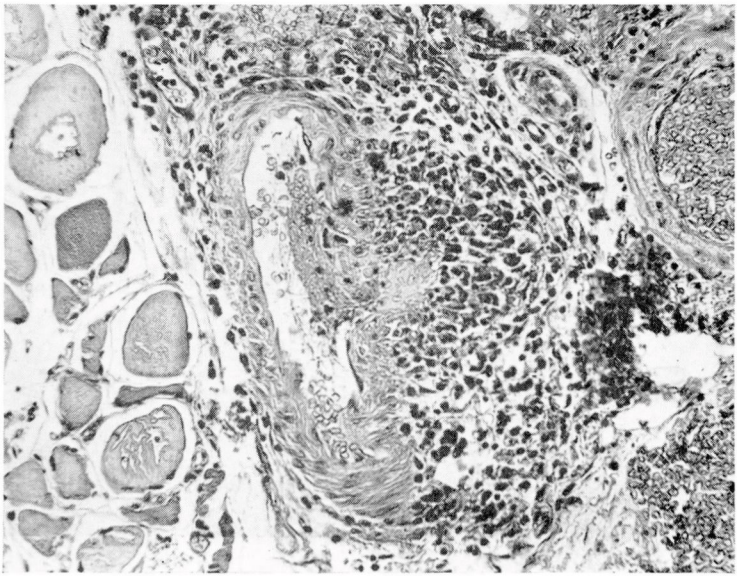

Fig. 1. Case 1. Muscle biopsy section showing segmental necrosis of arterial wall with early thrombus formation. Hematoxylin-eosin stain; magnification ×170. The patient is living one year later.

a necrosis in four. Nuclear fragmentation was notable in one case, and there were traces of this change in eight cases.

Outcome. Of the 15 patients, six died of disease apparently related to the angiitis three months to eight years after initiation of treatment; three are alive and well one to nine years later, with no complaints; and six have problems apparently related to the primary disease. Two autopsies were performed. One of the two patients died of infection secondary to drug therapy for carcinoma of the cervix eight years after muscle biopsy; evidence of previous vasculitis was present. The other patient died of myocardial infarction four months after diagnosis; no vasculitis was found. three of the remaining patients died with severe hypertension; no autopsies were performed. In the remaining patient the clinical findings of intestinal infarction developed soon after the muscle biopsy (*Fig. 2*) was performed. Subsequent resection of a segment of small bowel revealed arterial ranges identical to those seen in the muscle biopsy specimen, and a diagnosis of polyarteritis nodosa was made. The patient died three years later at home; no autopsy was performed.

SKIN BIOPSIES

Clinical features. Seven selected cases of primary arteritis of the skin are recognized. One man and six women were included, ranging in age

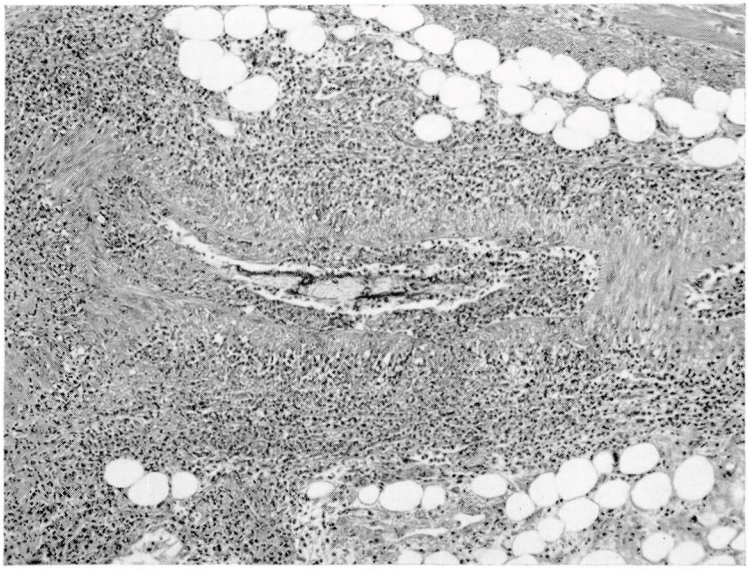

Fig. 2. Case 5. Muscle biopsy section showing severe arteritis. Evidence of similar vascular disease was found in the small bowel. Hematoxylin-eosin stain; magnification ×120. The patient died three years later.

from 23 to 59 years. Chief complaints were: rash (four patients); swelling of the legs (two patients); nodules on the legs (two patients); and generalized diffuse pain (one patient). Two patients had extremely high blood pressure when first examined. The duration of symptoms ranged from two months to one year. One patient had a long history of hay fever.

Pathologic features. Examination of the skin biopsy specimens showing none to have involvement of large arteries, four with medium- and small vessel disease (*Fig. 3*), and three with only small-vessel disease. Of the several patients, three showed predominantly polymorphonuclear infiltrate, the lymphocytic infiltrate, and one fibroblastic thickening of the vessel wall. The patients showed severe necrosis in medium-sized vessels; two showed no necrosis; and three, intermediate degrees of necrosis. Two patients had extensive nuclear fragmentation involving medium-sized vessels with predominantly polymorphonuclear infiltration.

Outcome. All of these seven patients are alive 1 to 11 years after treatment. Two apparently have persistent symptoms related to a generalized arteritis clinically. Of interest is the subsequent development in one patient each of sarcoidosis, giant follicular lymphoma, and polycythemia vera

MISCELLANEOUS BIOPSIES

Clinical features. The miscellaneous group includes five biopsies, on each of kidney, bladder, liver, cervix, and vas deferens. Three males and

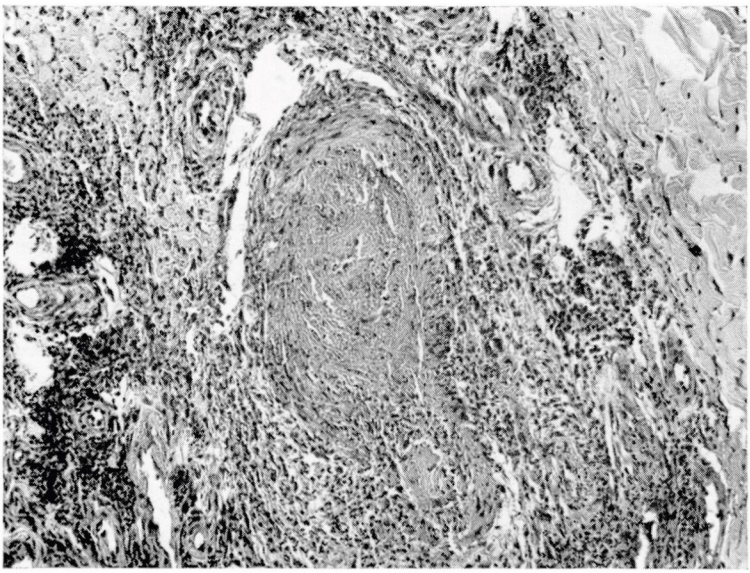

Fig. 3. Case 18. Biopsy section showing vasculitis in subcutaneous area. Hematoxylin-eosin tain; magnification ×150. The patient is alive four years later.

two females were included, ranging in age from 8 to 58 years. Symptoms varied considerably. One patient demonstrated allergy to sulfa drugs, with a history of recent ingestion (*Fig. 4*). One patient had large-vessel disease, two patients had medium-sized vessel disease, and two patients had involvement of medium and small arteries and arterioles. Necrosis was severe in two of the five patients and moderate in three patients. Nuclear fragmentation was severe in one patient, of intermediate severity in three patients, and absent in one patient.

Outcome. Of the five patients, all are alive 1 to 8 years later. Four are well; in one Peyronie's disease developed two years after biopsy of the gas deferens demonstrated a necrotizing vasculitis.

LUNG BIOPSIES (WEGENER'S GRANULOMATOSIS)

Clinicopathologic features. Three open-lung biopsies and one muscle biopsy were obtained in four patients who subsequently demonstrated the clinical picture of Wegener's granulomatosis. The findings observed in the lung biopsies were similar. The lung showed severe granuloma formation with numerous lymphocytes and Langhans' giant cells. Focal necrosis was present. Most striking was the vasculitis of large, medium, and small arteries and occasional veins. The walls of the vessels were infiltrated with lymphocytes and giant cells. Focal endothelial proliferation resulted in the

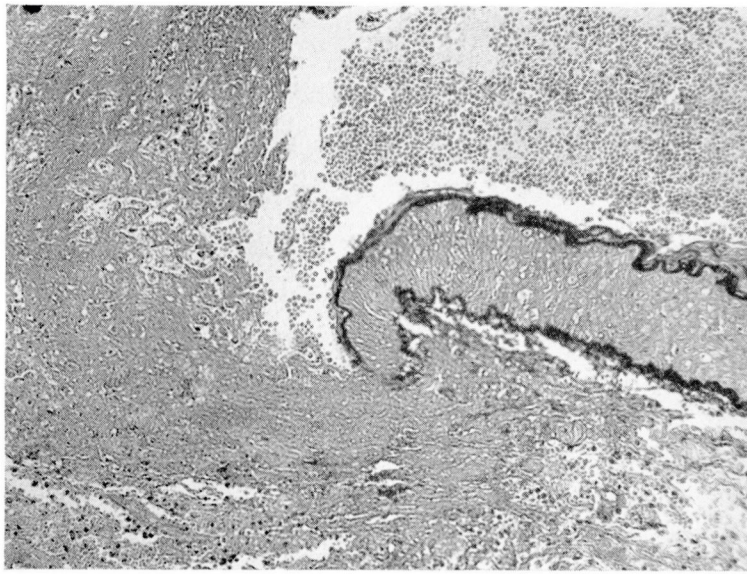

Fig. 4. Case 23. Biopsy section showing complete disruption of elastica in area of several inflammation occurring in the wall of a large peripelvic renal artery. Verhoeff's elastic stain; magnification ×150. The patient is living and well one year later.

partial occlusion of vascular lumens. The muscle biopsy specimen showed focal necrosis and infiltration of a small artery.

Outcome. Two patients responded well to treatment and are asympto matic 8 and 15 months later. One patient died from severe renal failure five years after biopsy; at autopsy there was no evidence of vasculitis.

SUMMARY OF PATHOLOGIC FINDINGS

In all 31 patients the biopsy specimens demonstrated unquestionable vascular disease: inflammation of all three coats of a vessel, frequently with necrosis. The sites of necrosis varied from the subintimal to the outer medial layers. The necrosis was characterized as amorphous basophilic material located circumferentially or segmentally in the artery wall. The was frequently accompanied by polymorphonuclear infiltrate and nuclear dust, that is, deeply basophilic granular material. Severe necrosis was uniformly accompanied by acute polymorphonuclear infiltrate, the chronic cellular infiltrates being associated with collagen deposition and fibroblastic infiltrate. Complete obstruction of the lumen was most often due to proliferation of intima with subintimal necrosis and eosinophilic fibrin-like thrombi. Chronic lesions demonstrated vascular occlusion caused by fibro blastic proliferation plus destruction of the normal vessel wall. Inflam-

mation often extended into the surrounding adipose tissue and adjacent venous structures. In no instance was only primary venous disease evident, although veins were involved in the lungs of three patients with Wegener's granulomatosis.

DISCUSSION

The differential diagnosis of polyarteritis nodosa and hypersensitivity angiitis on the basis of biopsy material presents a difficult problem. A distinction between these two forms of primary arteritis is accepted by many authors.[2, 4, 5, 8, 9] McCombs[10] maintains clear separation on clinical and morphologic bases. He characterizes polyarteritis nodosa as a severe illness with relentless progression, and hypersensitivity angiitis (systemic allergic vasculitis) as a benign disease, with recovery of the patient unless renal involvement occurs and death results.[5, 10] In another study[2] we were able to define morphologic differences between the polyarteritis type and the hypersensitivity type of primary vasculitis at autopsy.

Small arteries are involved in hypersensitivity angiitis, and medium-sized arteries in polyarteritis nodosa.[2, 10] In a single biopsy specimen the absence of vasculitis in a large artery does not rule out polyarteritis nodosa or does involvement of a medium-sized muscular artery eliminate the possibility that hypersensitivity angiitis is the primary disease.[10]

Wegener's granulomatosis is considered a variant of vasculitis by many observers, and causes systemic necrotizing vasculitis in addition to the lung and renal involvement.[11] This necrotizing vasculitis is nonspecific, and biopsy specimens of skin or muscle show changes similar to those of hypersensitivity angiitis.[12]

It is apparent that a diagnosis of polyarteritis nodosa or hypersensitivity angiitis on the basis of a single skin or muscle biopsy specimen is fraught with difficulty. Differential points that weigh heavily are the involvement of large muscular arteries with various stages of lesions in polyarteritis nodosa, and the absence of these features but the presence of small-artery and arteriole vasculitis all of similar stages in hypersensitivity angiitis. The anal biopsy provides additional help in distinguishing these disorders hence, necrotizing glomerulonephritis is also suggestive of the hypersensitivity type of vasculitis.[2, 8, 9]

With these considerations in mind it is pertinent to examine the results obtained in this series of patients with arteritis. One of the six patients in the muscle biopsy group who died, was proved to have generalized vasculitis after intestinal infarction occurred as a result of mesenteric vasculitis approved by histologic examination). The muscle biopsy specimen obtained three years before death showed severe necrosis and polymorphonuclear infiltration in a large artery and was therefore highly suggestive of poly-

arteritis nodosa. Large-artery vasculitis was also found in a patient who died of renal failure three years after biopsy. Similar large-vessel disease was found in another patient who is alive and well one year after severe focal vasculitis necessitated heminephrectomy. If the only criterion were involvement of large arteries, these three patients were most likely to demonstrate subsequent clinical polyarteritis nodosa. The danger in using this feature as a pathognomonic sign is exemplified by the absence of disease one year after the patient underwent heminephrectomy. The death from renal failure of one patient occurred at home, and information is not available concerning the status of the vessels. Thus, of three patients with large-vessel vasculitis, one had polyarteritis nodosa, and the final diagnosi is equivocal in the other two patients. This number is small as it is un usual to find many large arteries in biopsy material; this lack limits the finding of lesions characteristic of polyarteritis nodosa, and accounts in part for the lack of antemortem tissue diagnosis of this disease.

Another important consideration in explaining the failure to detect poly arteritis nodosa from biopsy is the infrequent involvement of organs most often biopsied. Muscle is involved in polyarteritis nodosa in only approxi mately one third to one half of the cases, though there is considerable varia tion in reported series.[1-3, 13] Random biopsy seems worthwhile in clinically suspected cases. Maxeiner, McDonald, and Kirklin[3] found that of 106 pa tients with suspected polyarteritis nodosa, 13 had positive muscle biopsies The skin is readily accessible to biopsy, and involvement occurs in ap proximately one fourth of the cases.[14] However, the range of dermatology conditions that include some form of vasculitis is extensive with a conse quent murkiness clouding the recognition of a primary vasculitis. Man cutaneous syndromes not of primary vascular origin are associated with arteriolar and small-artery disease. Of the seven skin biopsies in this series the largest vessels diseased were medium-sized, and in none of the patients has polyarteritis nodosa developed.

Fifteen patients each had a medium-sized vessel as the largest one in volved; since this is the size most frequently affected in polyarteritis nodosa these patients would also be expected to show serious disease. Neuropath was present in 5 of these 15 patients who are clinically suspected of having polyarteritis nodosa. However, only three of the patients have died, two with severe renal disease and hypertension, a course compatible with polyarteritis nodosa. In the other seven patients apparently no disabling vascular disease developed, but only one is well and free of symptoms This last group then must represent those patients with a hypersensitive ity angiitis that shows some medium-sized arterial involvement (*Fig. 5*).

Small-artery vasculitis alone was found in nine patients. One death oc curred eight years after biopsy, but the patient died from complications

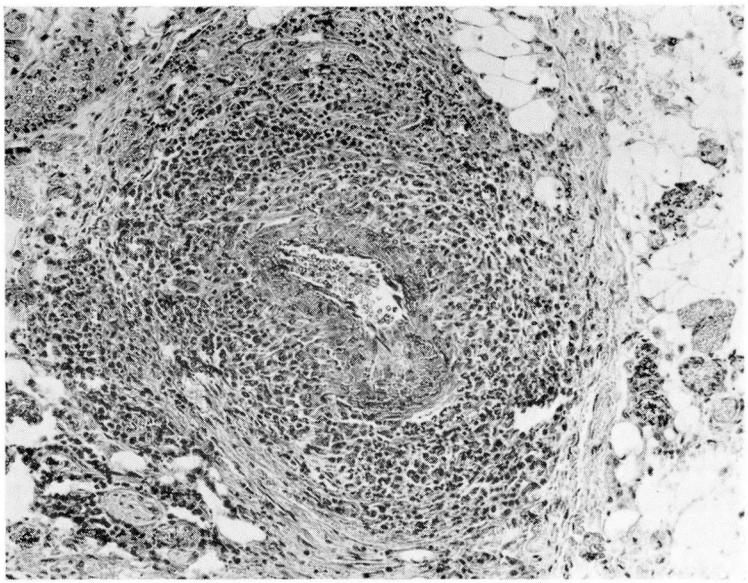

Fig. 5. Case 14. Muscle biopsy section showing severe vasculitis. Hematoxylin-eosin stain; magnification ×150. The patient is alive nine years later.

chemotherapy for carcinoma, and no vasculitis was present at autopsy. One patient is believed to have persistent generalized vasculitis, and the remaining seven patients show no illness attributable to vascular inflammation. Thus, this group with small-artery disease alone showed an overall good outcome that is characteristic of the benign course of most cases of hypersensitivity angiitis.[5, 10]

Although 16 of the 31 patients showed an eosinophilia on at least one occasion (a frequent finding in vasculitis), such was not reflected in the types of cellular infiltrates noted in the vessels, for in only one patient were significant numbers of eosinophils demonstrated in the areas of inflammation. Sixteen biopsies showed acute inflammation of vessels as indicated by the predominance of polymorphonuclear leukocytic infiltrations; eleven each showed a lesion that was usually healing; lesions in various stages were present in two only. Although lesions of different ages are most suggestive of polyarteritis nodosa, one of the patients is thought to have the disease, but the diagnosis in the other is somewhat doubtful. Since hypersensitivity angiitis is not so serious a disease and must go through a healing stage, it is reasonable to assume that some biopsies of vascular disease will show other than acute lesions, and such was seen in two cases where complete recovery ensued.

Wegener's granulomatosis is a disease characterized by: (1) upper or

lower, or both upper and lower, respiratory tract granuloma, ulceration, and vasculitis; (2) nephritis; and (3) general vasculitis.[11, 14-16] Of these three features the latter two are not diagnostic of Wegener's granulomatosis, occurring also in hypersensitivity angiitis. Biopsy of the upper respiratory tract reveals necrotizing ulceration of a nonspecific type. Lung biopsy remains the only way to obtain definitive tissue diagnosis of this disease. Such is exemplified in four patients, in our series, who have Wegener's granulomatosis clinically. Lung biopsy in three patients demonstrated vasculitis in areas of pulmonary necrosis and granuloma formation. All pulmonary cultures and special stains for acid-fast organisms and fungi were negative. A definite pulmonary vasculitis is necessary for diagnosis, or the microscopic pattern is indistinguishable from other granulomatous lung diseases. The other patient in this group initially had necrotizing angiitis found by muscle biopsy. Severe rhinitis and nephritis completed the triad, and the patient died five years later from sclerosing glomerulonephritis. No vasculitis was found at autopsy and the lungs were free from necrotizing lesions.

SUMMARY AND CONCLUSION

The findings in this present series of 31 patients with arteritis suggest that biopsy diagnoses of specific types should be approached with great caution. A biopsy diagnosis of polyarteritis nodosa indicates serious and usually fatal disease and should be made only when a highly characteristic vasculitis is seen. Hypersensitivity angiitis, on the other hand, is a relatively benign process in the absence of renal disease, and is suggested by small-artery damage. Biopsy remains the most helpful procedure in the diagnosis of primary arteritis, but exact interpretation should be tempered by the considerable limitation of the adequacy of the specimen.

Of the three of the four patients who had Wegener's granulomatosis with a substantiating pulmonary biopsy, two patients are asymptomatic and one patient died. The course of the fourth patient is not known at the present time.

Correlation between the clinical findings and the morphologic changes in the vessels suggests that polyarteritis nodosa and hypersensitivity angiitis are distinct but related entities with different prognostic implications. Differentiation on the basis of biopsy findings alone is most difficult and requires utmost caution.

REFERENCES

1. Patalano, V. J., and Sommers, S. C.: Biopsy diagnosis of periarteritis nodosa; glomerulonephritis and renal arteriolitis as aids. Arch. Path. **72:** 1–17, 1961.

2. Reidbord, H. E.; McCormack, L. J., and O'Duffy, J. D.: Necrotizing angiitis: II. Findings at autopsy in twenty-seven cases. Cleveland Clin. Quart. **32:** 191–204, 1965.

3. Maxeiner, S. R., Jr.; McDonald, J. R., and Kirklin, J. W.: Muscle biopsy in the diagnosis of periarteritis nodosa; an evaluation. S. Clin. North America **32:** 1225–1233, 1952.

4. Zeek, P. M.: Periarteritis nodosa: a critical review. Am. J. Clin. Path. **22:** 777–790, 1952.

5. McCombs, R. P.; Patterson, J. F., and MacMahon, H. E.: Syndromes associated with "allergic" vasculitis. New England J. Med. **255:** 251–261, 1956.

6. Winkelmann, R. K., and Ditto, W. B.: Cutaneous and visceral syndromes of necrotizing or "allergic" angiitis: a study of 38 cases. Medicine **43:** 59–89, 1964.

7. Plaut, A.: Asymptomatic focal arteritis of the appendix; eighty-eight cases. Am. J. Path. **27:** 247–263, 1951.

8. Zeek, P. M.; Smith, C. C., and Weeter, J. C.: Studies on periarteritis nodosa. III. The differentiation between the vascular lesions of periarteritis nodosa and of hypersensitivity. Am. J. Path. **24:** 889–917, 1948.

9. Moskowitz, R. W.: The Histopathologic Classification of Periarteritis Nodosa; a Study of 56 Cases. Thesis, Graduate School, University of Minnesota, Minneapolis, Minnesota, 1960, 103 p.

10. McCombs, R. P.: Periarteritis nodosa and related disorders of blood vessels. Dis. Month: 1–31, 1960.

11. Godman, G. C., and Churg, J.: Wegener's granulomatosis; pathology and review of the literature. A.M.A. Arch. Path. **58:** 533–553, 1954.

12. Reed, W. B.; Jensen, A. K.; Konwaler, B. E., and Hunter, D.: The cutaneous manifestations in Wegener's granulomatosis. Acta dermat.-venereol. **43:** 250–264, 1963.

13. Arkin, A.: A clinical and pathological study of periarteritis nodosa; report of five cases, one histologically healed. Am. J. Path. **6:** 401–426, 1930.

14. Fisher, I., and Orkin, M.: Cutaneous form of periarteritis nodosa—an entity? Arch. Dermat. **89:** 180–189, 1964.

15. Budzilovich, G. N., and Wilens, S. L.: Fulminating Wegener's granulomatosis. Arch. Path. **70:** 653–660, 1960.

16. Berman, D. A.; Rydell, R. E., and Eichenholz, A.: Wegener's granulomatosis; a clinicopathologic study of four cases. Ann. Int. Med. **59:** 521–530, 1963.