Approach to Systemic Vasculitis

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Systemic vasculitis is a confusing subject which has been difficult to classify and understand. Improvements in therapy increase the importance of early diagnosis. This paper reviews the clinical and pathological differences of the systemic vasculitides, and a working approach to the differential diagnosis of vasculitis is formulated based on the size of the vessel involved. Vessel size and histopathology determine to what group of diseases a particular syndrome belongs, thereby allowing subclassification and a more rational approach to management.

Systemic vasculitis is a confusing and controversial subject. Its complexity is attested to by the more than one dozen syndromes it encompasses. These syndromes differ not only pathologically, but also in their clinical settings and therapeutic responses. The development of relatively beneficial therapeutic regimens has heightened the need for early diagnosis. The most widely used classification devised by Zeek[1,2] and modified by Braverman[3] defines several syndromes by clinical and pathologic criteria (Figure 1). This classification, although quite helpful, is not entirely adequate because it is based on syndrome identification and does not emphasize the histopathologic changes within the vessels and the signs and symptoms directly due to circulatory compromise secondary to those changes. It is the purpose of this paper to present a pathophysiologic approach to the differential diagnosis of the systemic vasculitides.

This paper limits discussion to those syndromes characterized by a necrotizing vasculitis, that is, where there are inflammatory cells within the wall of the vessel during the acute stage of the illness and/or necrosis of part or all of the vessel wall. This necrotic material when stained with hematoxylin and eosin takes on the pinkish, homogeneous appearance of fibrin, hence the term "fibrinoid necrosis." A simple perivascular accumulation of inflammatory cells is sometimes seen in the early or later stages of vasculitis, but because such histopathology, by itself, is so nonspecific, its presence is not considered evidence of systemic necrotizing vasculitis.

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System of Classification

There are two characteristics that may help the clinician differentiate one vasculitic syndrome from the many others. These are vessel size and the cellular response to injury.

Size

There are four groups of arteries which can arbitrarily be envisioned. These are:

1. *Large arteries* – the large elastic arteries and their branches
2. *Medium arteries* – vessels which are visible to the naked eye; these are muscular and supply organs
3. *Small arteries*
   a. microscopic arteries – vessels 100 to 500 microns in diameter
   b. arterioles – vessels whose thickness is approximately equal to the size of the lumen; they are less than 100 microns in outside diameter
4. *Capillaries* – vessels with no media

Despite some overlap, one or two

vessel groups may predominate in a particular syndrome and the symptoms and signs that ensue can help the clinician distinguish among the vasculitic syndromes. Although veins and venules are often involved in many of the vasculitides, the clinical features of the disease are most often due to arterial involvement. Therefore, venous involvement, as such, is ignored.

Symptoms and signs of *large artery* occlusion stem from a compromise in the circulation to areas directly supplied by the occluded vessel. Involvement of the carotid or subclavian artery can induce a change in the pulse pressure or blood pressure. Involvement of the vessels of the lower or upper extremities may give intermittent claudication. Similarly, there may be symptoms of transitory cerebral ischemia or any of the myriad of syndromes that may follow occlusion of the cerebral vasculature.

Symptoms and signs of *medium artery* occlusion are extremely variable. Involvement of cutaneous vessels can cause ulcerations and gangrene. Raynaud's phenomenon may occur. There may be end-organ involvement in the central nervous system, kidney, pancreas, liver, lung, and heart, giving signs and symptoms of vascular insufficiency and clinical patterns related to disease in these organs. Visual disturbances are noted when the ophthalmic artery is involved, and there may be headaches as well as tenderness over the temporal artery when it is involved. It is important to note that angiography may be helpful in diagnosing medium vessel arteritis because of the aneurysms and occlusive changes visualized.[4]

Small artery involvement may also take many forms. Livedo reticularis is due partially to reflex capillary dilation secondary to arteriolar insufficiency.[5] Small artery occlusions may occur in the kidney, brain, and skin as well as other organs. Involvement of the vasa nervorum causes mononeuritis multiplex.[6] Nodules may be a consequence of small artery disease.[7]

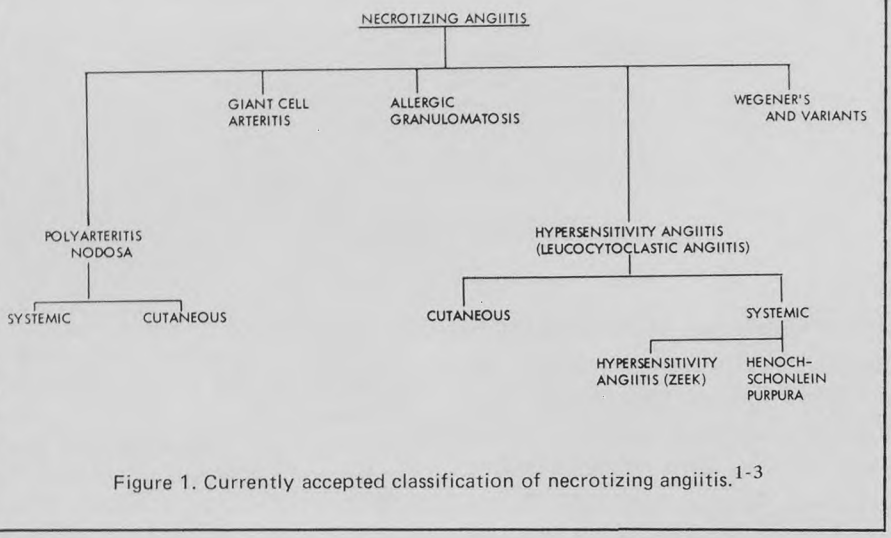

Figure 1. Currently accepted classification of necrotizing angiitis.[1-3]

Table 1. Arteritic Syndromes

HISTOPATHOLOGY	VESSEL SIZE		
	Large Vessel Syndromes Involving (Large arteries, medium arteries)	**Medium Vessel Syndromes** Involving (Medium arteries, small arteries)	**Small Vessel Syndromes** Involving (Small arteries, capillaries)
Granulomatous	Giant cell arteritis temporal arteritis cranial arteritis Takayasu's arteritis	Allergic angiitis of Churg and Strauss	Wegener's granulomatosis
Non-granulomatous (Acute or chronic inflammation depending on stage of disease)		Polyarteritis nodosa Rheumatoid arteritis Polyarteritis with a. Hepatitis associated antigen b. Methamphetamine	Hypersensitivity angiitis Henoch-Schönlein purpura Serum sickness Childhood dermatomyositis Subacute bacterial endocarditis Systemic lupus erythematosus Cryoglobulinemia

Finally, *capillary* disease has its own distinct features. Petechiae are the hallmark of capillaritis and are most easily seen in the skin, but may also be found in other organs including bowel, kidney, brain, and joints.

Histopathology

The second consideration is histopathology. There are two basic types of involvement: (1) *Granulomatous,* and (2) *Non-granulomatous.*

There are some syndromes which have granulomas and/or giant cells in the pathologic specimen regardless of when a biopsy is taken. Other syndromes are not ordinarily associated with granulomas. Instead, in the acute stage, polymorphonuclear leukocytes are found in the vasculitis lesion. As healing takes place, a mononuclear (chronic) reaction occurs. Keeping in mind that there is overlap and using the vessel size and histopathology as a foundation, a partial classification of the arteritic syndromes can be formulated (Table 1) which is somewhat different from that of Zeek (Figure 1).

Application of the Classification

Large Vessels with Granulomas

Giant cell arteritis, a syndrome peculiar to the elderly, is characterized by fever, headache, fatigue, and arthralgia. It often includes the polymyalgia rheumatica syndrome consisting of proximal myalgia and a striking increase in the erythrocyte sedimentation rate. Although examination of the muscles from patients with polymyalgia rheumatica is unrevealing, there is a typical histological lesion involving large and medium arteries, especially the carotid and its branches. This arteritis is a patchy, focal panarteritis (Figure 2) which, late in the disease, may result in fibrotic occlusion. Headaches, jaw claudication, blindness, cerebrovascular accidents, and myocardial infarctions are possible sequelae to giant cell arteritis. Because of the spotty distribution of the vascular lesions, a negative arterial (eg, temporal artery) biopsy does not exclude the diagnosis of giant cell arteritis. Therefore, Anderson and Bayles suggest that the diagnosis be made clinically. They reserve a temporal artery biopsy for those patients with known origin or when the diagnosis is clouded by psychogenic features.[8] However, others feel that a positive biopsy should be obtained before committing a patient to any potentially dangerous therapy. Although the polymyalgia rheumatica-giant cell arteritis syndrome is self-limiting, lasting one to two years, the end result may be a severe vascular catastrophe. *Takayasu's arteritis,* a syndrome of large vessel granulomatous arteritis with giant cells, is found predominantly in young women. Signs and symptoms may resemble those of polymyalgia rheumatica. In addition, arterial obstruction may be so severe that pulses may be quite decreased or absent. Obstructive lesions have been treated successfully by arterial grafts. Corticosteroids have provided an effective means of preventing thrombotic disasters and, if initiated early in the course of the disease, produce a dramatic remission in any one of the large vessel granulomatous syndromes.

Medium Vessels with Granulomas

Allergic granulomatosis was first described by Churg and Strauss,[9] and is similar to polyarteritis nodosa in its involvement of medium and small arteries. However, the pathology is somewhat different in that granulomata develop in and around the involved vessel and are most often accompanied by eosinophils. Symptoms are also different. Asthma and lung involvement are two features not usually noted in polyarteritis nodosa, although they are prominent in allergic granulomatosis.[10]

Medium Vessels with no Granulomas

Vasculitis of medium and small arteries (Figure 3) is called *polyarteritis nodosa.* Acute and chronic inflammation, especially at points of bifurcation, fibrinoid necrosis, and various stages of healing of the vessels are characteristic histological lesions. Vascular thrombosis and aneurysm formation contribute to the clinical picture. Fever, abdominal pain, hypertension, neuritis, and musculoskeletal complaints occur frequently. Approximately 80 percent of patients with polyarteritis nodosa will ultimately have renal involvement. The diagnosis is suggested by the multisystem signs and symptoms and is confirmed by the biopsy of involved organs or by deep muscle biopsy. Some investigators, as mentioned previously, have found angiography to be of great value in detecting aneurysms of the medium-sized branches of the renal, cerebral, and celiac arteries.[4,11] About ten percent of patients with polyarteritis nodosa will have a benign cutaneous variant manifested by a chronic or recurrent course and a variable response to corticosteroids, but with a favorable ultimate outcome.[12] These patients have a syndrome characterized by subcutaneous nodules, livedo reticularis, and myalgias.

A polyarteritis-like syndrome has been described in association with *methamphetamine abuse*[13] and with *hepatitis B infections.*[14] Two patients have recently been described who had hepatitis-associated-antigen (HAA) and antibody to hepatitis-associated-antigen present in the walls of the involved vessels.[14] *Rheumatoid vasculitis* is a disease also involving medium-sized vessels and clinically is characterized by a more severe rheumatoid disease, skin ulcers, gangrene, high rheumatoid factor titre, and occasionally hypocomplementemia.[15]

Small Vessels with Granulomas

Small arteries, capillaries and occasionally medium arteries are principally involved in *Wegener's granulomatosis* which may present clinically as sinusitis, focal glomerulitis, arthritis, or lower respiratory tract lesions. The diagnosis is confirmed by histological studies of soft tissue biopsies of the respiratory tract (Figure 4). Recently Liebow described several variants of Wegener's granulomatosis on the basis of histological structure and natural history.[16]

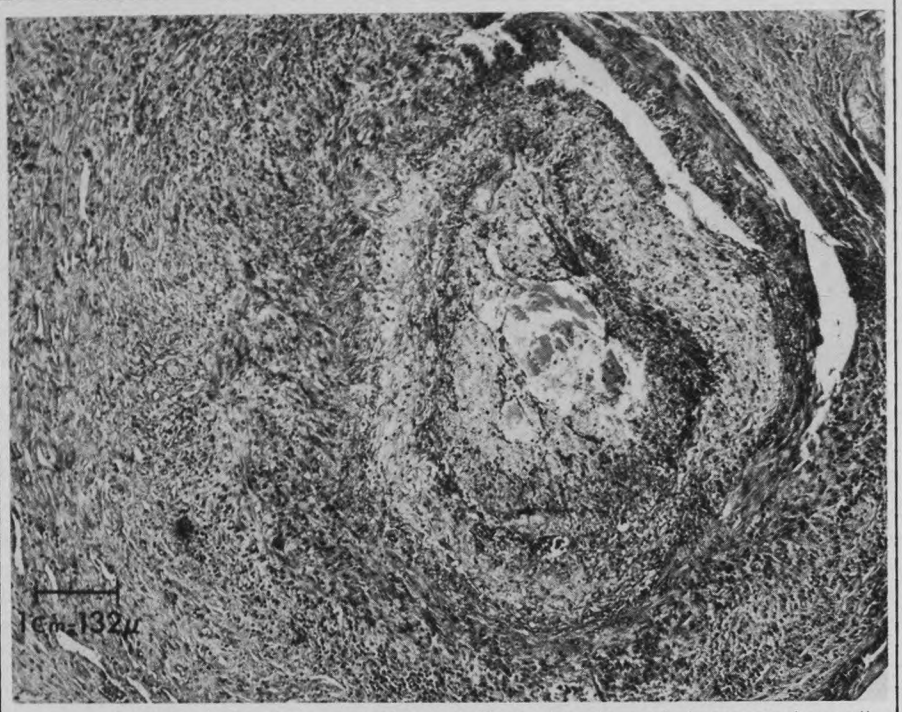

Figure 2. Periarteritis of a temporal artery illustrating the typical mononuclear cell infiltrate, focal necrosis, narrowed vascular lumen, and giant cells (Hematoxylin-eosin, X76).

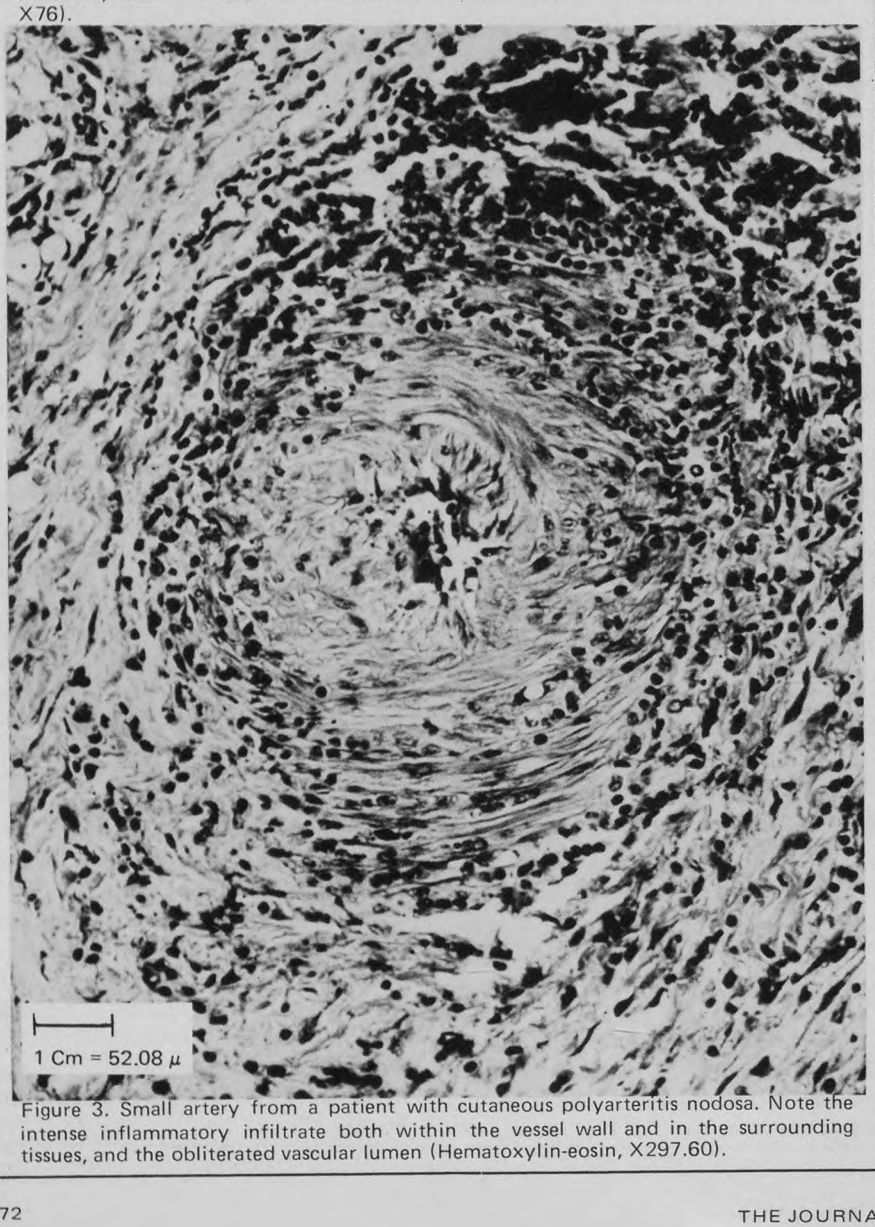

Figure 3. Small artery from a patient with cutaneous polyarteritis nodosa. Note the intense inflammatory infiltrate both within the vessel wall and in the surrounding tissues, and the obliterated vascular lumen (Hematoxylin-eosin, X297.60).

Small Vessels without Granulomas

The most commonly seen of the necrotizing angiitides is the group referred to as leukocytoclastic angiitis involving polymorphonuclear leukocytes throughout the wall of the small blood vessels, especially the arterioles, venules and capillaries (Figure 5). Leukocytoclasis, nuclear dust, and fibrinoid necrosis are the classical histological features. In most cases an etiology cannot be established, but occasionally an underlying systemic disorder such as *Henoch-Schönlein purpura, sub-acute bacterial endocarditis,* or *cryoglobulinemia* is present. The systemic manifestations of leukocytoclastic angiitis depend upon the organ involved but commonly involve the bowel, skin, joints, and kidney. Cutaneous lesions include erythematous macules, petechiae, ecchymoses, vesicles, and rarely necrotic pustules and urticaria. The small vessels may be involved more chronically with mononuclear cells, as is often seen in *systemic lupus erythematosus.*

Nodular or palpable purpura is not specific for any diagnosis or etiological agent, for it implies the presence of some degree of inflammatory response which is not found in purpura due to thrombocytopenia. Once a diagnosis of small vessel vasculitis is made, a thorough search for the etiology should be undertaken. Additional history should be obtained, such as detailed drug exposure and hepatitis exposure, to facilitate the diagnoses of serum sickness associated with certain drugs and serum sickness as a prodrome of HAA positive hepatitis. Appropriate diagnostic tests such as blood cultures, antinuclear antibody determinations, LE cell preparations, and cryoglobulin determinations should be done.

It is important to note that numerous infectious agents can damage endothelium and cause a systemic vasculitis. The most common organisms known to do this in man are the rickettsiae and neisseria. In addition, disseminated intravascular coagulation and thrombotic thrombocytopenia purpura may cause diffuse vascular occlusion. These syndromes should not be confused with a primary vasculitis disease even though they may mimic or accompany vasculitis. The clinician must recognize septicemia and disseminated intravascular coagu-

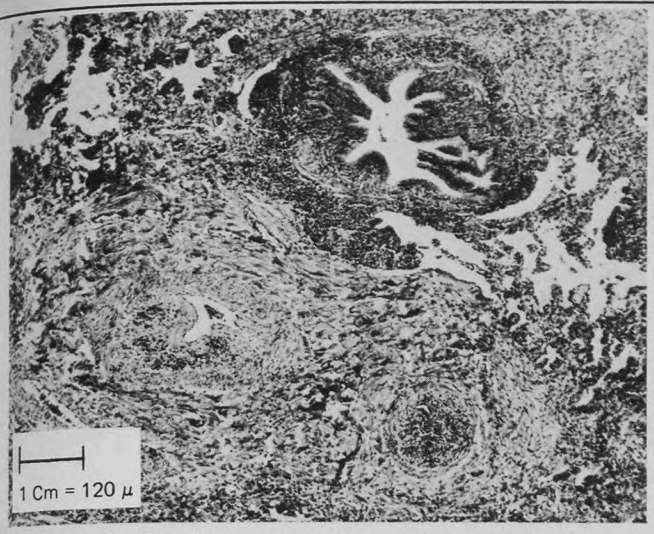

Figure 4. Section from a lung biopsy of a patient with Wegener's granulomatosis. Pathological changes consistent of arteritis and venulitis in addition to a peri-bronchiolar granuloma (Hematoxylin-eosin, X45).

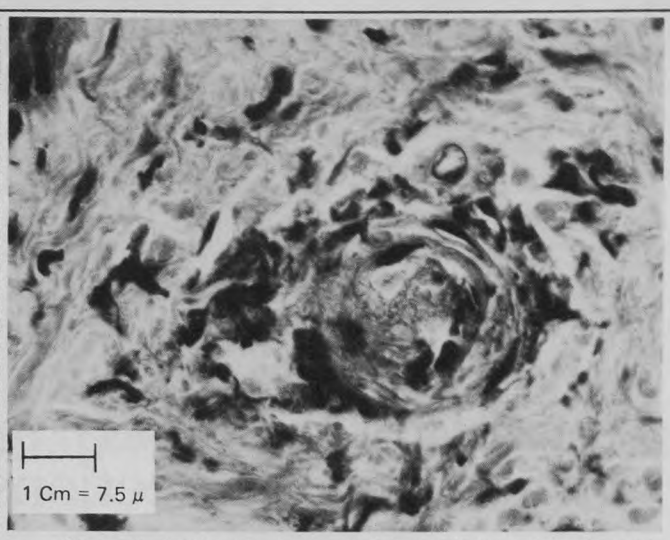

Figure 5. Leukocytoclastic angiitis involving a dermal arteriole. Note the endothelial disruption, nuclear dust, and mild perivascular inflammatory infiltrate (Hematoxylin-eosin, X750).

lation early despite the similarities of these specific syndromes to systemic vasculitis of undetermined etiology.

Approach to Treatment

The approach to treatment begins with making the correct diagnosis. The clinician should look for signs and symptoms that might enable him or her to distinguish the size of the vessel involved. When medium or large vessel disease is suspected, arteriograms may be helpful. Pathology is then important to distinguish the granulomatous from the non-granulomatous diseases. Once a histological diagnosis is made, a sub-diagnosis should then be sought. It must be remembered that there will be an occasional patient with an overlapping clinical picture. Cryoglobulinemia, for example, most often causes arteriolar and capillary disease, but may occasionally be associated with polyarteritis syndrome.[17]

Treatment should be limited and directed at as specific a syndrome as possible. Steroids are the drug of choice in the large vessel diseases and cytotoxic agents should probably be employed in severe cases of Wegener's granulomatosis.[18] Appropriate therapeutic measures should be employed in rheumatoid disease, hepatitis-associated polyarteritis, and meth-amphetamine-associated polyarteritis. Systemic steroids may be of benefit in alleviating symptoms of arthritis, dermatitis, or abdominal distress associated with vasculitis, but they should not be used indiscriminately.

At the present time any classification of necrotizing angiitis is a compromise. However, with increasing understanding of the pathophysiological mechanisms underlying inflammation and inflammatory vascular syndromes, a more rational approach to the vasculitides can be expected. Until that time comes, the classification of necrotizing angiitis presented here may be useful to the clinician caring for patients with vasculitic syndromes.

Acknowledgements

We are indebted to Drs. Marion Waller and Shaun Ruddy of the Division of Immunology and Connective Tissue Diseases, Medical College of Virginia, and Dr. Edward Abell of the Department of Dermatology, Medical College of Virginia for reviewing this manuscript. We also appreciate the cooperation of the Department of Pathology for the use of their pathologic material.

References

1. Zeek PM: Periarteritis nodosa: A critical review. Am J Clin Pathol 22:777-788, 1952
2. Zeek PM: Periarteritis nodosa and other forms of necrotizing angiitis. N Engl J Med 248:764-722, 1953
3. Braverman IM: Skin Signs of Systemic Disease. Philadelphia, WB Saunders, 1970, pp 199-238
4. Leonhardt ETG, Jakobson H, Ringvist OTA: Angiographic and clinico-physiologic investigation of a case of poly-arteritis nodosa. Am J Med 53:242-256, 1972
5. Fitzpatrick TB, Arndt KA, Clark WH, Jr, et al (eds): Dermatology in General Medicine. New York, McGraw-Hill, 1971, p 971
6. Conn L, McDuffie FC, Dyck PS: Immunopathologic study of sural nerves in rheumatoid arthritis. Arthritis Rheum 15:135-143, 1972
7. Sokoloff L, Orbison JL, Smith DE: The pathophysiology of peripheral blood vessels in collagen diseases. In Orbison JL, Smith DE (eds): The Peripheral Blood Vessels. Baltimore, Williams and Wilkins Co, 1963, pp 300-308
8. Anderson LG, Bayles TB: Polymyalgia rheumatica and giant cell arteritis. DM, January, 1974, p 16
9. Churg J, Strauss L: Allergic granulomatosis, allergic angiitis, and periarteritis nodosa. Am J Pathol 27:277-294, 1951
10. Sokolov RA, Rachmaninoff N, Kaine HD: Allergic granulomatosis. Am J Med 32:131-140, 1962
11. Bron KM, Gajaraj A: Demonstration of hepatic aneurysms in polyarteritis nodosa by arteriography. N Engl J Med 282:1024-1025, 1970
12. Borrie P: Cutaneous polyarteritis nodosa. Br J Dermatol 87:87-95, 1972
13. Citron BP, Halpern M, McCarron M, et al: Necrotizing angiitis associated with drug abuse. N Engl J Med 283:1003-1011, 1970
14. Gocke DJ, Hsu K, Morgan C, et al: Vasculitis in association with Australian antigen. J Exp Med 134:330S-336S, 1971
15. Franco A, Schur PH: Hypocomplementemia in rheumatoid arthritis. Arthritis Rheum 14:231-238, 1971