Eleven Themes in the History of Systemic and Nervous System Vasculitides

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KEYWORDS

• History • Vasculitides • Nervous system

KEY POINTS

- Vasculitis is defined as inflammation of blood vessel walls for at least some time during the course of the disease, and affects arteries and veins of varying caliber.
- Two Chapel Hill Consensus Conferences, 1 in 1994 and the other in 2012, provide consensus on nosology and definitions for the commonest forms of vasculitis.
- The category of single-organ vasculitis, suggesting the limited expression of a systemic vasculitis, includes primary central nervous system vasculitis and nonsystemic peripheral nervous system vasculitis.
- The historical aspects of systemic and limited forms of vasculitis are reviewed in 11 relevant themes.

NOMENCLATURE

Vasculitis is defined as inflammation of blood vessel walls for at least some time during the course of the disease, and affects arteries and veins of varying caliber. Two Chapel Hill Consensus Conferences (CHCCs), one in 1994[1] and the other in 2012,[2] provided consensus on nosology and definitions for the commonest forms of vasculitis. The revised CHCC nomenclature serves as a guide for the categorization of diverse forms of vasculitis based on the vessels involved, and provides a scheme for the neurologic aspects thereof (**Box 1**).

HISTORICAL THEMES

Theme One: The early history of vasculitis is debatable but one fact is clear, the earliest patients with systemic vasculitides had prominent neurologic involvement.

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Box 1
Childhood and adult vasculitides with nervous system involvement

Large vessel vasculitis
- Giant cell arteritis
- Takayasu arteritis
- Idiopathic aortitis (IgG4)

Medium vessel vasculitis
- Polyarteritis nodosa
- Kawasaki disease

Small vessel vasculitis
- ANCA-associated vasculitis
  - Microscopic polyangiitis
  - Granulomatosis with polyangiitis (Wegener)
  - Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
- Immune-complex vasculitis
  - Cryoglobulinemic vasculitis
  - IgA vasculitis (Henoch-Schönlein purpura)
  - Hypocomplementemic urticarial vasculitis (IgA vasculitis)

Variable vessel vasculitis
- Behçet disease
- Cogan syndrome

Primary CNS vasculitis

Vasculitis associated with collagen vascular disease
- Systemic lupus erythematosus
- Rheumatoid arthritis

Vasculitis due to substance abuse
- Amphetamines
- Cocaine
- Opioids

Vasculitis and infection
- Bacteria
- Viruses
- Neurosyphilis
- Mycoses
- Parasites
- Human immunodeficiency virus–AIDS

Kussmaul and Maier[3] provided the first complete gross and microscopic description of a patient with leg pains, cramps, and tenderness so prominent that trichinosis was considered in an article entitled, "A Hitherto Undescribed Peculiar Disease of the Arteries Which is Accompanied by Bright's Disease and a Rapidly Progressive General Paralysis of the Muscles." At postmortem examination, there was widespread arteritis that resembled syphilitic periarteritis. The disorder was named periarteritis for the inflammation around blood vessels. In 1908, Longcope[4] described the first American patient with periarteritis, a 35-year-old man with constitutional symptoms and subacute leg pains. Postmortem examination showed widespread necrotizing arteritis and nodules along small-sized and medium-sized vessels of the heart, liver, kidney, pancreas, testicles, brain, nerves, and skeletal muscles, sparing the lungs and spleen. The histologic lesions consisted of mononuclear cell infiltration, necrosis of internal and external elastic lamina of the media, fibrin deposition, aneurysmal dilatation, perivascular inflammation of the adventitia, and intimal proliferation resulting in narrowing

of arterial lumina. Kernohan and Woltman[5] summarized the clinical and neuropathologic aspects of adult polyarteritis nodosa (PAN), and Krahulik and colleagues[6] reported the postmortem neurologic findings of fulminant childhood PAN (cPAN). The dominant neurologic picture of both adult PAN and cPAN was a peripheral neuritis that occurred in one-half of patients early in the illness with a predilection for the legs. At postmortem examination, all had arteritic lesions along nutrient arteries of the peripheral nerves, and three-quarters had lesions in arteriae nervorum. The combination of acute and chronic lesions correlated with known exacerbations. Involvement of the central nervous system (CNS) was estimated to occur in 8% of cases, evident by clinically apparent brain infarcts resulting from occlusion of cerebral vessels, which was often insidious in its progression. In PAN, as in the other systemic necrotizing arthritides, the vasculitic lesion proceeded in a characteristic manner, commencing with invasion of the intima, media, and adventitia by polymorphonuclear, plasma cells, eosinophils, and lymphocytes, leading to swelling of the media, and fibrinoid necrosis that clusters around the vasa vasorum, with fragmentation of the internal elastic lamina. There was focal deposition of perivascular connective tissue, vascular necrosis, and denuding of the endothelium, followed by vascular thrombosis, ischemia, aneurysm formation, rupture, and hemorrhage. Healed lesions coexisted with active lesions. Harry Lee Parker conceptualized nerve and muscle biopsy in a discussion of the paper by Kernohan and Woltman[5] commenting, "It occurs to me that in any case in which polyarteritis nodosa may be suspected, it is advisable to take a biopsy from a peripheral nerve, muscle or artery." There are no published series confirming the correlation of the extent of systemic necrotizing arteritis that may be predicted by the singular finding of vasculitis in a cutaneous nerve biopsy specimen. A variant of PAN was recognized in very young children with mucocutaneous lymph node syndrome.[7,8] Although early publications used the term infantile PAN,[9,10] Kawasaki disease (KD) is the preferred term to describe this childhood syndrome with worldwide occurrence, affecting children of all ages and races. Both PAN and KD are prototypical examples of medium vessel vasculitides.

Theme Two: Contemporaneously, small vessel vasculitis (SVV) syndromes were recognized and differentiated from PAN.

First described by Wohlwill[11] in 1923, Davson and colleagues[12] and Wainwright and Davson[13] later described microscopic polyangiitis (MPA) in 34 patients that differed from PAN due to selective involvement of small microscopic arteries, arterioles, capillaries, and venules, including glomerular and pulmonary alveolar capillaries. Fever, arthralgia, purpura, hemoptysis, pulmonary hemorrhage, abdominal pain, and gastrointestinal bleeding likewise preceded the explosive phase of systemic necrotizing vasculitis that affected the kidney and lungs, with rapidly progressive glomerulonephritis and pulmonary capillaritis. Two of 5 deaths were attributed to CNS involvement by vasculitis during periods of disease, respectively at 4 and 8 months; however, that could not be confirmed because postmortem examinations were not performed. The disorder was later reclassified by the CHCC as a necrotizing SVV, with little or no immune-complex deposition that primarily affected the kidney and lungs. Medium-sized arteries might be involved even though the disease was predominantly considered to affect small-sized arteries, arterioles, capillaries, and venules of the 2 organs most affected, with variable systemic necrotizing vasculitis.

The first patient with eosinophilic granulomatosis with polyangiitis (EGPA) was probably Case 1 of Lamb,[14] reported in 1914 under the heading of PAN. That patient, a 26-year-old man with 2 years of worsening asthma, developed fever, palpable purpura, nodular skin lesions, hemoptysis, vomiting, urinary difficulty, and granular urinary casts. He died 1 month later and postmortem examination showed necrotizing arteritis

of small arteries, with dense collections of extravascular eosinophils and tissue eosinophilia in the heart, stomach, and kidney. Decades later, Churg and Strauss[15] described the clinical and postmortem findings of 13 patients with asthma, fever, and hypereosinophilia, accompanied by eosinophilic exudation, fibrinoid change, and granulomatous proliferation, that constituted the so-called allergic granuloma, that was found within vessels walls and in extravascular connective tissue of major organ systems, leading to cardiac, pulmonary, gastrointestinal, skin, peripheral nervous system (PNS), and CNS manifestations. In 1977, Chumbley and colleagues[16] described 30 asthmatic patients from the Mayo Clinic, over the period 1950 to 1974, with necrotizing vasculitis of small arteries and veins, with extravascular granulomas and infiltration of vessels, and perivascular tissue with eosinophilia. The lungs, peripheral nerves, and skin were most frequently involved, and renal failure was encountered in only 1 patient. Corticosteroids seemed to confer long-term survival. In 1984, Lanham and colleagues[17] emphasized that the combination of necrotizing vasculitis, tissue infiltration by eosinophils and extravascular granulomas suggested by Churg and Strauss[15] occurred contemporaneously in only a few patients. Moreover, such histologic findings could also be encountered in other granulomatous, vasculitic, and eosinophilic disorders in the absence of clinical asthma, allergic rhinitis, sinusitis, pulmonary infiltrates, and cardiac involvement pathognomonic of EGPA. The investigators described a phasic pattern of EGPA in which allergic disease preceded systemic vasculitis and eosinophilic tissue infiltrates might occur in the absence of peripheral blood eosinophilia. Pulmonary infiltrates and upper respiratory tract and gastrointestinal disease often preceded the vasculitic component of the syndrome, leading to cardiac, cutaneous, nervous system, renal, bone, and muscle involvement. In 1990, the American College of Rheumatology[18] developed criteria for the classification of EGPA that included ascertainment of 4 or more of the following: asthma, eosinophilia of greater than 10%, mononeuropathy or polyneuropathy, nonfixed pulmonary infiltrates on chest radiograph, paranasal sinus abnormality, and extravascular eosinophils on tissue biopsy that included an artery, arteriole, or venule. These criteria were inadequate in differentiating the various clinicopathological expressions of SVV and a patient with asthma and paranasal sinusitis could fit the designation of EGPA. The 1994 CHCC[1] characterized EGPA as an eosinophil-rich and granulomatous inflammatory process that involved the respiratory tract, with necrotizing vasculitis that affected small-sized to medium-sized vessels, such as capillaries, venules, arterioles, and arteries, with associated asthma and eosinophilia.

The syndrome of granulomatosis with polyangiitis (GPA), which included granuloma in the nasopharynx, sinuses, and lower respiratory tract with focal segmental glomerulonephritis and disseminated SVV, was described in 1954 by Godman and Churg.[19] Nervous system involvement in GPA was found in up to one-half of patients according to Drachman,[20] who also described a patient with 1 month of headache that awakened him from sleep followed by rhinitis, nasal obstruction, epistaxis, mononeuropathy multiplex, confusion, and hypertension. Active arteritis and necrotizing granuloma were found in the brain, not in peripheral nerves. Two decades later, Fauci and colleagues[21] and Hoffman and colleagues,[22] at the National Institutes of Health (NIH), respectively reported a prospective series of 85 patients with GPA and a retrospective assessment of 180 patients followed for 6 months to 24 years, describing nervous system involvement in up to 23% of patients. There was a preponderance of mononeuritis multiplex with CNS abnormalities in 8% to 10% of patients. CNS involvement included stroke, cranial nerve abnormalities, and diabetes insipidus. Fauci and colleagues[21] established the efficacy of cyclophosphamide and prednisone in achieving complete remissions in 93% of patients, as well as the tendency of

patients to relapse and accrue additive mortality from both disease and treatment; however, alternative immunosuppressive regimens were not equally effective.[22] In a landmark article, Godman and Churg[19] concluded that MPA, EGPA, and GPA were related to one another yet distinct from PAN. This astute conclusion was based mainly on pathologic features and was later substantiated by their common association with antineutrophil cytoplasmic antibody (ANCA) but not so for PAN.

Theme Three: There ensued a renaissance in the understanding of primary systemic vasculitis with convincing clinical evidence to support an important role for ANCA–associated vasculitides (AAVs).

Early observations of ANCA were provided by van der Woude and colleagues[23] in 1985, and Falk and Jennette,[24] followed by progress in the differentiation of these subtypes and understanding of the eponymous manifestations.[25] Proteinase 3 (PR3) is a serine protease found in the azurophilic granules of neutrophils and peroxidase-positive lysosomes of monocytes. Myeloperoxidase (MPO), which constitutes about 5% of the total protein content of the neutrophil cell, is localized to the same cellular compartment as PR3. However, PR3, in contrast to MPO, is also found on the plasma membrane of resting neutrophils and monocytes in many patients. Autoantibodies directed against PR3 and MPO are directed against multiple epitopes. Although sera from different patients may recognize different epitopes, all ANCA recognized restricted epitopes of PR3 involving its catalytic site. The AAV classification seems to better recognize ANCA disease and predict prognosis than other any existing clinical classification systems.[26] However, as with other autoimmune disorders, the etiologic factors and pathogenesis seemed multifactorial, involving the interplay of initiating and predisposing environmental and genetic factors. Important contributing factors to the mediation of vascular and extravascular inflammation included a loss of regulatory T-cell and B-cell function, acute neutrophilic cell injury with release of ANCA-antigens, cytokine priming of neutrophilic cells, subsequent complement activation by fragment crystallizable (Fc) and fragment antigen-binding 2 (Fab2) engagement, and enhancement of complement-dependent cytotoxicity with release of ANCA-antigens into the microenvironment. The ANCA lesion typical of GPA includes both vasculitic and granulomatous features in lung, with focal segmental glomerulonephritis typified pathologically by lysis of glomerular tufts, basement membrane disruption, accumulation of fibrinoid material, thrombosis of glomerular capillary loops, acute tubular necrosis, and cant deposition of immunoglobulin and complement.

There are genetic distinctions between MPO and GPA suggested by the strong association of PR3-ANCA disease with antigenic specificity of HLA-DP and the genes encoding a1-antitrypsin (*SERPINA1*) and PR3 (*PRTN3*), and HLA-DQ for MPO-ANCA.[27] An immunofluorescence technique (IFT) has been standard method for routine determination of ANCA in vasculitis, using ethanol-fixed human neutrophils as substrate. Two main immunofluorescence patterns are distinguished, a cytoplasmic ANCA and perinuclear ANCA. The 1999 “International Consensus Statement on Testing and Reporting anti-neutrophil cytoplasmic antibodies (ANCA)”[28] required laboratories to screen for ANCA by IFT and to confirm the specificity of fluorescent sera by enzyme-linked immunoassay (ELISA) for PR3 and MPO-ANCA. However, conventional ELISA using PR3 immobilized to the surface of the ELISA plate shows great variation in performance and often lacks sensitivity. Capture ELISA is superior in overall diagnostic performance to direct ELISA[29]; however, the sensitivity of capture ELISA may be reduced by the capturing antibodies hiding relevant epitopes. High-sensitivity PR3–ANCA ELISA, which immobilizes PR3 via a bridging molecule to the plastic plate and preserves nearly all epitopes for the binding of ANCA, was superior to direct and capture techniques in GPA.[30]

Theme Four: Hypersensitivity vasculitis leading to cutaneous vasculitis was conceptualized as an immunologic response to antigenic material associated with clinically evident purpura and small vessel inflammation affecting arterioles, capillaries, and postcapillary venules.

Between 1948 and 1952, Zeek[31,32] separated hypersensitivity vasculitis from allergic granulomatous angiitis, rheumatic arteritis, PAN, and giant cell arteritis (GCA). Hemorrhage into the skin or palpable purpura was noted in virtually all patients, resulting from extravasation of erythrocytes, pronounced endothelial swelling, polymorphonuclear, and later mononuclear cell infiltration; followed by fibrosis, necrosis, fibrinoid deposits, and visible polymorphonuclear debris, termed leukocytoclasia. Zeek[33] likened hypersensitivity vasculitis to the anaphylactoid Arthus reaction produced by the experimental injection of horse serum into rabbits.[34] Osler[35] first appreciated the relation of purpuric attacks to cerebral manifestations in the report of a patient with transient hemiparesis and 3 others with potentially fatal cerebral hemorrhages. Gairdner[36] described Henoch-Schönlein purpura (HSP) among 12 patients with anaphylactoid purpura, including 1 child who developed rash, colic, melanotic stools, intussusception, and hematuria, followed by a typical exanthema and convulsion. She died 3 months later and postmortem examination showed scattered cortical hemorrhages associated with cerebral necrotizing arteriolitis. Levitt and Burbank[37] described the clinicopathological findings in 2 previously nonallergic patients with recurrent fatal attacks of HSP after injection of penicillin and ingestion of strawberries, respectively, that included glomerulonephritis alone or with systemic arteriolitis. The finding of IgA deposits in cutaneous blood vessel walls and in glomerular mesangial biopsies of patients with HSP and IgA nephropath[38,39] was circumstantially convincing enough to substitute the term IgA vasculitis for HSP.

Wintrobe and Buell[40] described cryoglobulinemia in a patient with progressive frontal headache, facial pain, Raynaud symptoms, recurrent nosebleeds, exertional dyspnea, palpitation, and changes in the eye grounds due to central vein thrombosis. Postmortem examination showed infiltrating myeloma of the humerus and lumbar vertebra, and splenic enlargement. A unique plasma protein was detected that spontaneously precipitated with cold temperature and solubilized at high temperature and differed from the Bence-Jones proteinuria of other myeloma patients. Lerner and Watson[41] noted the association with purpura and, later, Lerner and Watson[42] described its occurrence in 10% of pathologic sera. Gorevic and colleagues[43] described mixed cutaneous vasculitis in 40 patients, the clinical features of which included palpable purpura in all patients; polyarthralgia in three-quarters; kidney involvement in slightly more than one-half; and deposits of IgG, IgM, and complement, or renal arteritis in a third of patients.

Recurrent attacks of erythematous, urticarial, and hemorrhagic skin lesions that last 24 hours at a time, associated with recurrent attacks of fever, joint swelling, abdominal distress, and low serum complement, indicate hypocomplementemia urticarial vasculitis (HUV) were described by McDuffie and colleagues[44] in 1973; however, small amounts of cryoglobulin were present at 1 time or another in the serum of each patient. When tested by immunodiffusion against purified preparations of rheumatoid factor and human C1q, 2 patients consistently produced bands against the former and 2 others reacted strongly with purified C1q. Skin biopsies showed leukocytoclasia characteristic of necrotizing vasculitis in 1 patient, anaphylactoid purpura in 2 others, and mild nonspecific perivascular infiltration another. Immunofluorescence of skin specimens performed in 3 patients showed fixation of immunoglobulin in the patient with necrotizing vasculitis, whereas in 2 others with a pathologic picture of anaphylactoid purpura or nonspecific dermal infiltrate, immunofluorescence was negative. Renal

biopsy in 2 patients showed mild to moderate glomerulonephritis indistinguishable for those seen in other forms of chronic membrane-proliferative glomerulonephritis. The differences from systemic lupus erythematosus (SLE) included more urticarial and purpuric skin lesions, with relatively mild or absent renal and other visceral involvement in the patients with HUV, which was atypical for SLE. Moreover, serum speckled antinuclear and anti-DNA antibodies, and basement membrane immunoglobulin deposits, were absent in those with HUV, also atypical for SLE. An etiopathogenesis related to chronic vascular inflammation, resulting from deposits of immune complexes in small vessel walls seemed likely. Zeiss and colleagues[45] characterized C1q IgG precipitins from HUV sera that precipitated C1q in agarose gel among 4 additional patients. Wisnieski and Naff[46] showed C1q binding activity in IgG from HUV sera, which suggested a relation to SLE but that view was later amended.

Theme Five: The historical account of the category of large vessel vasculitides (LVV) spanned more than a century, with notable advances in the past several years.

Hutchinson[47] provided the first clinical description of temporal arteritis, followed by a pathologic description by Horton and colleagues.[48] Temporal arteritis was named for the site of granulomatous giant cell inflammation and vessel involvement.[49] Those with biopsy-proven temporal arteritis and associated blindness due to vasculitis involvement of ophthalmic and posterior ciliary vessels were classified as having cranial arteritis.[50] The occasional finding of giant cell lesions along the aorta, its branches, and in other medium-sized and large-sized arteries at autopsy in other patients warranted the additional diagnosis of generalized GCA.[51] The pathologic heterogeneity of temporal arteritis was further demonstrated by the finding of intracranial granulomatous arteritic lesions.[52–57] The earliest lesions of GCA consist of vacuolization of smooth muscle cells of the media, with enlargement of mitochondria, infiltration of lymphocytes, plasma cells, and histiocytes. With progression, there is extension of inflammation into the intima and adventitia, leading to segmental fragmentation and necrosis of the elastic lamina, granuloma formation, and proliferation of connective tissue along the vessel wall. This eventuates in vascular thrombosis, intimal proliferation, and fibrosis.

One other LVV, described in the Japanese literature, was change in the central vessels of the retina in the absence of peripheral arterial pulses, typically in women.[58] This pulseless disease, also known as occlusive thromboaortopathy, or Takayasu arteritis, manifested constitutional complaints of malaise, fever, stiffness of the shoulders, nausea, vomiting, night sweats, anorexia, weight loss, and irregularity of menstrual periods weeks to months before the local signs of vasculitis were recognized in up to two-thirds of patients. It is the commonest large vessel vasculitis among Asian women.

Theme Six: One other form of inflammatory aortic disease, or aortitis, came to light in the surgical literature with equally broad and far-reaching implications for concepts of autoimmunity.

In 1972, Walker and colleagues[59] noted that 10% of 217 patients presenting with abdominal aneurysms at Manchester Royal Infirmary between 1958 and 1969 for resection showed excessive thickening of aneurysm walls and perianeurysmal adhesions at operation. Subsequent histologic examination of the walls of the aneurysms showed extensive active chronic inflammatory changes, including plasma-cell infiltration. The clinical features of patients with inflammatory aneurysms differed from those with atherosclerotic disease owing to generally younger age by a decade, lower incidence of rupture, lack of claudication of intermittent the limbs and presence of peripheral pulses, less likelihood of unusual presenting features, elevated erythrocyte sedimentation rate, and lack of calcification on preoperative abdominal radiographs.

In 1985, Pennell and colleagues[60] reported inflammatory aortic or iliac aneurysms in 4.5% of 2816 patients undergoing repair for abdominal aortic aneurysm from 1955 to 1985. Ultrasound and computed tomography imaging suggested the diagnosis in 13.5% and 50% of patients, respectively; the former showing a sonolucent halo with clear definition of the aortic wall posterior to the thickened anterior and lateral aortic walls. In 2000, Rojo-Leyva and colleagues[61] noted idiopathic aortitis in 43% of 1204 aortic specimens gathered over a period of 20 years. In 96% of the patients with idiopathic aortitis and aneurysm formation, aortitis was present only in the thoracic aorta. In 2001, Hamano and colleagues[62] noted a high concentrations of IgG4 associated with sclerosing pancreatitis characterized by obstructive jaundice, infrequent attacks of abdominal pain, irregular narrowing of the pancreatic duct, sonolucent swelling of the parenchyma, lymphoplasmacytic infiltration, fibrosis, and a favorable response to corticosteroid treatment. One year later, Hamano and colleagues[63] noted the association of sclerosing pancreatitis with raised concentrations of IgG4 among those with concomitant hydronephrosis that caused ureteral masses, which were later diagnosed as retroperitoneal fibrosis (RPF). Histologic examination of ureteral and pancreatic tissues revealed abundant tissue infiltration by IgG4-bearing plasma cells. In the same year, 2008, 3 important observations were made. First, Sakata and colleagues[64] concluded that inflammatory abdominal aortic aneurysm (IAAA) was related to IgG4 sclerosing disease. Second, Kasashima and colleagues[65] concluded that IAAA was an IgG4–related disease (RD) together with RPF. Third, Ito and colleagues[66] described a patient with IAAA, hydronephrosis caused by RPF, and high levels of IgG4, in whom treatment with corticosteroids led to clinical improvement and reduction in IgG4 levels. Histologic inspection of the aortic wall specimen showed lymphoplasmacytic infiltration. Immunohistochemical analysis of the tissue showed IgG4-positive plasma cells. The findings suggested that IAAA had an etiopathogenesis similar to autoimmune pancreatitis and that some cases of IAAA and RPF may be aortic and periaortic lesions of an IgG4-RD. One year later, in 2009, Khosroshahi and colleagues[67] described thoracic aortitis due to IgG4-RD with marked elevation of the serum IgG4 levels, with progression to autoimmune pancreatitis. Stone and colleagues[68] described IgG4-related thoracic aortitis with a media-predominant pattern of aortic wall infiltration and marked elevation of serum IgG4 levels, unequivocally linking IgG4-RD with thoracic lymphoplasmacytic aortitis.

Theme Seven: Two forms of variable vessel vasculitides: Behçet disease (BD) and Cogan syndrome (CS), were recognized with very different clinical presentations and systemic involvement.

Adamantiades[69] recognized the disorder of relapsing aphthous ulcers of the mouth, eye, and genitalia, the clinicopathological details of which were later described in detail by Behçet[70,71] in 2 Turkish patients. Nervous system involvement of a 28-year-old Yemenite, with relapsing oral, genital, and oral eruptions over 4 years, was accompanied by severe headache, memory loss, dizziness, lethargy, fatal seizures, and coma. Postmortem examination showed perivascular inflammatory cell infiltration of the meninges, brain, central retinal artery, and optic nerve, with necrotic cerebral lesions. Encephalomyelopathy was detailed at postmortem examination in 2 Australian patients with BD.[72] One presented with hemiparesis, whereas the other patient presented with pseudobulbar affect, vertical gaze palsy, nystagmus, and spastic paraplegias. Postmortem examination showed widespread lesions in cortical and brainstem white matter and hypothalamus, corresponding to small blood vessels, including arterioles and veins that showed perivascular mononuclear cell infiltration. The first well-documented American patient with nervous system involvement of BD was described by Wolf and colleagues.[73] She was a 22-year-old woman with a

5-year history of recurrent oral and genital ulceration, and a 2-year course of progressive visual loss, headache, hemiparesis, ataxia, tremor, dysarthria, cranial nerve palsy, cerebellar and corticospinal tract disease, and mental deterioration, which responded to prednisone therapy. Mogan and Baumgartner[74] described a 26-year-old man with recurrent pain, spasm, redness of the left eye with photophobia, excessive tearing, and marked conjunctival injection, followed by severe attack of dizziness, tinnitus, vertigo, nausea, vomiting, ringing in the ears, profuse perspiration, and deafness. A diagnosis of recurrent interstitial keratitis (IK) and explosive Menière disease was made. In retrospect, he was probably the first reported patient with CS of nonsyphilitic IK.

Vestibuloauditory symptoms were later described by Cogan.[75] Haynes and colleagues[76] set forth diagnostic criteria for typical CS according to the definitions established in a review of 30 patients seen at the National Eye Institute of the NIH by Cogan[75,77] and Norton and Cogan.[78] Symptoms of IK developed abruptly and gradually resolved, associated with photophobia, lacrimation, and eye pain, which may be unilateral or bilateral. Such symptoms tend to recur periodically for years before becoming quiescent. Vestibuloauditory dysfunction was manifested by sudden onset of Menière-like attacks of nausea, vomiting, tinnitus, vertigo, and (frequently) progressive hearing loss that characteristically occurred before or after the onset of IK. However, within 1 to 6 months of the onset of eye symptoms, auditory symptoms progressed to deafness over a period of 1 to 3 months, certainly no longer than 2 years. Cody and Williams[79] provided a description of atypical CS if another significant inflammatory eye lesion in addition to or instead of IK, such as scleritis, episcleritis, retinal artery occlusion, choroiditis, retinal hemorrhage, papilledema, exophthalmos, or tendonitis. Haynes and colleagues[76] defined acute CS as the presence of acute eye disease within 2 weeks of hearing loss, whereas inactive CS was applied to patients without active eye disease or vestibuloauditory dysfunction of greater than 2 weeks before the study. With less than 100 reported patients with this rare childhood and young adult disorder, most reported patients with typical CS appeared as single case reports or patient series, often without pathologic confirmation or evidence of systemic vasculitis in a biopsy or at postmortem examination.

Theme Eight: The concept and clinicopathologic expression of diverse syndromes associated with isolated or nonsystemic peripheral nerve vasculitis (NPNV) intrigued generations of morphologists who later found compelling evidence for distinctive clinicopathologic syndromes associated with inflammatory damage of peripheral nerve microvessels, termed microvasculitis (MV).

The very concept of NPNV, which presumes that the necrotizing vasculitis process is widespread within the PNS and not elsewhere in the body, may yet be called into question for 3 reasons. First, there are reports of equally silent lesions in medium-sized muscular arteries in patients with clinically isolated vasculitic neuropathy.[80] Vasculitis in muscle tissue is included in the definition of nonsystemic vasculitic neuropathy (NSVN),[81] supporting use of the term PNS vasculitis (PNSV) over NPNV. Second, the varied long-term follow-up in cases series ranged from 6 months to 22 years.[82] Third, the presence of only 2 proposed cases from clinicopathologic series have been used as examples of isolated PNSV, both with foci of vasculitis outside the PNS in a visceral organ[5] or the temporal artery,[83] making them anomalous examples of systemic vasculitis, at best.

Contemporaneously, investigators studied patients with inflammatory plexopathy or diabetic neuropathy, elucidating clinicopathologic syndromes characterized by MV in a cutaneous nerve biopsy in peripheral nerve microvessels with a diameter less than 70 μm[81] but with ischemic consequences for the peripheral nerves. Historically, in 1968, Raff and colleagues[84] documented infarctive lesions in a newly diagnosed

noninsulin-dependent diabetic, with mononeuritis multiplex and acute asymmetrical leg pain and weakness. Postmortem examination showed a multitude of unilateral small ischemic infarcts of the proximal major nerve trunks of the leg and lumbosacral plexus. In 1984, Bradley and colleagues[85] delineated the syndrome of painful lumbosacral plexopathy with elevated erythrocyte sedimentation rate among 6 patients, 3 of whom were diabetic, including 1 newly diagnosed, with PV in sural nerve biopsies. Johnson and colleagues[86] noted focal fascicular lesions distributed in proximal lumbosacral plexus trunks of 18 out of 32 samples obtained at autopsy from diabetic patients, a quarter of whom were insulin-dependent, using epoxy-embedded and teased nerve fiber sections. These findings suggested a possible propensity for the spontaneous evolution of lumbosacral plexopathy in patients with diabetic neuropathy. Said and colleagues[87] studied 10 noninsulin-dependent diabetics with painful proximal neuropathy and reported ischemic nerve lesions due to necrotizing vasculitis in 3 biopsies of the intermedius cutaneous nerve of the thigh, and 4 others with isolated mononuclear cell inflammation. In 1996, Younger and colleagues[88] characterized microvascular inflammatory lesions in 12 patients with proximal diabetic neuropathy and stepwise or slowly progressive proximal weakness, wasting, and pain, as well as axonopathy, on electrodiagnostic studies. Six nerves showed epineurial MV (**Fig. 1**) composed of cytotoxic-suppressor T cells with activated endoneurial lymphocytes that expressed immunoreactive cytokines, major histocompatibility class II antigens, and endoneurial and epineurial complement C3d and C5b-9. In addition, the nerve tissue of 2 patients with MV had focal pathologic findings indicating ischemia. Dyck and colleagues[89,90] characterized lumbosacral radiculoplexus neuropathy (LSRPN) with and without diabetes. At present, diabetes has not been considered a factor related to vasculitis[81] but there is consensus support for designating nondiabetic LSRPN as a variant of NSVN.[91]

There has also been support for the role of diabetes in both diabetic LSRPN (DLSRPN) and variant forms of diabetic neuropathy. Younger and colleagues[88] reported the clinicopathologic and immunohistochemical findings of sural nerve biopsy

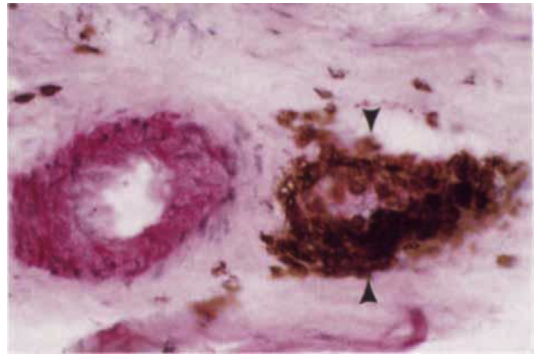

Fig. 1. Peripheral nerve MV in a diabetic. A focal-intense collection of CD3+ T cells efface the wall of a small epineurial blood vessel (*arrowheads*) in a patient with proximal diabetic neuropathy (lumbosacral radiculoplexus neuropathy). In deeper sections (not shown), the same structure stains red in double-labeling with antiactin smooth muscle antigen, a marker for the blood vessel wall (immunoperoxidase, original magnification ×400). (*From* Younger DS, Rosoklija G, Hays AP, Trojaborg W, Latov N. Diabetic peripheral neuropathy: a clinicopathologic and immunohistochemical analysis of sural nerve biopsies. Muscle Nerve 1996;19:722–27; with permission.)

tissues in a cohort of 20 patients with heterogeneous forms of diabetic neuropathy that was continued to a total of 107 patients,[92] of which 3 (3%) showed MV, and 3 (3%) showed necrotizing arteritis (including 2 patients with distal symmetric polyneuropathy and 1 with DLSRPN). The following year, Younger[93] affirmed the existence of DLSRPN in a living case. Despite treatment with 2 g/kg intravenous immunoglobulin for 5 days, followed by 750 mg of intravenous cyclophosphamide and 1000 mg of methylprednisolone intravenously for 3 additional days, the patient died of acute tubular necrosis, increasing lethargy, unresponsiveness, and aspiration pneumonia 4 weeks after admission. General autopsy showed no evidence of systemic or peripheral nerve vasculitis. There was no evidence of systemic vasculitis. Sections of extradural lumbar plexus, sciatic, and femoral nerve tissue showed perivascular epineurial inflammation with infiltration of adjacent endoneurium (**Fig. 2**).

Theme Nine: Diverse clinicopathologic and radiographic syndromes of potentially fatal adult and childhood primary CNS vasculitis have been described; however, none has stood the test of time as well as granulomatous angiitis.

It has been said that efforts to define a disease are attempts to understand the concept of the disease. In no other vasculitis disorder has this been more evident as in granulomatous angiitis of the CNS. No other vasculitis syndrome has captured the attention of so many neurologists and neuropathologists over the decades, and captured the focus of such vigorous debate. In 1922, Harbitz[94] described 2 patients with a previously unrecognized cerebral vasculitis. At age 26 years, a woman noted worsening headaches, mental change, and ataxia, culminating 2 years later in stupor, spastic paraparesis, coma, and death. The other patient, a 46-year-old man, developed hallucinations and confusion, progressing to gait difficulty, stupor, coma, and death in 9 months. At postmortem examination, both had granulomatous vasculitis of the meninges, composed of lymphocytes, multinucleate giant cells, and epithelioid cells, with vessel necrosis and extension into the brain along involved veins and arteries of varying caliber. Over the ensuing quarter century, additional patients reported under the rubric of allergic angiitis and granulomatosis,[95] GCA,[96] and sarcoidosis[97] were described. In 1959, Cravioto and Fegin[98] delineated the clinicopathologic syndrome of granulomatous angiitis, and so named it for the distinctive CNS pathologic findings. For 2 more decades, rare affected patients were identified; however, there was no effective treatment.

Several achievements of the 1980s further transformed the concept of the disorder. In 1983, Cupps and colleagues[99,100] influenced by their advances in the classification, diagnosis, and treatment of systemic vasculitis, advocated cerebral angiography for the diagnosis of isolated CNS angiitis, and prednisone and oral cyclophosphamide therapy for those affected. The angiographic pattern of beading (in 2 patients) or the sausage appearance (in 1 patient) of lesioned vessels, had previously been noted by Hinck and colleagues[101] in a case of giant cell granulomatous angiitis. In 1988, Younger and colleagues[102] analyzed pathologically verified cases of granulomatous angiitis related to herpes zoster virus (HZV) infection, lymphoma, and sarcoidosis, with idiopathic cases. Fever, headache, and mental changes, often leading to focal cerebral signs, with cerebrospinal fluid (CSF) pleocytosis, elevation of the protein content, and normal or nonspecifically abnormal angiographic findings, were found in most patients. In the same year, Calabrese and Mallek[103] reported on so-called primary angiitis of the CNS (PACNS)[103] and isolated angiitis of the CNS (IACNS),[99] emphasizing the restricted nature of the vasculitis, rather than the granulomatous histology, even though antemortem leptomeningeal biopsy of Case 5 of Calabrese and Mallek[103] showed granulomatous SVV affecting meningeal veins (**Fig. 3**) with proliferation of epithelioid cells along vascular walls, sparing the cortex. Cerebral angiography

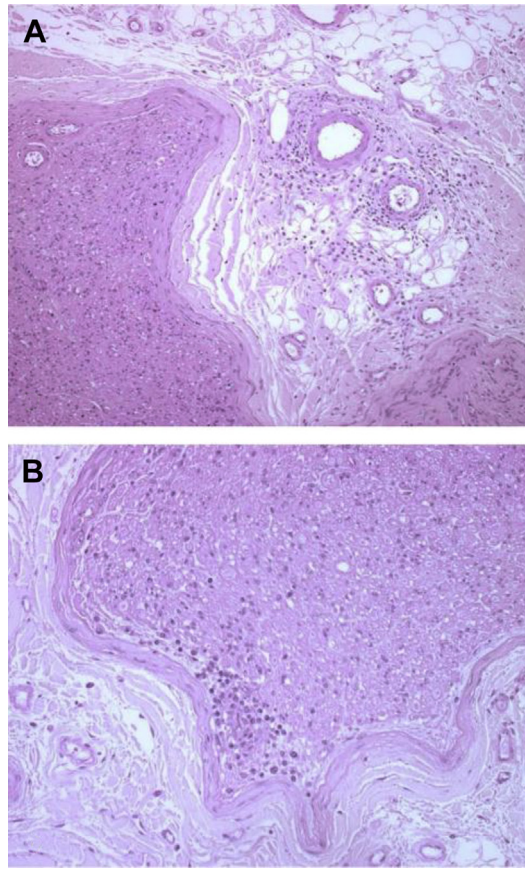

Fig. 2. Postmortem histopathology of patient with lumbosacral radiculoplexus neuropathy. (*A*) Transverse section of the left sciatic nerve shows perivascular chronic inflammation surrounding small blood vessels of the epineurium. (*B*) Transverse section of the left femoral nerve in addition shows perivascular chronic inflammation in the subperineurial area. Inflammatory cells infiltrate the adjacent endoneurium (paraffin, hematoxylin-eosin, original magnification ×200). (*From* Hughes T, Ture-Ozdemir F, Alibaz-Oner F, et al. Epigenome-wide scan identifies a treatment-responsive pattern of altered DNA methylation among cytoskeletal remodeling genes in monocytes and CD4+ T cells from patients with Behçet's disease. Arthritis Rheumatol 2014;66:1648–58; with permission.)

in that patient was negative, showing only tortuosity and some irregularity of the lumen of intracranial vessels without segmental or alternating stenosis and ectasia typical of arteritis. Patients with angiographically negative small-vessel PACNS closely resembled the childhood equivalent, small-vessel (SV)–childhood PACNS (cPACNS),[104] with the difference being that patients with SV-cPACNS are rarely investigated for prototypical granulomatous disease. The prevailing rationale for ignoring the significance of granulomatous disease has been that giant cells and epithelioid cells, usually found at autopsy, were an inconsistent finding in a meningeal and brain biopsy and, therefore, not necessary for antemortem diagnosis.

To illustrate the problem, Younger and colleagues[102] reported that 10 patients with granulomatous angiitis diagnosed antemortem by brain and meningeal biopsy were

Fig. 3. Section of the leptomeninges (Case #5) showing focal, often eccentric, granulomatous Vasculitis predominantly around veins. Note focal proliferation and collection of epithelioid cells (arrowheads) along the vascular walls. (*From* Calabrese HL, Mallek JA. Primary angiitis of the central nervous system: report of 8 new cases, review of the literature, and proposal for diagnostic criteria. Medicine 1988;67:20–39; with permission.)

improved for up to 7 months, whether treated with prednisone, alone (in 3 patients) or with cyclophosphamide (in 3 patients) or azathioprine (in 3 patients); or cyclophosphamide alone (in 1 patient). Similarly, in a historical survey of 54 pathologically proven cases (**Table 1**),[105] 17 of 94% of untreated patients died, indicating that without therapy the disease was usually fatal. Treatment with corticosteroids, alone or in combination with cyclophosphamide, was associated with a considerable reduction in mortality; with the 70% so treated surviving either improved (50%) or clinically

Table 1
Outcome of 54 patients with granulomatous angiitis of the nervous system

Outcome	CS	CS + CYT	CS + AZA	None	Total
Improved	8/0	9/0	1/0	0	18/0
Same	3/0	4/0	0	1/0	8/0
Died	0/6	3/1	0	1/17	4/24

Abbreviations: AZA, azathioprine; CS, corticosteroids; CYT, cyclophosphamide.
Patients diagnosed antemortem in the numerator and postmortem in the denominator.
From Weiss N, Miller F, Cazaubon S, et al. The blood-brain barrier in brain homeostasis and neurological diseases. Biochim Biophys Acta 2009;1788:842–57; with permission.

unchanged. The achievements of the 1980s proved to be the lessons of the 1990s for 2 reasons. First, enthusiasm for the empiric treatment of cerebral vasculitis waned because of the recognition of the unreliability of cerebral angiography in its diagnosis. Several similar patients with beading on cerebral angiography had a benign course without immunosuppressive therapy. Calabrese and colleagues[106] found so-called benign angiopathy of the CNS among young women with the prior diagnosis of PACNS who differed in the onset with a focal cerebral deficit, normal CSF, beading or other previously suggestive features of vasculitis on a cerebral angiogram, lack of progression, and spontaneous resolution. A second factor that lessened interest in empiric therapy with cyclophosphamide for CNS vasculitis, was the recognition of permanent side effects in up to 40% of patients treated with oral cyclophosphamide for GPA. With increasing interest in the etiopathogenic basis of granulomatous angiitis disease, there has been general acceptance for the inclusion of associated disorders; for example, GCA, sarcoidosis, HZV, and lymphoma; and others are emerging.

Commensurate with the refinement in clinical trials methods, the literature reflects a move away from small or single-case series to the experience of larger cohorts of CNS vasculitides, with 1 retrospective series from the Mayo Clinic,[107] a multicenter prospective cohort from the French Vasculitis Study Group, French NeuroVascular Society, and the French Internal Medicine Society,[108] and the PedVas Initiative of AAV (GPA) and PACNS (NIH identifier, NCT02006134). The approach to diagnosis and management of CNS vasculitides in children differs from adults in that suspected cases of cPACNS are first placed into the larger group of inflammatory brain diseases, and then differentiated by angiography and other blood and CSF biomarkers, rarely leptomeningeal and cortical biopsy, to exclude angiography-positive and angiography-negative, brain biopsy-positive mimickers.[109] Notwithstanding, the empiric management of cPACNS with cytotoxic therapy was set back by the early outcome results of the PedVas Initiative, using corticosteroids, cyclophosphamide, methotrexate, or rituximab for remission-induction of childhood GPA,[110] that showed a remission status of 42% and visceral organ damage in 63% of cases so treated.

Theme Ten: Vasculitis due to drug abuse captured the interest of successive generations of investigators.

The earliest reports of misuse of amphetamine sulfate occurred in 1937 when it was used by students to avoid sleep during examination periods.[111] This was followed by reports of death by those who ingested the drug repeatedly as a stimulant for the same purpose[112] in a suicide attempt that resulted in a fatal intracerebral hemorrhage,[113] or accidentally, when dexamphetamine and phenelzine were fatally ingested together decades later.[114] During the Second World War, amphetamine and methamphetamine was used clinically and illicitly but its abuse soared in San Francisco after

1962, wherein it was illegally produced and distributed.[115] By 2009, the United Nations Office on Drugs and Crime estimated that 16 to 51 million persons between the age of 15 and 64 years consumed amphetamine drugs, with more than half using methamphetamine,[116] exceeding the combined consumption of all other drugs of abuse except cannabis.[117] Such drugs agents comprise a large spectrum of agents available in powder, capsule, tablet, and injectable fluid form that can be swallowed, snorted or taken intranasally, smoked, or injected with highly variable purity and dosage equivalence. Histologically confirmed cerebral vasculitis due to amphetamine, methamphetamine, and related agents is exceedingly rare, which is surprising given the number of substances that could cause this disorder if there was a true association.

Theme Eleven: Finally, there has been extraordinary research in the blood–brain barrier (BBB) over the past decade.

Once considered a static anatomic barrier to the traffic of molecules in and out of the CNS when fully developed in adults, and otherwise irrelevant to neuroscience and disease, the BBB is now known to be fully functional in development, and vital in cerebrovascular angiogenesis.[118–122] First postulated as a barrier at the level of the cerebral vessels by Bield and Kraus,[123] and later by Goldman[124] and Lewandowsky,[125] at the turn of the twentieth century, the cellular components and other molecular constituents of the BBB are contained in a neurovascular unit (NVU) protecting the CNS from injury and disease by limiting the passage of toxins, pathogens, and inflammatory effectors of the immune system. In essence, the NVU of the BBB is composed of capillary vascular and neural cells, extracellular matrix components, and a variety of immune cells that mediate local immunity. The schematized and electron microscopic appearance of cerebral capillaries in the BBB shown in **Fig. 4** demonstrate layers of pericytes adherent to the abluminal or parenchymal surface of endothelial cells, together surrounded by a layer of basal lamina composed of proteins and molecules of the extracellular matrix. The endfeet of the neighboring astrocyte processes ensheathe the blood vessels. Monolayers of adjacent endothelial cells that form tight junctions connect adjacent endothelial cells by adhesions of transmembrane occludin, claudin, and junctional associated molecules across the intercellular space, whereas cytoplasmic scaffolding and regulatory proteins, such as zona occludens types 1 and 2 provide linkage to the actin cytoskeleton and initiate several signaling mechanisms via protein–protein interactions. Endothelial BBB cells are also linked by adherens junctions composed of vascular endothelial (VE)-cadherin, which

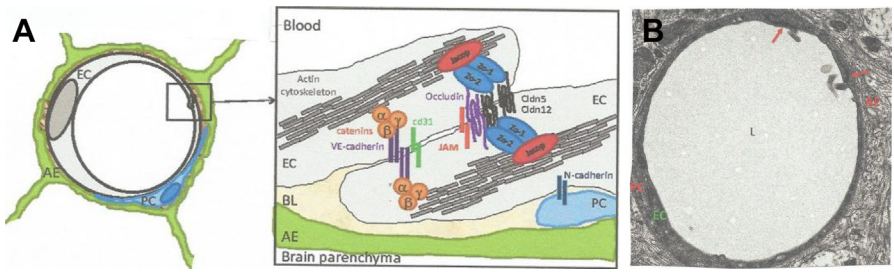

Fig. 4. Human BBB. (*A*) Schematic of a capillary in the human BBB over an endothelial tight junction (*left*). Molecular composition of tight and adherens junctions (*right*). AE, astrocyte endfeet; BL, basal lamina; EC, endothelial cells; PC, pericytes; JAM, junctional associated molecule; VE, vascular endothelial; ZO, zona occludens. (*B*) Electron micrograph of a capillary in the adult murine BBB in which endothelial cells are held together by tight junctions (*red arrows*). (*From* United Nations Office on Drugs and Crime. UNODC 2009 world drug report. Vienne (Austria): United Nations; 2009; with permission.)

mediate cell–cell adhesion interactions, linking adherens junctions to the actin cytoskeleton via catenins. Perivascular and resident macrophages that reside between astrocyte endfeet and the vessel wall act as antigen-presenting cells where novel antigens stimulate naive autoreactive T cells in in the trimolecular complex in the presence of class II main histocompatibility complex molecules, otherwise known as the body's immune playbook. Circulating leukocytes that penetrate the intact BBB via interactions with endothelial cell adhesion molecules that mediate bidirectional crosstalk between immune cells and endothelium for normal surveillance, thereby constituting the extended NVU. Disruption of the BBB is recognized as an important factor in a variety of primary neurologic diseases; however, such disturbances, although common to primary and vasculitis of the CNS, have yet to be critically analyzed but remain a critical element in the search for more effective chemotherapeutic interventions and the establishment of a more favorable metabolic milieu for health and disease in clinically affected patients with vasculitides.

The past several years have witnessed an explosion in the number of genetic and epigenetic association studies respectively termed genome-wide and epigenome-wide association studies (EWAS). Genome-wide association studies investigate the entire genome using single-nucleotide polymorphisms in contrast to specifically testing a small number of specified genetic regions, whereas EWAS analyze the heritable molecular modifications that are independent of the primary DNA sequence. Epigenetic modification occurs at various developmental stages throughout the lifespan and is analyzed by using DNA methylation (DNAm) as a marker for the perturbation that has taken place, whether causally or consequential to the disease phenotype under investigation. The main type of DNAm occurs at cytosines within 5'-cytosine-phosphate-guanine-3' (CpG) dinucleotides, known to be involved in gene expression regulation. Many human diseases, including the vasculitides, arise from genetic and environmental factors and thus the interplay between genes and environment. An EWAS of patients with BD[126] studied 383 CpG sites in blood monocytes, and 125 sites in CD4+ T cells, showing differential methylation between patients and controls. Bioinformatic analysis supported a pattern of aberrant DNAm among genes that regulate cytoskeletal dynamics, suggesting a contribution to BD pathogenesis. Treatment modified these differences with widespread reversal of the direction of DNAm. By studying the epigenome in well-characterized cohorts of vasculitides, it should be possible to discover novel genes and pathways by which genetic factor and environmental exposures influence disease development. Properly performed and with a careful consideration of the characteristics of samples, study design, and key research questions, spurious associations due to confounding and reverse causation can be eliminated from these analyses, leaving the challenge to relate them to accurate epidemiologic data. Genetic research of the vasculitides, integrating multiple phenotypic determinants and biobank data from discrete populations within well-defined geographic boundaries, is the next frontier to uncover novel aspects of disease pathogenesis, and the identification of new targets for monitoring and treatment.

REFERENCES

1. Jennette JC, Falk RJ, Andrassay K, et al. Nomenclature of systemic vasculitides. Proposal of an international conference. Arthritis Rheum 1994;37:187–92.
2. Jennette JC, Falk RJ, Bacon PA, et al. 2012 Revised international chapel hill consensus conference nomenclature of vasculitides. Arthritis Rheum 2013;65:1–11.

3. Kussmaul A, Maier R. Ueber eine bisher nicht beschriebene eigenthümliche Arterienerkrankung (Periarteritis nodosa), die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellähmung einhergeht. Deutsches Arch f klin Med 1866;1:484–518.
4. Longcope WT. Periarteritis nodosa with report of a case with autopsy, vol. 1. Philadelphia: Bull Auyer Clin Lab, Pennsylvania Hospital; 1908.
5. Kernohan JW, Woltman HW. Periarteritis nodosa: a clinicopathologic study with special reference to the nervous system. Arch Neurol 1938;39:655–86.
6. Krahulik L, Rosenthal M, Loughlin EH. Periarteritis nodosa (necrotizing panarteritis) in childhood with meningeal involvement. Report of a case with study of pathologic findings. Am J Med Sci 1935;190:308–17.
7. Kawasaki T. MLNS showing particular skin desquamation from the finger and toe in infants. Allergy 1967;16:178–89.
8. Tanaka N, Naoe S, Kawasaki T. Pathological study on autopsy cases of mucocutaneous lymph node syndrome. J Jap Red Cross Cent Hosp 1971;2:85–94.
9. Chamberlain JL, Perry LW. Infantile periarteritis nodosa with coronary and brachial aneurysms: a case diagnosed during life. J Pediatr 1971;78:1039–40.
10. Landing BH, Larson EJ. Are infantile periarteritis nodosa with coronary artery involvement and fatal mucocutaneous lymph node syndrome the same? Comparison of 20 patients from North America with patients from Hawaii and Japan. Pediatrics 1977;59:651–2.
11. Wohlwill F. Uber die mur mikroskopisch erkenbarre form der periarteritis nodosa. Arch Pathol Anat 1923;246:377–411.
12. Davson J, Ball M, Platt R. The kidney in periarteritis nodosa. QJM 1948;17:175–202.
13. Wainwright J, Davson J. The renal appearance in the microscopic form of periarteritis nodosa. J Pathol Bacteriol 1950;62:189–96.
14. Lamb AR. Periarteritis nodosa-a clinical and pathological review of the disease with a report of two cases. Arch Intern Med 1914;14:481–516.
15. Churg J, Strauss L. Allergic granulomatosis, allergic angiitis, and periarteritis nodosa. Am J Pathol 1951;27:277–301.
16. Chumbley LC, Harrison EG, DeRemee RA. Allergic granulomatosis and angiitis (Churg-Strauss syndrome). Report and analysis of 30 cases. Mayo Clin Proc 1977;52:477–84.
17. Lanham JG, Elkon KB, Pussey CD, et al. Systemic vasculitis with asthma and eosinophilia: a clinical approach to the Churg-Strauss syndrome. Medicine (Baltimore) 1984;63:65–81.
18. Masi AT, Hunder GG, Lie JT, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (Allergic granulomatosis and angiitis). Arthritis Rheum 1990;33:1094–100.
19. Godman GC, Churg J. Wegener's granulomatosis: pathology and review of the literature. Arch Pathol 1954;58:533–53.
20. Drachman DA. Neurological complications of Wegener's granulomatosis. Arch Neurol 1963;8:45–55.
21. Fauci AS, Haynes BF, Katz P, et al. Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients over 21 years. Ann Intern Med 1983;98:76–85.
22. Hoffman GS, Kerr GS, Leavitt RY, et al. Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med 1992;116:488–98.

23. van der Woude FJ, Rasmussen N, Lobatto S, et al. Autoantibodies against neutrophils and monocytes: tool for diagnosis and marker of disease activity in Wegener's granulomatosis. Lancet 1985;1:425–9.
24. Falk RJ, Jennette JC. Anti-neutrophil cytoplasmic autoantibodies with specificity for myeloperoxidase in patients with systemic vasculitis and idiopathic necrotizing and crescentic glomerulonephritis. N Engl J Med 1988;318:1651–7.
25. Gadola SD, Gross WL. The renaissance of granulomatous inflammation in AAV. Nat Rev Rheumatol 2012;8:74–6.
26. Lionaki S, Blyth ER, Hogan SL, et al. Classification of anti-neutrophil cytoplasmic autoantibody vasculitides: the role of anti-neutrophil cytoplasmic autoantibody specificity for myeloperoxidase or proteinase 3 in disease recognition and prognosis. Arthritis Rheum 2012;64:3452–62.
27. Lyons PA, Rayner TF, Trivedi S, et al. Genetically distinct subsets within ANCA-associated vasculitis. N Engl J Med 2012;367:214–23.
28. Savige J, Gillis D, Benson E, et al. International consensus statement on testing and reporting of anti-neutrophil cytoplasmic antibodies (ANCA). Am J Clin Pathol 1999;111:507–13.
29. Csernok E, Holle J, Hellmich B, et al. Evaluation of capture ELISA for detection of antineutrophil cytoplasmic antibodies against proteinase-3 in Wegener's granulomatosis: first results from a multicenter study. Rheumatology 2004;43:174–80.
30. Hellmich B, Csenok E, Fredenhagen G, et al. A novel high sensitivity ELISA for detection of antineutrophil cytoplasm antibodies against proteinase-3. Clin Exp Rheumatol 2007;25(Suppl 44):S1–5.
31. Zeek PM, Smith CC, Weeter JC. Studies on periarteritis nodosa. III. The differentiation between the vascular lesions of periarteritis nodosa and of hypersensitivity. Am J Pathol 1948;24:889–917.
32. Zeek PM. Periarteritis nodosa-a critical review. Am J Clin Pathol 1952;22:777–90.
33. Zeek PM. Periarteritis nodosa and other forms of necrotizing angiitis. N Engl J Med 1953;248:764–72.
34. Arthus M, Breton M. Lesions cutanées produites par les injections de sérum de cheval chez le lapin anaphylactisé par et pour ce sérum. Compt Rend Soc de Biol 1903;55:1478–80.
35. Osler W. The visceral lesions of purpura and allied conditions. BMJ 1914;1:517–25.
36. Gairdner D. The Schönlein-Henoch syndrome (anaphylactoid purpura). QJM 1948;17:95–122.
37. Levitt LM, Burbank B. Glomerulonephritis as a complication of the Schonlein-Henoch syndrome. N Engl J Med 1953;248:530–6.
38. Faille-Kuyber EH, Kater L, Kooiker CJ, et al. IgA-deposits in cutaneous blood-vessel walls and mesangium in Henoch-Schonlein syndrome. Lancet 1973;1:892–3.
39. Conley ME, Cooper MD, Michael AF. Selective deposition of immunoglobulin A1 in immunoglobulin A nephropathy, anaphylactoid purpura nephritis, and systemic lupus erythematosus. J Clin Invest 1980;66:1432–6.
40. Wintrobe MM, Buell MV. Hyperproteinemia associated with multiple myeloma. With report of a case in which an extraordinary hyperproteinemia was associated with thrombosis of the retinal veins and symptoms suggesting Raynauds disease. Bull Johns Hopkins Hosp 1933;52:156–65.

41. Lerner AB, Watson CJ. Studies of cryoglobulins. I. Unusual purpura associated with the presence of a high concentration of cryoglobulin (cold precipitable serum globulin). Am J Med Sci 1947;214:410–5.
42. Lerner AB, Watson CJ. Studies of cryoglobulins. II. The spontaneous precipitation of protein from serum at 5°C in various disease states. Am J Med Sci 1947; 214:416–21.
43. Gorevic PD, Kassab HJ, Levo Y, et al. Mixed cryoglobulinemia: clinical aspects and long-term follow-up of 40 patients. Am J Med 1980;69:287–308.
44. McDuffie FC, Sams WM, Maldonado JE, et al. Hypocomplementemia with cutaneous vasculitis and arthritis. Possible immune complex syndrome. Mayo Clin Proc 1973;48:340–8.
45. Zeiss CR, Burch FX, Marder RJ, et al. A hypocomplementemic vasculitic urticarial syndrome: Report of four new cases and definition of the disease. Am J Med 1980;68:867–75.
46. Wisnieski JJ, Naff GB. Serum IgG antibodies to C1q in hypocomplementemic urticarial vasculitis syndrome. Arthritis Rheum 1989;32:1119–27.
47. Hutchinson J. On a peculiar form of thrombotic arteritis of the aged which is sometimes productive of gangrene. Arch Surg 1890;I:323–9.
48. Horton BT, Magath BT, Brown GE. Arteritis of temporal vessels: report of 7 cases. Mayo Clin Proc 1937;12:548–53.
49. Jennings GH. Arteritis of the temporal vessels. Lancet 1938;1:424–8.
50. Bruce GM. Temporal arteritis as a cause of blindness: review of the literature and report of a case. Trans Am Ophthalmol Soc 1949;47:300–16.
51. Gilmour JR. Giant-cell chronic arteritis. J Pathol Bacteriol 1941;53:263–77.
52. Jellinger K. Giant cell granulomatous angiitis of the central nervous system. J Neurol 1977;215:175–90.
53. Kjeldsen M, Reske-Nielsen E. Pathological changes of the central nervous system in giant cell arteritis. Acta Ophthalmol 1968;46:49–56.
54. McLean C, Gonzalez M, Dowling J. Systemic giant cell arteritis and cerebellar infarction. Stroke 1993;24:899–902.
55. Morrison A, Abitol M. Granulomatous arteritis with myocardial infarction. Ann Intern Med 1955;42:691–700.
56. Ritama V. Temporal arteritis. Ann Med Exp Fenn 1951;40:63–87.
57. Save-Soderbergh J, Malmvall B, Anderson R, et al. Giant cell arteritis as a cause of death. JAMA 1986;255:493–6.
58. Takayasu M. Case with unusual changes of the central vessels in the retina [Japanese]. Acta Soc Ophthal Jap 1908;12:554–5.
59. Walker DI, Bloor K, Williams G, et al. Inflammatory aneurysms of the abdominal aorta. Br J Surg 1972;59:609–14.
60. Pennell RC, Hollier LH, Lie JT, et al. Inflammatory abdominal aortic aneurysms: a thirty year review. J Vasc Surg 1985;2:859–69.
61. Rojo-Leyva F, Ratliff NB, Cosgrove DM, et al. Study of 52 patients with idiopathic aortitis from a cohort of 1,204 surgical cases. Arthritis Rheum 2000;43:901–7.
62. Hamano H, Kawa S, Horiuchi A, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. N Engl J Med 2001;344:732–8.
63. Hamano H, Kawa S, Ochi Y, et al. Hydronephrosis associated with retroperitoneal fibrosis and sclerosing pancreatitis. Lancet 2002;359:1403–4.
64. Sakata N, Tashiro T, Uesugi N, et al. IgG4-positive plasma cells in inflammatory abdominal aortic aneurysm: The possibility of an aortic manifestation of IgG4-related sclerosing disease. Am J Surg Pathol 2008;32:553–9.

65. Kasashima S, Zen Y, Kawashima A, et al. Inflammatory abdominal aortic aneurysm: Close relationship to IgG4-releated periaortitis. Am J Surg Pathol 2008;32:197–204.
66. Ito H, Kalzaki Y, Noda Y, et al. IgG4-related inflammatory abdominal aortic aneurysm associated with autoimmune pancreatitis. Pathol Int 2008;58:421–6.
67. Khosroshahi A, Stone JR, Pratt DS, et al. Painless jaundice with serial multiorgan dysfunction. Lancet 2009;373:1494.
68. Stone JH, Khosroshahi A, Hilgenberg A, et al. IgG4-related systemic disease and lymphoplasmacytic aortitis. Arthritis Rheum 2009;60:3139–45.
69. Adamantiades B. Sur un cas d'iritis a hypopion recidivant. Ann D'Ocul 1931;168:271–8.
70. Behçet H. Ueber rezidivierende, aphthöse, durch ein virus verursachte Geschwüre am Mund, am Auge und an den Genitalien. Dermat Wchnschr 1937;105:1152–7.
71. Behçet H, Matteson EL. On relapsing, aphthous ulcers of the mouth, eye and genitalia caused by a virus. 1937. Clin Exp Rheumatol 2010;28(Suppl 60):S2–5.
72. McMenemey WH, Lawrence BJ. Encephalomyelopathy in Behcet's disease. Report of necropsy findings in two cases. Lancet 1957;2:353–8.
73. Wolf SM, Schotland DL, Phillips LL. Involvement of nervous system in Behçet's syndrome. Arch Neurol 1965;12:315–25.
74. Mogan RF, Baumgartner CJ. Meniere's disease complicated by recurrent interstitial keratitis: Excellent results following cervical ganglionectomy. West J Surg 1934;42:628.
75. Cogan DG. Syndrome of nonsyphilitic interstitial keratitis and vestibuloauditory symptoms. Arch Ophthal 1945;33:144–9.
76. Haynes BF, Kaiser-Kupfer MI, Mason P, et al. Cogan's syndrome: Studies in thirteen patients, long-term follow-up, and a review of the literature. Medicine 1980;59:426–41.
77. Cogan DG. Nonsyphilitic interstitial keratitis with vestibuloauditory symptoms. Report of four additional cases. Arch Ophthalmol 1949;42:42–9.
78. Norton EWD, Cogan DG. Syndrome of nonsyphilitic interstitial keratitis and vestibuloauditory symptoms. A long-term follow-up. Arch Ophthalmol 1959;61:695–7.
79. Cody DTR, Williams HL. Cogan's syndrome. Laryngoscope 1960;70:447–78.
80. Said G, Lacroix C, Fujimura H, et al. The peripheral neuropathy of necrotizing arteritis: a clinicopathologic study. Ann Neurol 1988;23:461–5.
81. Collins MP, Dyck PJ, Gronseth GS, et al. Peripheral Nerve Society Guideline on the classification, diagnosis, investigation, and immunosuppressive therapy of non-systemic vasculitic neuropathy: executive summary. J Peripher Nerv Syst 2010;15:176–84.
82. Dyck PJ, Benstead TJ, Conn DL, et al. Nonsystemic vasculitic neuropathy. Brain 1987;110:843–53.
83. Torvik A, Berntzen AE. Necrotizing vasculitis without visceral involvement. Postmortem examination of three cases with affection of skeletal muscles and peripheral nerves. Acta Med Scand 1968;184:69–77.
84. Raff MC, Sangalang V, Asbury AK. Ischemic mononeuropathy multiplex associated with diabetes mellitus. Arch Neurol 1968;18:487–99.
85. Bradley WB, Chad D, Verghese JP, et al. Painful lumbosacral plexopathy with elevated erythrocyte sedimentation rate: a treatable inflammatory syndrome. Ann Neurol 1984;15:457–64.

86. Johnson PC, Doll SC, Cromey DW. Pathogenesis of diabetic neuropathy. Ann Neurol 1986;19:450–7.
87. Said G, Goulon-Goeau C, Lacroix C, et al. Nerve biopsy findings in different patterns of proximal diabetic neuropathy. Ann Neurol 1994;35:559–69.
88. Younger DS, Rosoklija G, Hays AP, et al. Diabetic peripheral neuropathy: a clinicopathologic and immunohistochemical analysis of sural nerve biopsies. Muscle Nerve 1996;19:722–7.
89. Dyck PJ, Norell JE, Dyck PJ. Non-diabetic lumbosacral radiculoplexus neuropathy: natural history, outcome and comparison with the diabetic variety. Brain 2001;124:1197–207.
90. Dyck PJB, Windebank AJ. Diabetic and nondiabetic lumbosacral radiculoplexus neuropathies: new insights into pathophysiology and treatment. Muscle Nerve 2002;25:477–91.
91. Collins MP, Hadden RD. The nonsystemic vasculitic neuropathies. Nat Rev Neurol 2017;13:302–16.
92. Younger DS. Diabetic neuropathy: a clinical and neuropathological study of 107 patients. Neurol Res Int 2010;2010:140379.
93. Younger DS. Diabetic lumbosacral radiculoplexus neuropathy: a postmortem studied patient and review of the literature. J Neurol 2011;258:1364–7.
94. Harbitz F. Unknown forms of arteritis with special reference to their relation to syphilitic arteritis and periarteritis nodosa. Am J Med Sci 1922;163:250–72.
95. Neuman W, Wolf A. Noninfectious granulomatous angiitis involving the central nervous system. Trans Am Neurol Assoc 1952;77:114–7.
96. McCormack H, Neuberger K. Giant cell arteritis involving small meningeal and intracerebral vessels. J Neuropathol Exp Neurol 1958;17:471–8.
97. Meyer J, Foley J, Campagna-Pinto D. Granulomatous angiitis of the meninges in sarcoidosis. Arch Neurol 1953;69:587–600.
98. Cravioto H, Fegin I. Noninfectious granulomatous angiitis with a predilection for the nervous system. Neurology 1959;9:599–607.
99. Cupps TR, Moore PM, Fauci AS. Isolated angiitis of the central nervous system. Prospective diagnostic and therapeutic experience. Am J Med 1983;74:97–105.
100. Cupps T, Fauci A. Central nervous system vasculitis. Major Probl Intern Med 1981;21:123–32.
101. Hinck V, Carter C, Rippey C. Giant cell (cranial) arteritis. A case with angiographic abnormalities. Am J Roentgenol Radium Ther Nucl Med 1964;92:769–75.
102. Younger DS, Hays AP, Brust JCM, et al. Granulomatous angiitis of the brain. An inflammatory reaction of diverse etiology. Arch Neurol 1988;45:514–8.
103. Calabrese HL, Mallek JA. Primary angiitis of the central nervous system: report of 8 new cases, review of the literature, and proposal for diagnostic criteria. Medicine 1988;67:20–39.
104. Benseler SM, deVeber G, Hawkins C, et al. Angiography-negative primary central nervous system vasculitis in children. Arthritis Rheum 2005;52:2159–67.
105. Younger DS, Calabrese LH, Hays AP. Granulomatous angiitis of the nervouse system. Neurol Clin 1997;15:821–34.
106. Calabrese LH, Graff LA, Furlan AJ. Benign angiopathy: a distinct subset of angiographically defined primary angiitis of the central nervous system. J Rheumatol 1993;20:2046.
107. Salvarani C, Brown RD Jr, Christianson TJH, et al. Adult primary central nervous system vasculitis: treatment and course. Arthritis Rheum 2015;67:1637–45.

108. De Boysson H, Arquizan C, Touze E, et al. Treatment and long-term outcomes of primary central nervous system vasculitis. Stroke 2018;49:1946–52.
109. Twilt M, Benseler SM. Central nervous system vasculitis in adults and children. Handb Clin Neurol 2016;133:283–300.
110. Morishita KA, Moorthy LN, Lubieniecka JM, et al. Early outcomes in children with antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2017; 69:1470–9.
111. Editorial: Benzedrine sulfate “pep pills". JAMA 1937;108(23):1973–4.
112. Smith L. Collapse with death following the use of amphetamine sulfate. JAMA 1939;113:1022–3.
113. Gericke O. Suicide by ingestion of amphetamine sulfate. JAMA 1945;128: 1098–9.
114. Lloyd JT, Walker DR. Death after combined dexamphetamine and phenelzine. BMJ 1965;2:168–9.
115. Anglin MD, Burke C, Perrochet B, et al. History of the methamphetamine problem. J Psychoactive Drugs 2000;32:137–41.
116. United Nations Office on Drugs and Crime. UNODC 2009 world drug report. Vienne (Austria): United Nations; 2009.
117. United Nations Office on Drugs and Crime. World drug report 2000. New York: United Nations; 2000.
118. Daneman R. The blood-brain barrier in health and disease. Ann Neurol 2012;72: 648–72.
119. Benarroch EE. Blood-brain barrier. Neurology 2012;78:1268–76.
120. Hawkins BR, Davis TP. The blood-brain barrier/Neurovascular unit in health and disease. Pharmacol Rev 2005;57:173–85.
121. Weiss N, Miller F, Cazaubon S, et al. The blood-brain barrier in brain homeostasis and neurological diseases. Biochim Biophys Acta 2009;1788:842–57.
122. Neuwelt EA, Bauer B, Fahlke C, et al. Engaging neuroscience to advance translational research in brain barrier biology. Nat Rev Neurosci 2011;12:169–82.
123. Bield A, Kraus B. Über eine bisher unbekannte toxische Wirkung der Gallensauren auf das Zentralnervensystem. Zhl Inn Med 1898;19:1185–200.
124. Goldmann EE. Vitalfarbung am Zentral-nervensystem. Abh Preuss Akad Wissensch. Physkol Mathem Klasse 1913;1:1–60.
125. Lewandowsky M. Zür lehre der cerebrospinal flüssigkeit. Z für Klinische Med 1900;40:480–94.
126. Hughes T, Ture-Ozdemir F, Alibaz-Oner F, et al. Epigenome-wide scan identifies a treatment-responsive pattern of altered DNA methylation among cytoskeletal remodeling genes in monocytes and CD4+ T cells from patients with Behçet’s disease. Arthritis Rheumatol 2014;66:1648–58.