# Lessons from Animal Models of Vasculitis

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Vasculitis can occur as a primary disease or as a secondary manifestation of either another illness or a type-III hypersensitivity response to a foreign antigen. Over the past four decades, a number of animal models of vasculitis have been described. These models have served as important tools for enhancing our understanding of the basic mechanisms underlying the pathogenesis of vasculitis. In addition, animal models have made possible the preclinical testing of new therapeutic agents. Animal models of vasculitis can be broadly classified into two types—those that are experimentally induced and those that occur spontaneously. Vasculitis can be experimentally induced in animals through the stimulation of a type-III hypersensitivity response to a variety of foreign antigens, by viral or bacterial infection of vascular cells and the immune response to that infection, or by the in-vivo administration of antineutrophil cytoplasmic antibodies, estrogen, or mercuric chloride ($HgCl_2$). Systemic vasculitis spontaneously develops in several strains of mice and rats. This paper reviews the current state of knowledge of several animal models of vasculitis and the lessons that have been learned from them.

## Introduction

Vasculitis can occur as a primary disease, as a secondary manifestation of another illness (*eg*, viral or bacterial infections, systemic lupus erythematosus [SLE], or rheumatoid arthritis), or as a consequence of a type-III hypersensitivity response to a foreign antigen (*eg*, a drug or a microorganism). Vasculitis may affect small, medium, or large arteries or veins and can lead to vascular necrosis, fibrosis, or thrombosis. Morphologically, the inflammatory infiltrates that occur in vasculitic lesions are predominantly composed of either mononuclear cells (lymphocytes and macrophages) or neutrophils. Mononuclear cell infiltrates are seen, for example, in Wegener's granulomatosis and giant cell arteritis, whereas neutrophils are the major inflammatory cells in immune complex-mediated (type-III hypersensitivity reaction-induced) vasculitides. The clinical manifestations of vasculitis are protean and may affect many different organs [1,2,3•].

Over the past four decades, a number of animal models of vasculitis have been described. Because of inherent difficulties in studying human patients with vasculitis (*eg*, difficulties in obtaining sufficient numbers of patients to study because of the low prevalence of many types of vasculitis, limited ability to perform in-vivo manipulations in humans, limited availability of involved tissues, and so forth), these models have served as important tools for enhancing our understanding of the basic mechanisms underlying the pathogenesis of vasculitis. In addition, animal models are useful for the preclinical testing of new therapeutic agents.

Animal models of vasculitis can be broadly classified into two types—models that are experimentally induced and models that occur spontaneously (Table 1). This paper reviews our current state of knowledge of the major animal models of vasculitis and the lessons that have been learned from them.

## Experimentally Induced Animal Models of Vasculitis

Vasculitis can be experimentally induced in animals through the induction of a type-III hypersensitivity response to a variety of foreign antigens, including bovine serum albumin (BSA) and a number of microorganisms, by viral or bacterial infection of vascular cells and the immune response to that infection, and by the in-vivo administration of antineutrophil cytoplasmic antibodies (ANCA), estrogen, or mercuric chloride ($HgCl_2$). The cellular and molecular mechanisms by which the latter reagents induce vascular inflammation have not been fully elucidated.

### Vasculititis induced by type-III hypersensitity responses

*Acute serum sickness*

Acute serum sickness, which is the prototypic model of immune complex-mediated disease, was one of the first animal models of vasculitis to be described. Our current understanding of the cellular and molecular mechanisms responsible for the inflammation and tissue damage that occurs in immune complex-mediated diseases, such as in SLE or hypersensitivity vasculitis, is based to a large extent on knowledge gained from the elucidation of the immunopathogenesis of acute serum sickness in animals.

In this model, following the injection of a single large dose of BSA, rabbits develop a humoral immune response to the foreign protein, with the subsequent formation of circulating BSA–anti-BSA immune complexes and deposi-

**Table 1. Animal models of vasculitis**

| Vasculitis type | Species | Strain | Inducing agent | Organ involved | Pathology | Reference |
|---|---|---|---|---|---|---|
| Induced | Mink | | Aleutian virus | 1 | Necr | Porter [6]; Henson [7]; Ingram [8]; Porter [10] |
| | Rat | LEW/N | *Borrelia burgdorferi* | 2,3,4 | M | Moody [22] |
| | | H/C | Estrogen | 5 | Necr | Cutts [31] |
| | | BN | $HgCl_2$ | 6 | Necr | Esnault [24]; Hisrch [29]; Mathieson [30] |
| | Rabbit | NZW | BSA | 1 | Necr, M | Kniker [4]; Neild [5] |
| | | | *Chlamydia pneumoniae* | 4 | M, Necr | Fong [19]; Laitinen [20] |
| | Mice | BALB/C | ANCA | 7 | M | Harper [25]; Tomer [26] |
| | | C3H/BiDa | Polynoma virus | 4,7 | Necr | Kajima [15] |
| | | BaLB/C, C57BL/6 | *Lactobacillus casei* | 2 | Necr | Fong [19] |
| Spontaneous | Rat | SHR | | 5,8,9,10 | M | Suzuki [32] |
| | Mice | MRL/lpr | | 9,11,12 | M, N, Necr | Moyer [33]; Berden [35]; Tarkowski [43]; Vogelweid [44] |
| | | NZB | | 7,9,13 | M | Holmes [36] |
| | | NZB/W | | 7,9 | M, Necr | Luzina [39]; Jabs [40] |
| | | PN | | 7,9,13,14 | M | Luzina [39] |
| | | SNF1 | | 9 | M | Kalled [49•] |

1—small arteries; 2—heart; 3—joint; 4—aorta; 5—mesentric vessels; 6—gut; 7—lung; 8—pancreas; 9—kidney; 10—testes; 11—lymph node; 12—salivary gland; 13—liver; 14—brain.
ANCA—antineurtrophil cytoplasmic antibodies; BSA—bovine serum albumin; M—mononuclear infiltrate; N—neutrophilic; Necr—necrotizing.

tion of those immune complexes in various tissues, including the glomerulus, synovium, and the walls of blood vessels. The first component of complement, C1q, binds to the Fc portion of IgG or IgM antibodies in the deposited immune complexes and activates the classical pathway of complement activation. Activated complement components (C5a) with chemotactic properties are generated, which attract neutrophils to the area and activate them. The activated neutrophils bind to the deposited immune complexes through their Fc and complement receptors and attempt to phagocytize the complexes, but they are unable to do so. As a consequence of this "frustrated" phagocytosis, the neutrophils degranulate and highly lytic enzymes are released into the local environment. When this sequence of events occurs in blood vessels, it causes an acute, necrotizing, leukocytoclastic vasculitis [2,4]. A similar immunopathogenic mechanism underlies the glomerulonephritis, synovitis, serositis, and dermatitis that occur in animals with acute serum sickness or in patients or animals with any immune complex-mediated disease.

If left untreated, the involved blood vessels in animals with acute serum sickness develop fibrinoid necrosis of the media and prominent mononuclear cell infiltrates around the blood vessels and in all layers of the vessel wall [5]. Treatment of rabbits with acute serum sickness with cyclosporine inhibits the development of mononuclear cell infiltrates in or around arteries, but does not prevent the development of severe vascular injury. These data demonstrate that the formation and maintenance of mononuclear cell infiltrates in acute serum sickness is a T-cell-dependent phenomenon.

*Virus-induced vasculitis*

A number of viral infections in humans and animals are complicated by the occurrence of vasculitis. The deposition of virus–anti-virus immune complexes in vessel walls appears to play a central role in the pathogenesis of many virus-associated vasculitides, including the vasculitis that occurs in patients infected with hepatitis B or hepatitis C virus or in animals infected with Aleutian mink virus (AMV) [6–8], murine lymphocytic choriomeningitis virus (LCM) [9], and polyoma virus.

Aleutian mink disease, which is caused by the AMV, was one of the first animal models of vasculitis to be described [10]. The disease is characterized by weight loss, anemia, glomerulonephritis, plasmacytosis, hypergammaglobulinemia, and a widespread necrotizing, immune complex-mediated arteritis of small muscular arteries [10,11].

Lymphocytic choriomeningitis virus infects mice, Syrian hamsters, rats, guinea pigs, dogs, monkeys, and may be transmitted to humans as well [12,13]. Susceptible strains of mice that are infected neonatally with LCM virus develop a disease characterized by hypergammaglobulinemia, glomerulonephritis, extensive interstitial lymphoid infiltration in many tissues, focal hepatic necrosis, and necrotizing arteritis with infiltrating neutrophils and macrophages [14,15]. The glomerulonephritis and probably

the arteritis that occurs in AMV-injected mink and LCM-injected mice are immune complex-mediated.

C3H/BiDa mice-bearing tumors induced by polyoma virus develop two types of necrotizing arterial lesions: a noninflammatory lesion that appears to result from cytolytic viral infection of the arterial wall, and an inflammatory vasculitis that resembles polyarteritis nodosa (PAN) in humans, with a dense neutrophilic infiltrate in the arterial wall, acute fibrinoid necrosis, fragmentation and loss of elastic laminae, microaneurysm formation, endothelial cell proliferation, intimal and medial fibrosis, and intravascular thrombosis [16]. The inflammatory vasculitis is probably immune complex-mediated, although it has been reported to not stain immunohistochemically for viral capsid antigen, indicating that viral antigen is either not present or is masked in immune complexes by antiviral antibody.

Vasculitis may also result from infection of vascular cells by virus and the immune response to that infection. This mechanism appears, for example, to be important in the pathogenesis of vascular inflammation in mice infected with murine cytomegalovirus (MCMV). MCMV infection is widely used as a model system for studying many aspects of human cytomegalovirus infection. MCMV-infected suckling BALB/c and C57BL/6 mice developed aortic inflammation with mononuclear cell infiltrates in the intima and adventia [17,18•]. Irradiated, but not nonirradiated, adult BALB/c mice also develop severe aortic inflammation following neonatal MCMV infection, and the aortitis persist for longer periods of time in interferon-γ receptor knockout mice. These data suggest a protective role of radiosensitive cells and one or more populations of interferon-γ receptor-positive cells. By immunohistology, CD4+ T cells and CD8+ T cells are present predominantly in the adventitial infiltrates, with fewer T cells in the medial and intimal infiltrates. MCMV antigens have been detected in the walls of affected blood vessels. These data suggest that the MCMV-associated aortitis is due to MCMV infection of vascular cells by and the subsequent immune response to that infection.

Vascular inflammation also occurs as a complication of viral infections (*eg*, equine viral arteritis, hog cholera, porcine reproductive and respiratory syndrome virus, and bovine malignant catarrhal fever) in larger animals. Genetically susceptible chickens infected with Marek's disease virus (MDV) develop inflammatory infiltrates with mononuclear cells in coronary arteries, the aorta, and its major arterial branches, which appear to be due to MDV infection of vascular smooth muscle cells and the immune response to that infection.

*Vasculitis associated with bacterial infections*

Systemic vasculitis can occur as a complication of several types of bacterial infections in animals. New Zealand rabbits infected intranasally or intratracheally with *Chlamydia pneumoniae* develop a vasculitis with perivascular cuffs of lymphocytes and macrophages involving the aorta, numerous aterioles, and veins. Infected rabbits also develop a bronchiolitis and pneumonia with perivascular and peribronchial inflammatory infiltrates consisting mainly of lymphocytes and eosinophils [19,20]. *C. pneumoniae* antigen has been demonstrated in intimal endothelial cells, medial smooth muscle cells, and macrophages, and the organism has been cultured from affected aorta. These data suggest that *C. pneumoniae*-associated vasculitis is due to active vascular infection and the resulting immune response to that infection.

Following a single intraperitoneal injection of nonviable cell-wall fragments derived from *Lactobacillus casei*, C57BL/6 mice develop a coronary arteritis with histopathology that resembles the vasculitis seen in children with Kawasaki's disease. The media and adventitia of the coronary arteries are infiltrated primarily by lymphocytes and histiocytes [21]. The lesions also contain some neutrophils and occasional fibroblasts, plasma cells, and macrophages. Nuclear dust, presumably from neutrophils, is frequently seen in active lesions. Interestingly, the vasculitis has a limited tissue distribution: liver, spleen, and kidney show no evidence of disease. The pathogenesis of the coronary arteritis in this model has not yet been fully elucidated; however, studies using inbred mice with various inherited immunodeficiencies suggest that the induction of the arteritis is macrophage-dependent and does not require intact T-cell, B-cell, or NK-cell function [21].

Infant LEW/N rats inoculated with *Borrelia burgdorferi* develop a systemic disease characterized by the presence of arthritis, tendonitis, bursitis, myocarditis, and aortitis, with exudation of neutrophils into joint spaces and mononuclear cell infiltrates in the synovium, myocardium, and aorta, and perivascular accumulation of mononuclear cells in the lamina propria of the urinary bladder [22]. No significant lesions are found in other tissues, including peripheral nerves or central nervous system. Early during the course of disease, organisms are present in capillary and postcapillary venous endothelium in periarticular connective tissues, synovium, and tendons. Later in the disease, the organism is no longer visible; however, IgG reactivity occurs against progressively more Borrelia antigens with time, suggesting the existence of continued antigenic stimulation from persistent spirochetal infection. Thus, vasculitis and the other inflammatory lesions in this model appear to be secondary to Borrelia infection of the involved tissues and the immune response to that infection.

## Antineutrophil cytoplasmic antibodies-associated vasculitis

In humans, several types of systemic vasculitis (*ie*, Wegener's granulomatosis and microscopic polyangiitis) are associated with the production of ANCA [23]. Several animal models of ANCA-associated vaculitis have been described. Established by selective breeding from MRL/Mp-lpr/lpr and BXSB/Mp mice, SCG/Kj mice spontane-

ously produce circulating P-ANCA with specificity for MPO, and they develop a systemic vasculitis affecting predominantly small vessels. Circulating ANCA, especially anti-MPO antibodies, have been demonstrated in the sera of rats with $HgCl_2$-induced autoimmunity [24] and MRL/lpr mice with lupus [25]. In both of these models, vasculitis is a prominent component of the autoimmune disease in the animal.

Tomer *et al.* [26,27] have reported that the immunization of mice with a pathogenic human IgG-enriched ANCA with anti-PR3 reactivity induces perivascular mononuclear leukocyte infiltrates in the lung. In contrast to the histologic findings in patients with Wegener's granulomatosis, no giant cells or granuloma were seen; nor were there any pathologic changes present in the kidneys of the immunized mice.

The pathogenic role of these antibodies has not been fully established. It is thought that the target antigens detected by ANCA may be expressed on the cell membrane as well as in the cytoplasm of neutrophils. The interaction of ANCA with cell surface target antigen may result in the activation of the neutrophil with subsequent induction of vasculitis.

### Vasculitis induced by mercuric chloride and other substances

$HgCl_2$ is a T-cell-dependent, polyclonal B-cell activator that induces an autoimmune syndrome in Brown Norway (BN) rats, characterized by lymphoproliferation, hypergammaglobulinemia, the production of a number of IgG autoantibodies [28,29], including ANCA/anti-MPO antibodies [24], and widespread tissue injury, including a necrotizing leukocytoclastic vasculitis, which particularly affects the gut [30]. The mechanisms underlying the pathogenesis of vasculitis in this model have not yet been fully elucidated. Circulating immune complexes have been detected and may be deposited in the walls of blood vessels. The $HgCl_2$–induced vasculitis can be inhibited by pretreatment of the rats with a number of antibiotics; however, antibiotic treatment does not affect anti-MPO antibody titers. These data suggest that ANCA/anti-MPO antibodies alone are not the cause of $HgCl_2$-induced vasculitis.

Prolonged stimulation of H/C rats with estrogen induces mammary tumors and the development of a widespread, systemic necrotizing vasculitis, involving most prominently mesenteric vessels, which histopathologically resembles the vasculitis seen in human polyarteritis nodosa, with intimal thickening and localized aneurysmal dilatations [31]. The vascular infiltrates are composed predominantly of neutrophils, eosinophils, and plasma cells. The lesions are widespread and confined to arteries; arterioles are rarely involved. The media and adventitia are destroyed and replaced by a thick band of proliferating smooth muscle cells, which gradually merge with vascular granulation tissue containing many neutrophils, eosinophils, and plasma cells [31]. The mechanisms underlying the pathogenesis of vasculitis in these animal models are unknown.

### Animal models with spontaneously occurring vasculitis

Systemic vasculitis spontaneously develops in several strains of mice and rats. Older spontaneously hypertensive (SHR) rats develop a polyarteritis nodosa-like arteritis, characterized by early neutrophil and lymphocyte infiltration of the vascular wall, associated with intimal proliferation and medial fibrinoid necrosis. Perivascular mononuclear cells are predominant in the early stages, but are less common in late stages. The lesion is most common in the mesenteric arteries, pancreas, kidneys, and testes [32]. Vascular lesions resembling polyarteritis nodosa have also been noted in deer, cattle, and mice [32].

Vasculitis is a prominent pathologic feature in most murine models of SLE, including MRL/lpr, NZB, NZB/W, BXSB, $SNF_1$, and PN mice. MRL/lpr mice spontaneously develop an autoimmune disease that is characterized by the presence of immune complex-mediated glomerulonephritis, systemic vasculitis, inflammatory polyarthritis, keratoconjunctivitis, marked lymphoid hyperplasia due to the accumulation of CD4- CD8- (double negative) T cells in lymphoid organs and other tissues, and significant alterations in T-cell and B-cell function that result in polyclonal B-cell activation, and production of multiple autoantibodies, including antidouble-stranded DNA, anti-Sm, antiphospholipid and anti-MPO antibodies, and rheumatoid factor. Beginning at 8 to 10 weeks of age, MRL/lpr mice develop, in multiple organs, a perivasculitis, characterized by concentric perivascular cuffing of lymphocytes and macrophages. At approximately 12 weeks of age, these lesions progress to become a systemic vasculitis with adventitial infiltration by lymphocytes and, to a lesser extent, plasma cells, monocytes, and histiocytes. By 16 weeks of age, the inflammatory vascular lesions evolve into an acute necrotizing neutrophilic vasculitis [33–35].

NZB and NZB/W mice also develop immune complex-mediated glomerulonephritis, perivascular mononuclear infiltrates in kidneys, lungs, and liver [36–38], and an angiodestructive vasculitis in the lungs [38].

Beginning at approximately 3 months of age, PN mice develop perivascular mononuclear cell infiltrates around arteries and veins, with an associated venulitis, in the kidney and liver (Fig. 1) [39]. The venulitis is characterized by subendothelial accumulation of inflammatory cells, associated with lifting of endothelial cells from their underlying surface. The severity and extent of the venulitis and perivasculitis increase with age. By age 10 to 13 months, venulitis and perivascular infiltrates are present in the liver, brain, lungs and, most prominently, kidneys of PN mice.

Several studies have investigated the phenotype of the mononuclear cells in the perivascular and vascular infiltrates of lupus mice. In several studies, the majority of lymphocytes in the perivascular/vascular infiltrates in kidneys [40–43] and central nervous system [44] of MRL/lpr mice have been shown to be CD4+ T cells. In contrast, Moyer *et al.* [33,45] have reported that double negative (CD4- CD8)

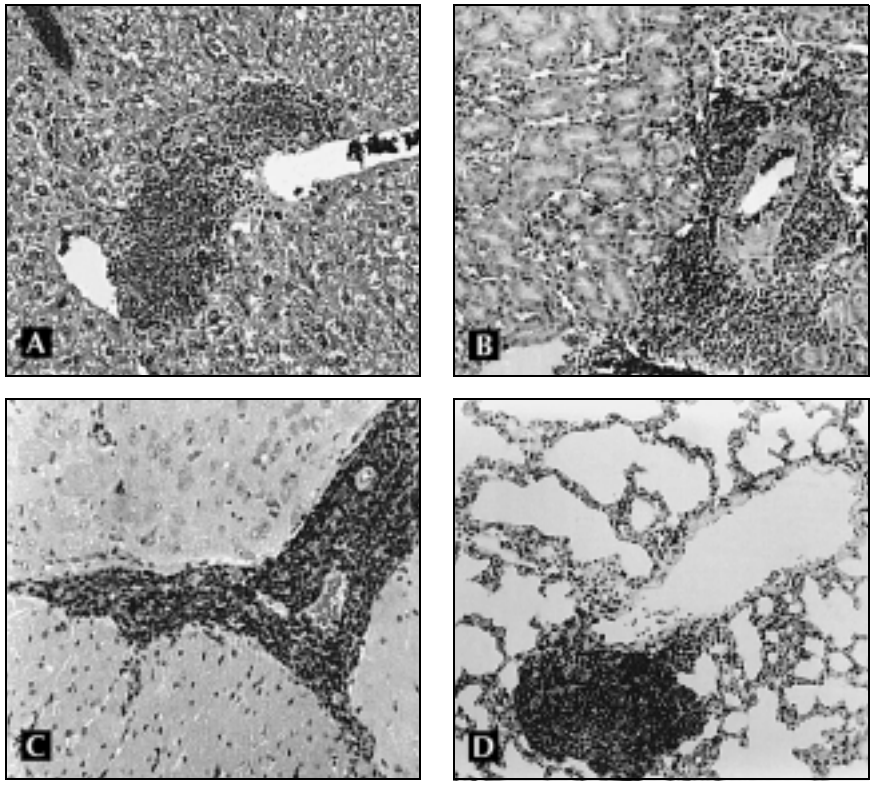


**Figure 1.** Histologic evaluation of vascular and perivascular infiltrates of Palmerston North (PN) mice. Formalin-fixed tissue from 10- to 13-month-old female PN mice were embedded in paraffin and stained with hematoxylin and eosin. Sections are from the liver (**A**), kidney (**B**), brain (**C**), and lung (**D**).

T cells are the predominant cells in the vasculitic lesions of MRL/lpr mice.

In contrast to MRL/lpr mice, the majority of cells in the perivascular and vascular infiltrates in PN mice are Thy $1^+$ $B220^+$ $CD4^+$ T cells. Approximately equal numbers of those cells are TCR $\alpha/\beta^+$ or TCR $\gamma/\delta^+$. Cells expressing this unique phenotype appear to preferentially localize to perivascular tissues in PN mice. The reason that Thy $1^+$ $B220^+$ $CD4^+$ cells and TCR $\gamma/\delta^+$ cells accumulate in the perivascular and vascular tissues of PN mice is unknown, but could be related to the presence on those cells of TCR or homing receptors that recognize molecules that are preferentially found in perivascular and vascular sites.

Cytokines are important regulators of immune responses. Several lines of evidence support a pivotal role for cytokines in the initiation and maintenance of autoimmunity. Specifically, many studies have demonstrated alterations in the balance of type-1 and type-2 cytokines in animals and humans with lupus and other autoimmune diseases [46,47]. To date, only one study has documented the nature of the cytokines produced by the cells in the perivascular or vascular infiltrates of animals or humans with vasculitis. Luzina *et al.* [39] have demonstrated by immunohistologic staining that the cells in the infiltrates in 10- to 13-month-old PN mice produce interleukin (IL)-4, IL-6, and IL-10, but not IL-2, interferon (IFN)-γ, tumor growth factor (TGF)-β, tumor necrosis factor (TNF)-α, or IL-1β; by RT-PCR, the kidneys of older PN mice express markedly elevated levels of IL-4, IL-6, and IL-10, mRNA. Many studies have previously demonstrated decreased production of type-1 cytokines and increased production of type-2 cytokines by peripheral blood mononuclear cells from patients with SLE and spleen cells from PN and NZB/W mice, mice with graft-versus-host-induced lupus [47], and mice that are immunized with IgG-ANCA [27] and develop a vasculitis that is similar to Wegener's granulomatosis in humans.

To further evaluate the role of IL-4 and IL-10 in lupus-like disease and vasculitis in PN mice, we have backcrossed IL-4 and IL-10 knockout genes onto the PN background. (N3xN3) PN IL-4 -/- and (N3xN3) PN IL-10 -/- knockout mice were unable to produce IL-4 or IL-10, respectively; nevertheless, both groups of cytokine-deficient mice developed a lupus-like disease that closely resembled the lupus-like disease that occurs in wild-type PN mice, with a similar glomerulonephritis and mononuclear cell vasculitis/perivasculitis. These data demonstrate that neither IL-4 nor IL-10 are absolutely required for the initiation and maintenance of immune complex-mediated glomerulonephritis or inflammatory vascular disease in PN mice.

## Treatment of Vasculitis in Animal Models of Lupus

Several investigators have evaluated the therapeutic effects of immunomodulatory agents on the vasculitis that occurs in murine models of lupus. Treatment of (NZB x NZW) $F_1$ mice with either cyclophosphamide or corticosteroids prolongs survival, suppresses autoantibody production, and inhibits the development of glomerulonephritis. In contrast, these agents have no effect on anti-DNA antibody

production or glomerular pathology in PN mice. Interestingly, however, the development of perivasculitis and vasculitis in the kidneys of PN mice is inhibited by both cyclophosphamide and hydrocortisone. The reasons for the disparity in therapeutic responses between the two strains of lupus mice are unknown. The ability of cyclophosphamide and corticosteroids to inhibit renal vasculitis and perivasculitis in PN mice, but not glomerulonephritis or anti-DNA antibody production, support the observation that the immunologic mechanisms underlying the development of lupus nephritis and vascular inflammation in PN mice are different. The glomerulonephritis is immune complex-mediated, whereas the vasculitis appears to be mediated by an unusual subset of T cells.

Data from many laboratories strongly suggest that $CD4^+$ T cells play a critical role in the immunopathogenesis of both murine and human lupus. In this regard, Wofsy *et al.* [48] have demonstrated that treatment of NZB/NZBW $F_1$ mice with anti-CD4 monoclonal antibodies (mAb) significantly diminished the diverse histologic manifestations of murine lupus, including the sialitis, focal hepatitis, immune complex-mediated glomerulonephritis, and vasculitis.

CD40-CD40L interactions, which are important in T-cell–B-cell and T-cell–antigen-presenting cell interactions, may play a critical role in the immunopathogenesis of murine lupus. Treatment of $SNF_1$ mice with anti-CD40 mAb prolongs survival and diminishes glomerulonephritis and renal vasculitis [49]. Similarly, treatment of NZB/W mice with anti-CD40L mAb has been shown to inhibit the development of glomerulonephritis and prolonged survival [50].

Ornithine decarboxylase (ODC) is a critical enzyme in the biosynthesis of cellular polyamine. Treatment of MRL/lpr mice with difluoromethylornithine, an irreversible inhibitor of ODC, prolongs survival, inhibits anti-DNA antibody production, and reduces lymphadenopathy, glomerulonephritis, and perivasculitis and vasculitis in the kidneys [51].

Gallium nitrate has been shown to be of therapeutic benefit in a variety of experimental autoimmune diseases, including murine lupus. Gallium treatment of MRL/lpr mice markedly inhibits the development of glomerulonephritis and renal vasculitis [52].

## Conclusions

Over the past four decades, two broad types of animal models of vasculitis have been described—models that are experimentally induced and models that occur spontaneously. Vasculitis can be experimentally induced through the stimulation of a type-III hypersensitivity response to a variety of foreign antigens, such as BSA or microbial antigens; by viral or bacterial infection of vascular cells, with organisms such as MCMV, murine LCM, Marek's disease virus, *Borrelia burgdorferi* and *C. pneumoniae*, and the immune response to that infection; or by the in-vivo administration of ANCA, estrogen, or $HgCl_2$. Vasculitis spontaneously develops in several strains of lupus-prone mice and in SHR rats. Our understanding of the mechanisms underlying the immunopathogenesis of immune complex-mediated vasculitis is based to a large extent on knowledge that has been gained from relevant animal models, particularly acute serum sickness in BSA-stimulated rabbits and immune complex-mediated disease in animals infected with Aleutian mink virus, murine LCM, or polyoma virus. The availability of animal models has also made possible the performance preclinical studies of new therapeutic agents. Animal models of vasculitis undoubtedly will continue to play an important role in furthering our understanding of the human vasculitides.

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