

27 CHAPTER 27 Immune Complexes and Type III Hypersensitivity

27.1 KEY POINTS

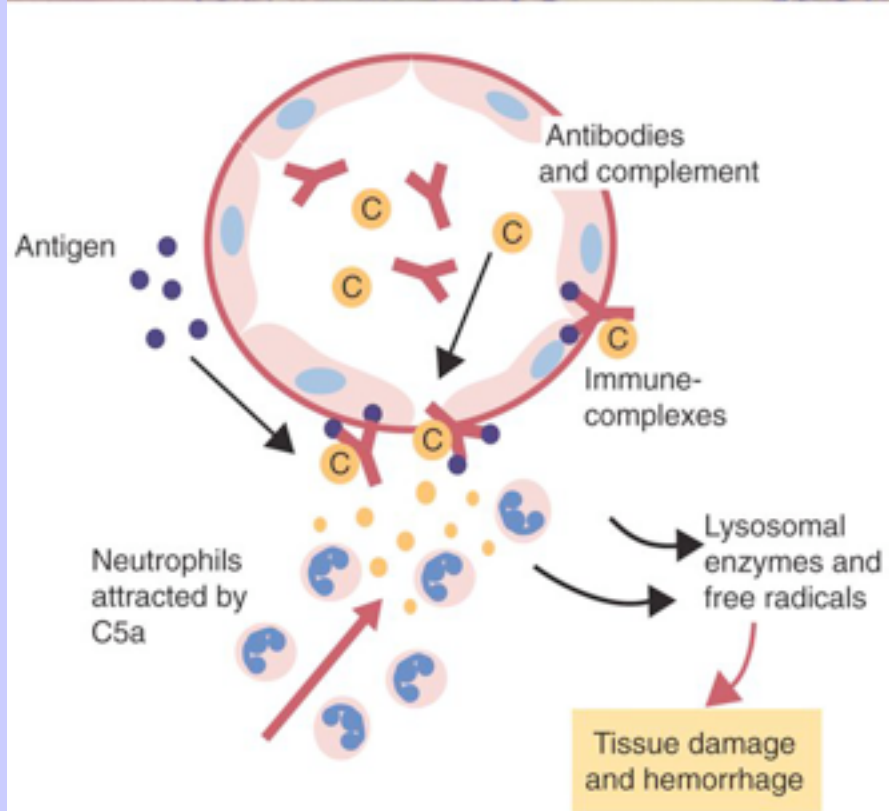
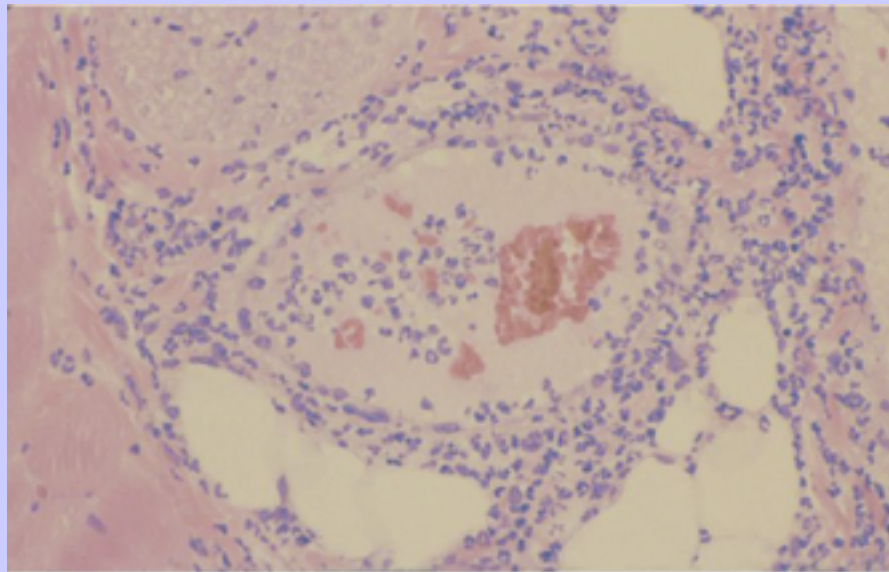
- When antigens and antibodies combine, they form immune complexes. Immune complexes can cause severe inflammation when deposited in large amounts in tissues. This type of inflammation is classified as type III hypersensitivity.
- Local deposition of immune complexes in the lungs following inhalation of antigenic dusts causes hypersensitivity pneumonitis.
- Immune complexes formed in the bloodstream are deposited in the glomeruli of the kidney and cause membranoproliferative glomerulonephritis.
- Type III hypersensitivity is a feature of many viral diseases, especially if the virus is not neutralized by antibodies and, as a result, large amounts of immune complexes are generated.

Acute inflammation can be triggered by the presence of immune complexes in tissues. Immune complexes formed by the combination of antibodies with antigen activate complement. When these immune complexes are deposited in tissues, the activated complement generates chemotactic peptides that attract neutrophils. The accumulated neutrophils may then release oxidants and enzymes, causing acute inflammation and tissue destruction. Lesions generated in this way are classified as type III or immune complex-mediated hypersensitivity reactions.

27.2 CLASSIFICATION OF TYPE III HYPERSENSITIVITY REACTIONS

The severity and significance of type III hypersensitivity reactions depend, as might be expected, on the amount and site of deposition of immune complexes. Two major forms of reaction are recognized. One form includes local reactions that occur when immune complexes form within tissues. The second form results when large quantities of immune complexes form within the bloodstream. This can occur, for example, when an antigen is administered intravenously to an immune recipient. Immune complexes generated in

FIGURE 27-1 The mechanisms of an Arthus reaction, as well as a histological section of an Arthus reaction in the skin of a cat 6 hours after intradermal inoculation of chicken red blood cells. (Courtesy Dr. A. Kier.)



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the bloodstream are deposited in glomeruli in the kidney, and the development of glomerular lesions (glomerulonephritis) is characteristic of this type of hypersensitivity. If the complexes bind to blood cells, anemia, leukopenia, or thrombocytopenia may also result. Complexes may also be deposited in blood vessel walls to cause a vasculitis or in joints to cause arthritis.

It might reasonably be pointed out that the combination of an antigen with antibody always produces immune complexes. However, the occurrence of clinically significant type III hypersensitivity reactions results from the formation of excessive amounts of these immune complexes. For example, several grams of an antigen are needed to sensitize an animal, such as a rabbit, in order to produce experimental type III reactions. Minor immune complex-mediated lesions probably develop relatively frequently following an immune response to many antigens without causing clinically significant disease.

27.3 LOCAL TYPE III HYPERSENSITIVITY REACTIONS

If an antigen is injected subcutaneously into an animal that already has precipitating antibodies in its bloodstream, acute inflammation will develop at the injection site within several hours. This is called an Arthus reaction after the scientist who first described it. It starts as a red, edematous swelling; eventually local hemorrhage and thrombosis occur, which, if severe, culminate in local tissue destruction.

The first histological changes observed following antigen injection are neutrophil adherence to vascular endothelium followed by their emigration into the tissues. By 6 to 8 hours, when the reaction has reached its greatest intensity, the injection site is densely infiltrated by large numbers of these cells ([Figure 27-1](#)). As the reaction progresses, destruction of blood vessel walls results in hemorrhage and edema, platelet aggregation, and thrombosis. By 8 hours, mononuclear cells appear in the lesion, and by 24 hours or later, depending on the amount of antigen injected, they become the predominant cell type. Eosinophils are not a significant feature of this type of hypersensitivity.

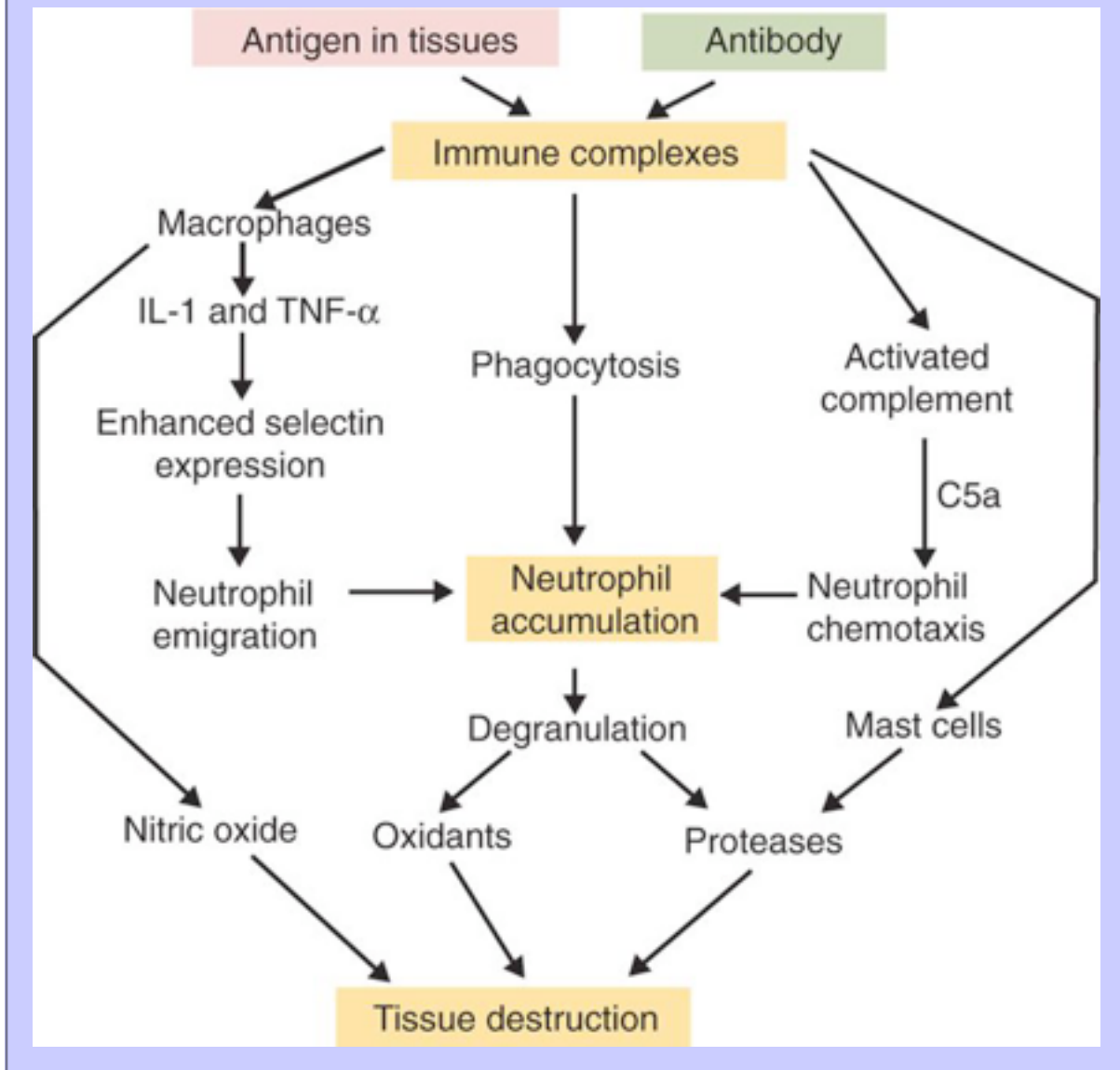
The fate of the injected antigen can be followed using a direct fluorescent antibody test. The antigen first diffuses away from the injection site through tissue fluid. When small blood vessels are encountered, the antigen diffuses into the vessel walls, where it encounters circulating antibodies. Provided the antibodies involved are both precipitating and complement activating (and are therefore usually immunoglobulin G [IgG]), immune complexes form and are deposited between and beneath vascular endothelial cells.

The immune complexes act on two major cell types: mast cells and neutrophils. The relative contribution of each varies among tissues.

Immune complexes formed in tissues must be removed. This is done by binding to Fc and complement receptors on cells. The most widespread of these Fc receptors is Fc γ RIIa on sentinel cells. Immune complexes binding to these receptors on macrophages stimulate production of nitric oxide, leukotrienes, prostaglandins, cytokines, and chemokines. Immune complexes also bind to mast cells through Fc γ RIII. This binding triggers the mast cells to release their vasoactive molecules. Among the molecules released by mast cells are neutrophil chemotactic factors and proteases that activate complement, cytokines, kinins, and lipid mediators. All these mediators promote inflammation by acting on vascular endothelium and stimulating neutrophil adherence and emigration.

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FIGURE 27-2 Some of the mechanisms involved in the pathogenesis of the Arthus reaction.



The immune complexes activate complement to generate the chemotactic peptide C5a (Figure 27-2). The neutrophils, attracted by C5a as well as mast cell–derived chemotactic factors, emigrate from the blood vessels, adhering to immune complexes and promptly phagocytosing them. Eventually the immune complexes are eliminated. During this process, however, proteases and oxidants are released into the tissues. When neutrophils attempt to ingest immune complexes attached to a structure such as a basement membrane, they secrete their granule contents directly into the surrounding tissues. Neutrophil proteases disrupt collagen fibers and destroy ground substances, basement membranes, and elastic tissue. Normally tissues contain antiproteases that inhibit neutrophil enzymes. However, neutrophils can subvert these inhibitors by secreting OCI^- . The OCI^- destroys the inhibitors and allows tissue destruction to proceed.

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Although it has long been assumed that immunoglobulin molecules do not themselves damage antigens, recent evidence has shown that they can kill microorganisms and cause tissue damage. When provided with singlet oxygen from phagocytic neutrophils, antibodies catalyze the production of oxidants including ozone. This ozone not only kills bacteria but also kills nearby cells. Biopsies from Arthus reactions contain detectable amounts of ozone.

Neutrophil proteases also act on C5 to generate C5a, which stimulates neutrophil degranulation and enzyme release and so promotes further neutrophil accumulation and degranulation. Other enzymes released by neutrophils make mast cells degranulate or generate kinins. As a result of all this, inflammation and destruction of tissues (especially of blood vessel walls) result in the development of the edema, vas-culitis, and hemorrhage characteristic of an Arthus reaction.

Although the classical direct Arthus reaction is produced by local administration of an antigen to hyperimmunized animals, any technique that deposits immune complexes in tissues will stimulate a similar response. A reversed Arthus reaction can therefore be produced if antibodies are administered intradermally to an animal with a high level of circulating antigen. Injected, preformed immune complexes, particularly those containing a moderate excess of an antigen, will provoke a similar reaction, although, as might be anticipated, there is less involvement of blood vessel walls and the reaction is less severe. A passive Arthus reaction can be produced by giving antibody intravenously to a nonsensitized animal followed by an intradermal injection of an antigen, and real enthusiasts can produce a reversed passive Arthus reaction by giving antibody intradermally followed by intravenous antigen.

Although it is unusual for pure hypersensitivity reactions of only a single type to occur under natural conditions, there are some diseases in the domestic animals in which type III reactions play a major role. The classical Arthus reaction is usually produced in the skin, since that is the most convenient site at which to inject the antigen. However, local type III reactions can occur in many tissues, with the precise site depending on the location of the antigen.

27.3.1 Blue Eye

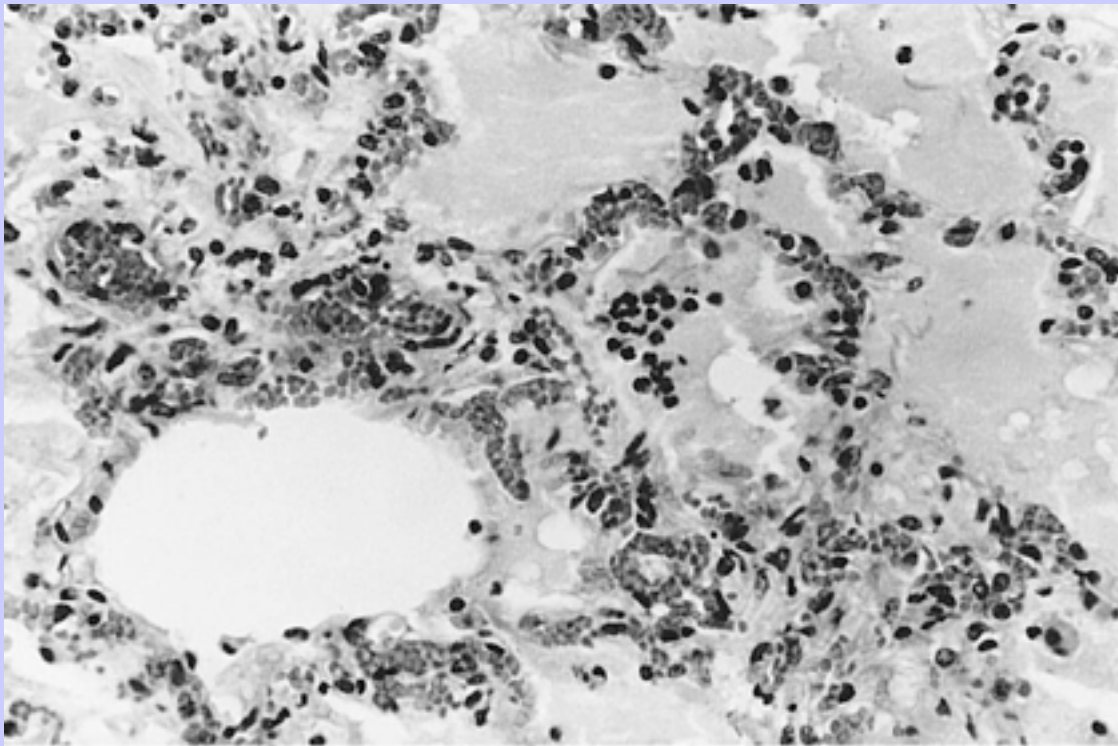
Blue eye is a condition seen in a small proportion of dogs that have been either infected or vaccinated with live canine adenovirus type 1 (see [Chapter 23](#), [Figures 23-7](#) and [23-8](#)). The lesion in blue eye is an anterior uveitis leading to corneal edema and opacity. The cornea is infiltrated by neutrophils, and virus-antibody complexes can be detected in the lesion. Blue eye develops about 1 to 3 weeks after the onset of infection and usually resolves spontaneously as virus is eliminated.

27.3.2 Hypersensitivity Pneumonitis

Type III hypersensitivity reactions may occur in the lungs when sensitized animals inhale antigens. For example, cattle housed during the winter are usually exposed to dust from hay. Normally, these dust particles are relatively large and are deposited in the upper respiratory tract, trapped in mucus, and eliminated. If, however, hay is stored when damp, bacterial growth and metabolism will result in heating. As a result of

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FIGURE 27-3 A histological section of the lung from a cow that died suddenly 24 hours after being fed moldy hay. The alveoli are full of fluid and the alveolar walls are thickened and inflamed. This acute alveolitis is probably due to a hypersensitivity reaction to inhaled actinomycete spores. Original magnification $\times 400$. (Courtesy Dr. B.N. Wilkie.)



this warmth, thermophilic actinomycetes will grow. One of the most important of these thermophilic actinomycetes is *Saccharopolyspora rectivirgula* (*Micropolyspora faeni*), an organism that produces large numbers of very small spores (1 μm in diameter). On inhalation, these spores can penetrate to the alveoli (see [Chapter 19, Figure 19-4](#)). If cattle are fed moldy hay for long periods, constant inhalation of *S. rectivirgula* spores will result in sensitization and in the development of high-titered precipitating antibodies to *S. rectivirgula* antigens in serum. Eventually inhaled spore antigens will encounter antibodies within the alveolar walls, and the resulting immune complexes and complement activation will cause a pneumonia (or pneumonitis), the basis of which is a type III hypersensitivity reaction.

The lesions of this hypersensitivity pneumonitis consist of an acute alveolitis together with vasculitis and exudation of fluid into the alveolar spaces ([Figure 27-3](#)). The alveolar septa may be thickened, and the entire lesion is infiltrated with inflammatory cells. Since many of these cells are eosinophils and lymphocytes, it is obvious that the reaction is not a pure type III reaction. Nevertheless, examination of the lungs of affected cattle by immunofluorescence demonstrates deposits of immunoglobulin, complement, and antigen. In animals inhaling low levels of an antigen over a long period, proliferative bronchiolitis and fibrosis may be observed.

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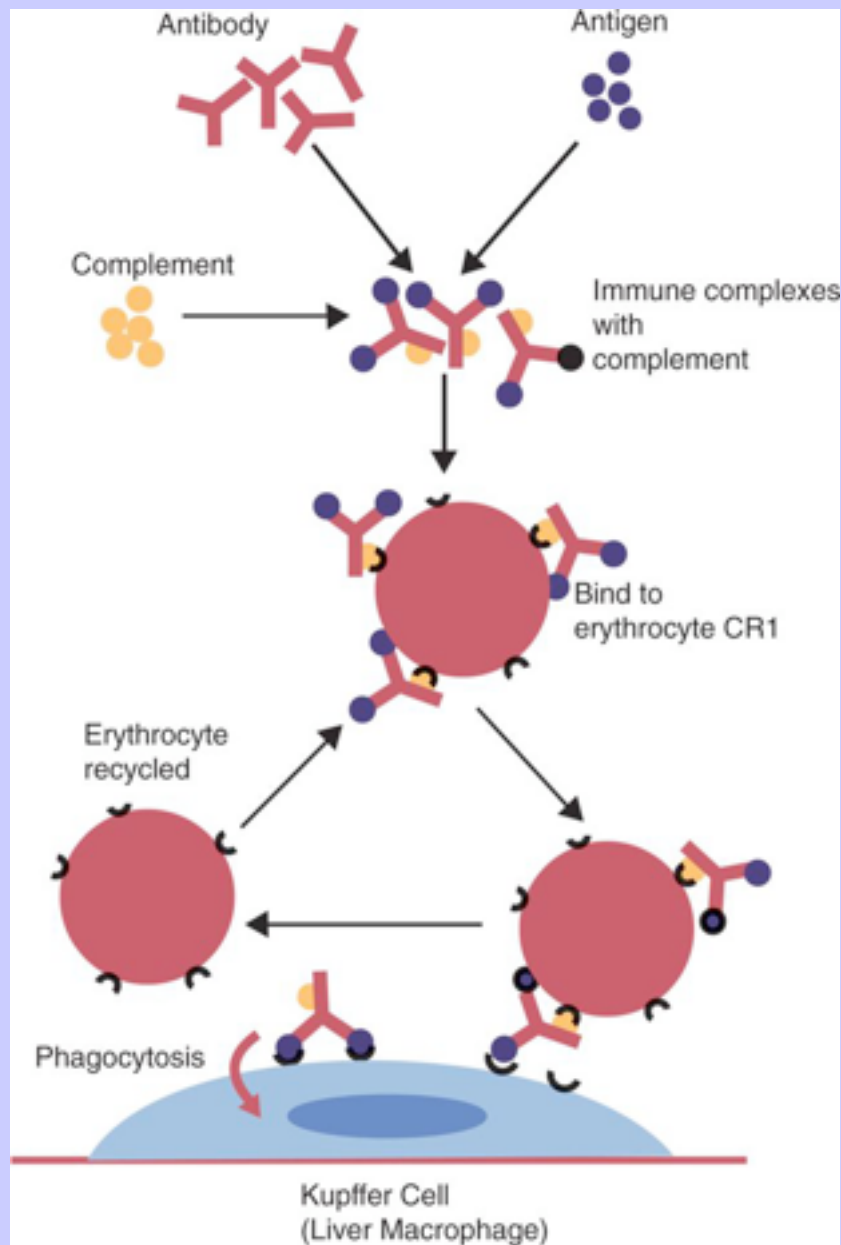
Clinically, hypersensitivity pneumonitis presents as a pneumonia occurring between 5 and 10 hours after acute exposure to grossly moldy hay. The animal may have difficulty breathing and develop a severe cough. In chronically affected animals, the dyspnea may be continuous. The most effective method of managing this condition is by removing the source of the antigen. Administration of steroids may be beneficial.

A hypersensitivity pneumonitis also occurs in farmers chronically exposed to *S. rectivirgula* spores from moldy hay and is called farmer's lung. Many other syndromes in humans have an identical pathogenesis and are usually named after the source of the offending antigen. Thus pigeon breeder's lung arises following exposure to the dust from pigeon feces, mushroom grower's disease is due to hypersensitivity to inhaled spores from actinomycetes in the soil used for growing mushrooms, and librarian's lung results from inhalation of dusts from old books. Hay sickness is a hypersensitivity pneumonitis seen in horses in Iceland that is probably an equine equivalent of farmer's lung.

Two forms of chronic respiratory disease occur in horses. Recurrent airway obstruction (RAO) is seen in older horses, and inflammatory airway disease (IAD) is seen in horses of any age. Both are forms of chronic bronchiolitis associated with mold and other allergen exposure in dusty stable air. RAO occurs most obviously in horses that inhale large amounts of organic dusts. It includes obstructive pulmonary disease seen in stabled horses and summer pasture-associated obstructive pulmonary disease. Characteristically horses with RAO suffer from respiratory difficulty (heaves) even while at rest. Horses with IAD, in contrast, show poor performance, exercise intolerance, and coughing. The disease is not associated with obvious infections. Horses with these syndromes may show positive skin reactions to intradermal inoculation of actinomycete and fungal extracts (such as *Rhizopus nigricans*, *Candida albicans*, *S. rectivirgula*, or *Geotrichum deliquescens*). They may also respond to aerosol challenge with extracts of these organisms by developing respiratory distress. Clinical signs may resolve on removal of the moldy hay and reappear on reexposure. However, there is little correlation between skin test results and severity of disease. Affected animals usually have large numbers of neutrophils or eosinophils in their small bronchioles, and high titers of antibodies to equine influenza in their bronchial secretions. The significance of the latter is unclear. However, high levels of the chemokine CXCL8 (interleukin-8 [IL-8]) are found in the bronchoalveolar washings of affected animals. Affected horses may react more strongly than normal to histamine. Removal of clinically affected horses to air-conditioned stalls results in improvement of the disease, but this is reversed if the horses are returned to dusty stables. It has been suggested that continuous prolonged activation of bronchoalveolar macrophages by dust particles and air-borne endotoxins leads to excessive production of neutrophil chemotactic chemokines such as CXCL8 and CXCL2. These neutrophils then

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FIGURE 27-4 In primates, immune complexes are removed by binding to complement receptors on red blood cells. They are then carried to the liver, where they are transferred to Kupffer cells for phagocytosis. In the absence of complement components, significant accumulation of immune complexes occurs in tissues. In other mammals, immune complexes bind to receptors on platelets.



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cause lung damage as a result of secretion of proteases, peroxidases, and oxidants. IAD affects up to 30% of young horses in training. Although commonly linked to bacterial or viral infections, in many cases no infectious agent can be isolated. Affected animals have airway inflammation associated with a neutrophil infiltration, but occasionally eosinophils and mast cells may be increased.

27.3.3 Staphylococcal Hypersensitivity

Staphylococcal hypersensitivity is a pruritic pustular dermatitis of dogs. Skin testing with staphylococcal antigens suggests that types I, III, and IV hypersensitivity may be involved. The histological findings of neutrophilic dermal vasculitis suggest that the type III reaction may predominate in some cases.

27.4 GENERALIZED TYPE III HYPERSENSITIVITY REACTIONS

If an antigen is administered intravenously to animals with a high level of circulating antibodies, immune complexes form in the bloodstream. These immune complexes are normally removed by binding to either erythrocytes or platelets ([Figure 27-4](#)), or, if very large, they are removed by the mononuclear phagocyte system. However, if complexes are produced in excessive amounts, they may be deposited in the walls of blood vessels, especially medium-sized arteries, and in vessels where there is a physiological outflow of fluid such as glomeruli, synovia, and the choroid plexus ([Figure 27-5](#)). An excellent example of this type of hypersensitivity is serum sickness.

27.4.1 Serum Sickness

Many years ago, when the use of antisera for passive immunization was in its infancy, it was observed that human patients who had received a very large dose of equine antitetanus serum developed a characteristic reaction about 10 days later. This reaction, called serum sickness, consisted of a generalized vasculitis with erythema, edema, and urticaria of the skin, neutropenia, lymph node enlargement, joint swelling, and proteinuria. The reaction was usually of short duration and subsided within a few days. A similar reaction can be produced experimentally in rabbits by administration of a large intravenous dose of antigen. The development of lesions coincides with the formation of immune complexes in the circulation as a result of the immune response to circulating antigens ([Figure 27-6](#)). The experimental disease may be acute if it is caused by a single, large injection of an antigen or chronic, if caused by multiple small injections. In either case, animals develop a glomerulonephritis ([Figure 27-7](#)) and an arteritis.

27.4.2 Glomerulonephritis

When immune complexes are deposited in the glomeruli, they cause basement membrane thickening and stimulate glomerular cells to proliferate. Any or all of the three glomerular cell populations—epithelial cells, endothelial cells, and mesangial cells—can proliferate. The lesion is therefore called membranoproliferative glomerulonephritis (MPGN). If immune complexes are deposited only in the mesangium, mesangial cell proliferation will result in a mesangioproliferative glomerulonephritis. MPGN lesions are classified into three major types based on their histopathology ([Figure 27-8](#)).

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FIGURE 27-5 The mechanisms involved in the pathogenesis of acute serum sickness.

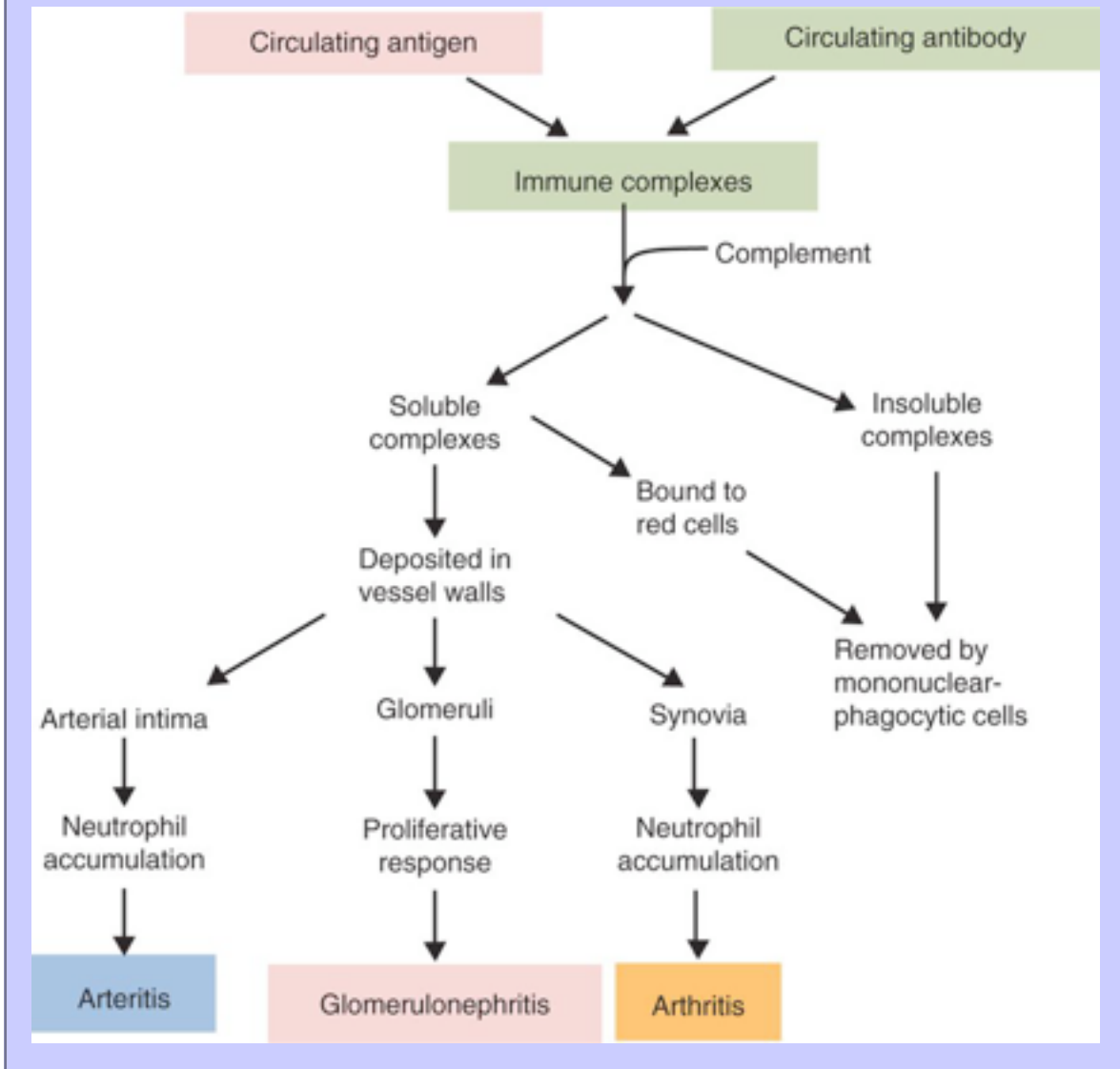
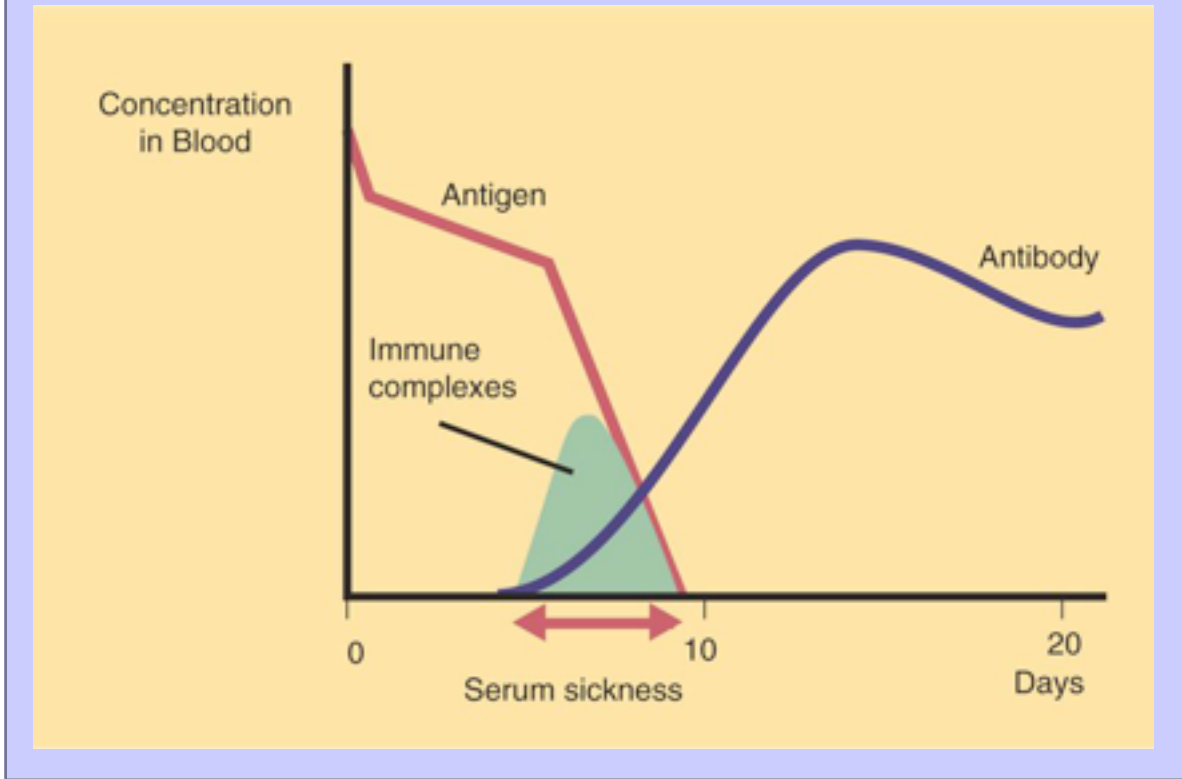


FIGURE 27-6 The time course of acute serum sickness. The appearance of the disease coincides with the generation of immune complexes in the bloodstream.



27.4.2.1

Type I Membranoproliferative Glomerulonephritis

Type I MPGN is caused by immune complex deposition in glomerular vessels. These complexes usually penetrate the vascular endothelium but not the basement membrane and are therefore trapped on the endothelial side, where they stimulate endothelial cell swelling and proliferation (Figure 27-9). If an animal is given repeated injections of small doses of an antigen over a long period, continued damage to the glomerular cells by immune complexes leads to production of transforming growth factor- β (TGF- β). This cytokine stimulates nearby cells to produce fibronectin, collagen, and proteoglycans. This results in a thickening of the basement membrane to form the so-called wire

FIGURE 27-7 The structure of a typical glomerulus. Immune complexes may be deposited on either side of, or within, the glomerular basement membrane.

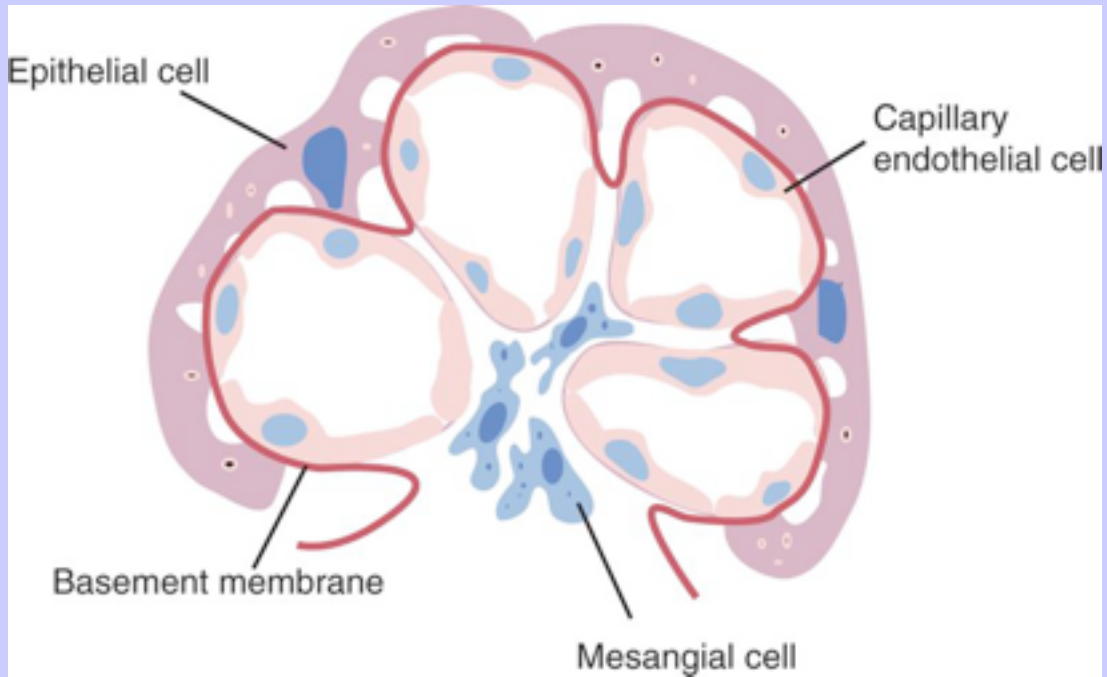
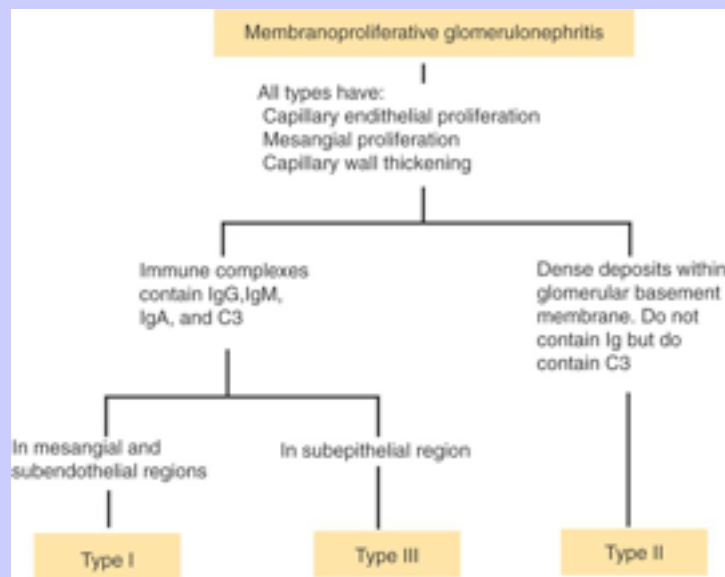


FIGURE 27-8 A classification of different forms of membranoproliferative glomerulonephritis.



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loop lesion (also called a membranous glomerulonephritis). Alternatively, the immune complexes may be deposited in the mesangial region of glomeruli. Mesangial cells are modified smooth muscle cells. As such they can release cytokines and prostaglandins and take up immune complexes. They respond to the immune complexes by proliferation and release of IL-6 and TGF- β . The IL-6 stimulates autocrine growth of the mesangial cells. The TGF- β stimulates production of extracellular matrix. This mesangioproliferative glomerulonephritis eventually interferes with glomerular function. By immunofluorescence it can be shown that lumpy aggregates of immune complexes are deposited in capillary walls and on the epithelial side of the glomerular basement membrane ([Figure 27-10](#)).

27.4.2.2 Type II Membranoproliferative Glomerulonephritis

Type II MPGN (or dense deposit disease) is similar to the type I disease in that there is endothelial and mesangial proliferation. However, it is characterized by the presence of homogeneous, dense deposits within the glomerular basement membrane (in the lamina densa) rather than on its surface (see [Chapter 5, Figure 5-17](#)). The deposits may contain C3 but not immunoglobulin. Type II MPGN results from uncontrolled complement activation and is seen in factor H deficiency in pigs (see [Chapter 5](#)).

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27.4.2.3 Type III Membranoproliferative Glomerulonephritis

Type III MPGN is a variant of type I MPGN. It differs from typical type I disease by the presence of immune complexes on both the endothelial and epithelial sides of the basement membrane. It is believed that very small immune complexes penetrate the basement membrane and are deposited where they stimulate epithelial cell swelling and proliferation. If excessive, these proliferating cells may fill the glomerular space to form epithelial crescents. A single case of unknown cause has been described in a cat.

27.5 CLINICAL FEATURES OF GLOMERULONEPHRITIS

Type I MPGN develops when prolonged antigenemia persists in the presence of antibodies. It is therefore characteristic of chronic viral diseases such as equine infectious anemia, infectious canine hepatitis, Aleutian disease of mink, and African swine fever; parasitic diseases such as leishmaniasis; and chronic bacterial diseases such as Lyme disease and ehrlichiosis ([Table 27-1](#)). Clinically it should be suspected in an animal with proteinuria without evidence of infection although definitive diagnosis requires a renal biopsy and histological evaluation. Type I MPGN has also been reported in dogs with pyometra, chronic pneumonia, distemper encephalitis, acute pancreatic necrosis, and bacterial endocarditis. In animals with tumors, large amounts of antigen may be shed into the bloodstream and give rise to a type I MPGN. This is, for example, a feature of feline leukemia. It has also been reported in animals with lymphosarcoma, osteosarcoma, and mastocytoma. Circulating immune complexes and renal lesions have been found in dogs with systemic lupus erythematosus (see [Chapter 33](#)), discoid lupus, generalized demodicosis, and recurrent staphylococcal pyoderma. Some cases may be due to deficiencies of complement components. As a result of these deficiencies, removal

FIGURE 27-9 The pathogenesis of different forms of immune complex-mediated glomerulonephritis. Remember, however, that more than one type of lesion may be present in an animal at the same time.

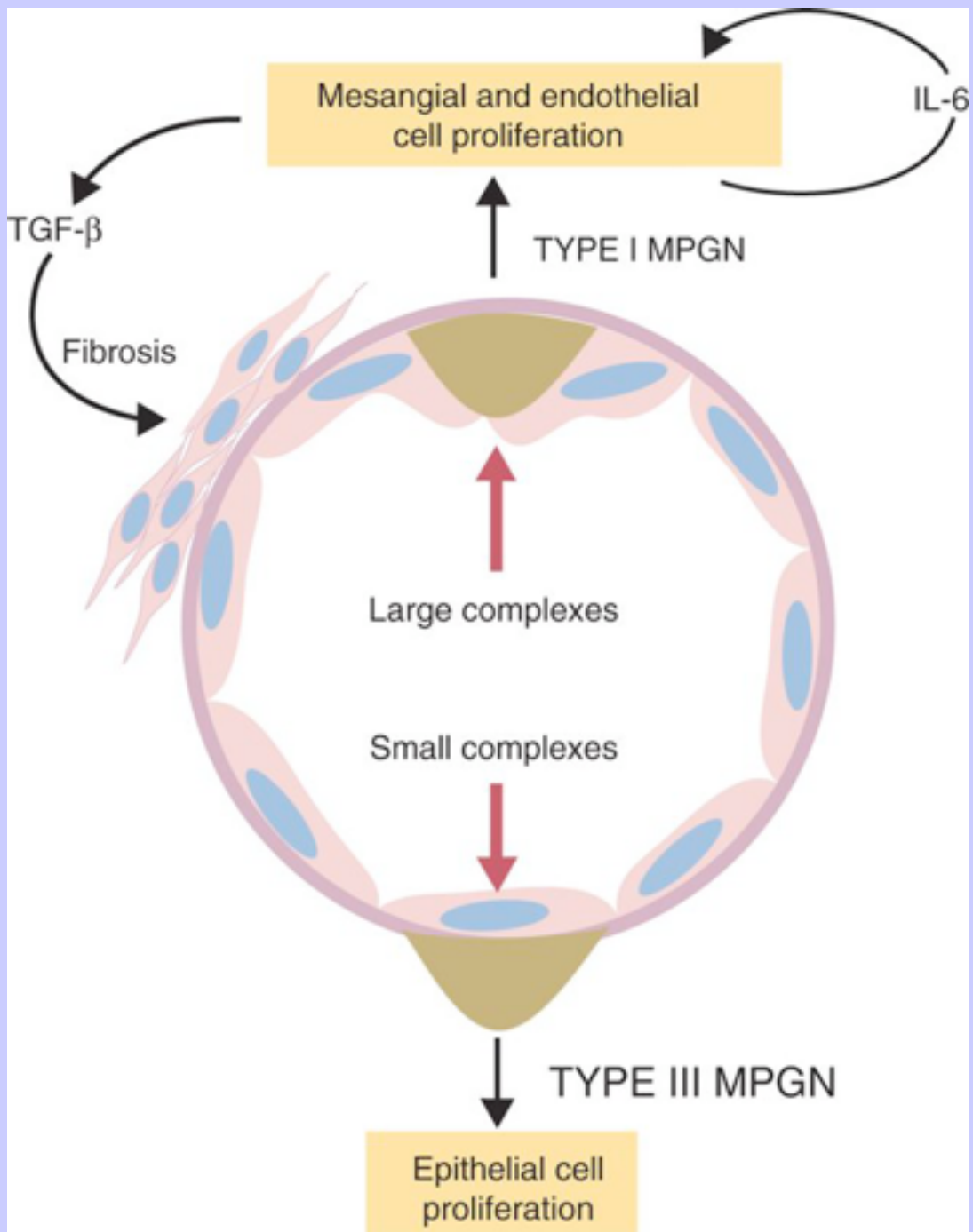
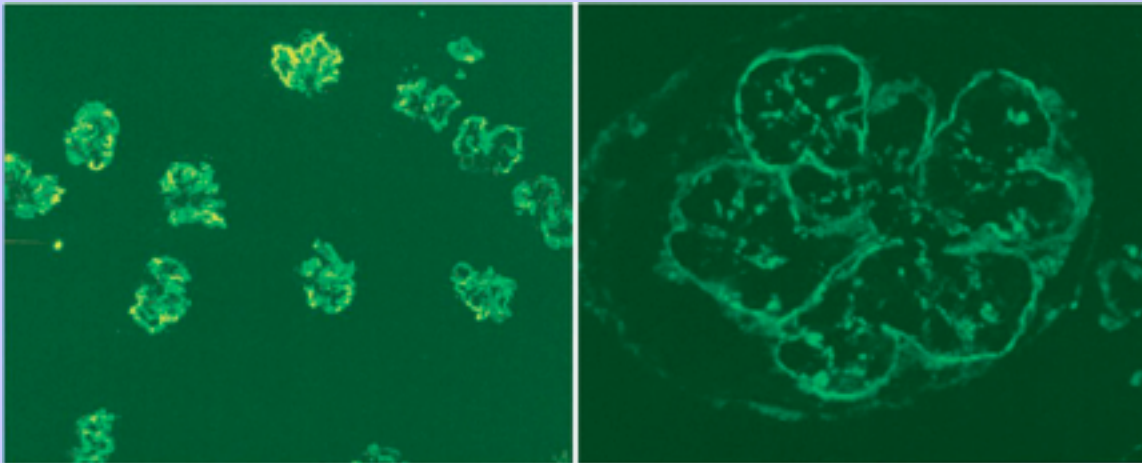


FIGURE 27-10 fluorescent micrographs of a section of glomerulus from a Finnish-Landrace lamb with immune complex-mediated glomerulonephritis. The labeled antisheep globulin reveals the presence of “lumpy-bumpy” deposits characteristic of type I membranoproliferative glomerulonephritis in many glomeruli. (From Angus KW, Gardiner AC, Morgan KT, et al: *J Comp Pathol* 84:319-330, 1974.)



of immune complexes is impaired and they accumulate in glomeruli. Many cases of type I MPGN develop in the absence of an obvious predisposing cause.

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Table 27-1 Infectious Diseases with a Significant Type III Hypersensitivity Component

Organism or Disease	Major Lesion
<i>Erysipelothrix rhusiopathiae</i>	Arthritis
<i>Mycobacterium johnei</i>	Enteritis
<i>Streptococcus equi</i>	Purpura
<i>Staphylococcus aureus</i>	Dermatitis
<i>Borrelia burgdorferi</i>	Glomerulonephritis
Ehrlichiosis	Glomerulonephritis
Canine adenovirus 1	Uveitis, glomerulonephritis
Canine adenovirus 2	Glomerulonephritis
Feline leukemia	Glomerulonephritis
Feline infectious peritonitis	Peritonitis, glomerulonephritis
Aleutian disease	Glomerulonephritis, anemia, arteritis
Hog cholera	Glomerulonephritis
African swine fever	Glomerulonephritis
Bovine virus diarrhea	Glomerulonephritis
Equine viral arteritis	Arteritis
Equine infectious anemia	Anemia, glomerulonephritis
Visceral leishmaniasis	Glomerulonephritis
<i>Dirofilaria immitis</i>	Glomerulonephritis

The presence of immune complex lesions within glomeruli stimulates cells such as neutrophils, mesangial cells, macrophages, and platelets to release thromboxanes, nitric oxide, and platelet-activating factor. These increase basement membrane permeability to macromolecules; as a result, plasma proteins, especially albumin, are lost in the urine. This loss, if severe, may exceed the ability of the body to replace the protein. As a result, albumin levels drop, the plasma colloid osmotic pressure falls, fluid passes from blood into tissue spaces, and the animal may become edematous and ascitic. The loss of fluid into tissues results in a reduction of blood volume, a compensatory increase in secretion of antidiuretic hormone, increased sodium retention, and accentuation of the edema. The decreased blood volume also results in a drop in renal blood flow, reduction in glomerular filtration, retention of urea and creatinine, azotemia, and hypercholesterolemia. Although all these may occur as a result of immune complex deposition in glomeruli, the development of this nephrotic syndrome is not inevitable. In fact, the clinical course of these conditions is extremely unpredictable, with some animals showing a progressive deterioration in renal function and others showing spontaneous remissions. Many animals may be clinically normal in spite of the presence of immune complexes in their glomeruli, and immune complexes are commonly observed in old, apparently healthy dogs, horses, and sheep. The most common initial signs are anorexia, weight loss, and vomiting. Polyuria and polydipsia occur when about two thirds of glomeruli are destroyed. Azotemia occurs when 75% are destroyed. Development of nephrotic syndrome (proteinuria, hypoproteinemia, edema, or ascites) only occurs in

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about 15% of affected dogs but in up to 75% of affected cats. Some dogs become hypertensive. Thromboembolic disease may also develop. Because of the unpredictable occurrence of spontaneous remissions, it is difficult to judge the effects of treatment. It has been usual to treat affected animals with corticosteroids and immunosuppressive drugs, but the rationale and effectiveness of this treatment are open to question except when the glomerulonephritis is associated with concurrent autoimmune disease such as systemic lupus erythematosus. Recently encouraging responses have been obtained with angiotensin-converting enzyme inhibitors (captopril) and experimental thromboxane synthase inhibitors. Protein restriction may help reduce the clinical signs of renal failure. If the glomerulopathy is secondary then clearly the underlying cause should be treated. The glomerular lesion is not inflammatory, and although the lesion in primary immune complex glomerulonephritis contains immunoglobulins, there is no evidence to suggest that it is caused by hyperactivity of the immune system. Steroid treatment of rabbits with experimental immune complex disease has been shown to exacerbate the condition.

27.5.1 IgA Nephropathy

By far the most important cause of renal failure in humans is IgA nephropathy. In this form of type I MPGN, patients have elevated serum IgA and IgA-containing immune complexes that are deposited in the mesangial region. The resulting cellular proliferation and glomerulonephritis can frequently lead to renal failure. The cause of IgA nephropathy is unknown. IgA deposits can be found in the glomeruli of up to 35% of some human populations and up to 47% of dogs. In these dogs, the IgA is deposited in the mesangial and paramesangial areas and is associated with mesangial proliferation. Dogs with enteritis or liver diseases show the highest incidence of glomerular IgA deposition. A slightly different condition has also been described in dogs aged 4 to 7 years. The animals developed a type III MPGN with mild hematuria, proteinuria, and hypertension. IgA-containing immune complexes formed in both the subepithelial and subendothelial locations. IgA nephropathy has also been described in pigtailed macaques (*Macaca nemestrina*).

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27.5.2 Swine Glomerulopathy

Spontaneous type I MPGN is observed in pigs. It is especially common in Japan, where it appears to be due to deposition of immune complexes containing IgG (and IgA) antibodies against *Actinobacillus pleuropneumoniae*. In other cases, it may be secondary to chronic virus infections such as hog cholera or African swine fever. Occasionally, however, a proliferative glomerulonephritis develops spontaneously. In most cases epithelial crescent formation suggests that the proliferating cells are epithelial in origin. However, occasional mesangioproliferative lesions are observed as well. There is usually strong staining for C3 and weaker staining for IgM using immunofluorescence assays. Pigs rarely have IgG or IgA deposits. Affected pigs are relatively young (less than 1 year). There is a high prevalence of gastric ulcers in affected animals, but whether this is related is unclear. An inherited complement factor H deficiency in Yorkshire pigs results in the development of a lethal type II MPGN called porcine dense deposit disease (see [Chapter 5](#)).

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27.5.3 Porcine Dermatitis and Nephropathy Syndrome

Porcine dermatitis and nephropathy syndrome is mainly seen in nursery and growing animals between 2 and 7 months of age. The clinical signs include weight loss, skin lesions, and, most commonly, sudden death. Clinically affected pigs may have high mortality, although this is highly variable. Skin lesions are seen in most cases. They present as flat or slightly raised multiple, reddish areas affecting the skin over the hamstrings, perineum, and ventral abdomen. In surviving animals, these lesions resolve in 2 to 3 weeks. The kidneys are enlarged, are congested, and may show multiple red spots. The skin lesions are associated with a widespread vasculitis involving medium and small arteries in the dermis and subdermis. Infarction leads to epidermal

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necrosis. The kidney lesions consist of a glomerulonephritis that may be acute and necrotizing or may be proliferative. Vasculitis is also seen in vessels in the kidney, lymph nodes, spleen, and liver. Some pigs may have renal lesions or skin lesions alone. This syndrome appears to be an immune complex disease affecting vascular epithelium. Immunoglobulins (IgG and IgM) and complement are deposited in and around the necrotic vessels in the early stages of the disease. The cause of the syndrome is unknown, but both bacteria and viruses have been implicated. Thus *Pasteurella multocida*-specific antigen has been isolated from affected kidney tissue. On the other hand, the lesions may be secondary to infections by porcine reproductive and respiratory syndrome virus or by porcine circovirus 2 (PCV2). The syndrome is commonly associated with porcine postweaning multisystemic wasting syndrome, a disease that may also be caused by PCV2 infection (see [Chapter 35](#)). Pigs suffering from the combined syndromes have higher morbidity and mortality.

27.5.4 **Dirofilariasis**

Some dogs heavily infected with the heartworm *Dirofilaria immitis* develop glomerular lesions and proteinuria. The lesions include thickening of the glomerular basement membrane with minimal endothelial or mesangial proliferation. Since IgG1-containing deposits may be found on the epithelial side of the basement membrane (type III MPGN), it has been suggested that immune complexes formed by antibodies to heartworm antigens provoke these lesions. Other investigators dispute the immune complex nature of this condition and claim that the lesions develop in response to the physical presence of microfilariae in glomerular blood vessels. The fact that infected dogs may develop amyloidosis (see [Chapter 4](#)) suggests that they mount a significant immune response to the worms.

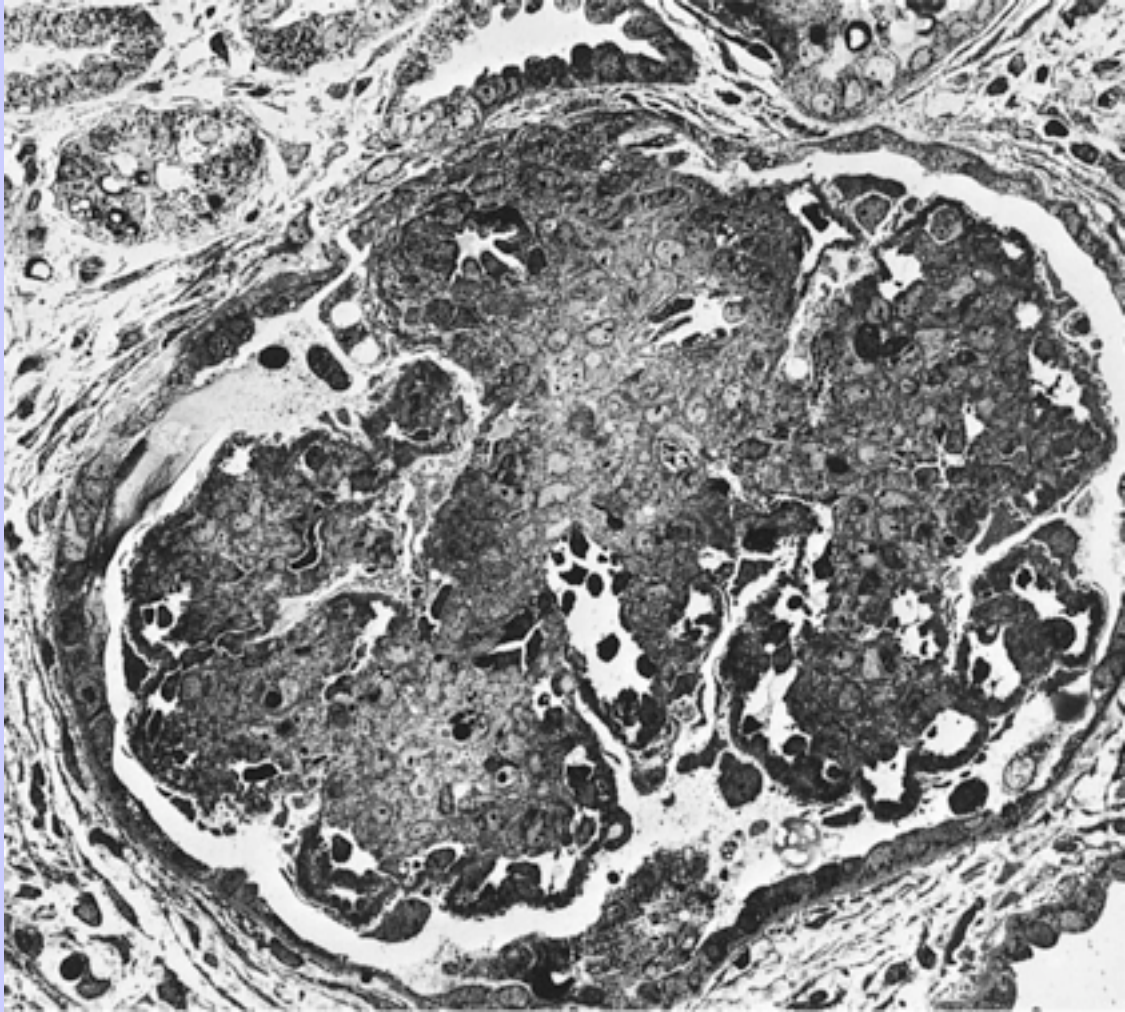
27.5.5 **Finnish-Landrace Glomerulopathy**

Some lambs of the Finnish-Landrace breed die when about 6 weeks of age as a result of renal failure due to a type I MPGN. The glomerular lesions are similar to those seen in chronic serum sickness, with mesangial cell proliferation and basement membrane thickening ([Figure 27-11](#)). In extreme cases epithelial cell proliferation may result in epithelial crescent formation. Neutrophils may be present in small numbers within glomeruli, and the rest of the kidney may exhibit diffuse interstitial lymphoid infiltration and necrotizing vasculitis. Deposits containing IgM, IgG, and C3 are found in the glomeruli and choroid plexus, and serum C3 levels are low. The lesions are therefore probably produced as a result of immune complex deposition within these organs, although the nature of the inducing antigen is unknown.

27.5.6 **Canine Glomerulopathy**

C3 deficiency inherited as an autosomal recessive condition has been described in Brittany Spaniels (see [Chapter 5](#)). Many of these dogs develop type I MPGN, which may result in renal failure. The lesions are typical with mesangial proliferation, thickening of the glomerular capillary wall, and deposition of electron-dense deposits in the mesangium and subendothelial space. The deposits contain both IgG and IgM. A familial glomerulopathy has been observed in Bernese

FIGURE 27-11 A thin section of glomerulus from a Finnish-Landrace lamb with type I membranoproliferative glomerulonephritis. The primary lesion in this case is mesangial proliferation with some basement membrane thickening. (From Angus KW, Gardiner AC, Morgan KT, et al: *J Comp Pathol* 84:319-330, 1974.)



Mountain Dogs. It is associated with MPGN and interstitial nephritis.

27.6 OTHER IMMUNE COMPLEX-MEDIATED LESIONS

27.6.1 Purpura Hemorrhagica

Two to four weeks after an acute *Streptococcus equi* infection (or vaccination against *S. equi*), horses may develop urticaria, followed by severe subcutaneous edema, especially involving the limbs, and the development

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of hemorrhages in the mucosa and subcutaneous tissues. Affected horses are anorexic and depressed and have a high fever. Immune complexes containing *S. equi* antigens (M-protein or R-protein) may be found in the bloodstream of affected animals. These immune complexes cause an acute vasculitis, as well as a type I MPGN with resulting proteinuria and azoturia. Other triggers of purpura hemorrhagica in the horse include infections with *Corynebacterium pseudotuberculosis*, equine influenza virus, equine herpesvirus type 1, and *Rhodococcus equi*. In some cases it develops in the absence of any obvious infection. Horses usually recover if aggressively treated with systemic glucocorticosteroids.

Pigs may also suffer from sporadic cases of an immune complex-mediated thrombocytopenic purpura syndrome. The animals have thrombocytopenia, anemia, excessive bleeding, with membranoproliferative lesions in their glomeruli. The cause is unknown.

27.6.2 Dietary Hypersensitivity

If an antigenic milk replacer, such as soy protein, is fed to very young calves before the development of ruminal function, the foreign antigen may be absorbed and stimulate antibody formation and a type III hypersensitivity. As a result, the calves become unthrifty and lose weight. However, the precise pathogenesis of this condition is unclear. A small proportion of calves develop an IgE response and a type I hypersensitivity.

27.6.3 Polyarthritis

Immune complexes can be readily found in the blood and synovial fluid of animals with rheumatoid arthritis and in many with osteoarthritis. In rheumatoid arthritis they are believed to have a major role in the progression of disease. Their role in osteoarthritis is unclear, but they may be a secondary result of local trauma. Important examples of this type of arthritis are the nonerosive polyarthritides seen in foals and puppies and described in [Chapter 33](#).

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27.6.4 Drug Hypersensitivities

In the previous chapter, it was pointed out that if a drug attached itself to a cell such as an erythrocyte, the immune response against the drug could lead to elimination of the cell. A similar reaction may occur through type III hypersensitivity reactions if immune complexes bind to host cells. In this case, the cells are recognized as opsonized and are removed by phagocytosis. As might be predicted, if immune complexes bind to erythrocytes, anemia results; if they bind to platelets, thrombocytopenia and purpura result. Binding to granulocytes leads to a granulocytopenia and, consequently, recurrent infection. Severe skin reactions may follow deposition of antibody-drug complexes in the blood vessels of the dermis. However, in many cases it is difficult to distinguish between the toxic effects of a drug and type III hypersensitivity unless specific antibodies can be eluted from affected cells.

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27.7 SOURCES OF ADDITIONAL INFORMATION

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