5 CHAPTER 5 The Complement System

5.1 KEY POINTS

- The complement system is a major component of both the innate and acquired immune systems.
- Complement proteins are found in normal serum.
- The complement system is activated by two innate pathways: the alternative pathway and the lectin pathway.
- The complement system is activated by antibodies bound to antigen—the classical pathway.
- Complement components, especially C3b, bind covalently to invading microbes and so opsonize them.
- Complement components may form a membrane-attack complex and punch holes in microbes.
- The complement system plays a key role in triggering inflammation through the release of the potent chemoattractant C5a.
- Deficiencies of some complement components lead to increased susceptibility to infections.

Protection from infection requires an immediate response by the innate immune system. A very important component of this response is the complement system. The complement system is a defense mechanism activated by both innate and acquired immune mechanisms. It consists of many different serum proteins together with an associated group of cell membrane proteins. These proteins have inflammatory, protective, and immunoregulatory functions (Figure 5-1).

Complement proteins act through enzymic pathways that cause specific proteins to bind covalently (and hence irreversibly) to the surface of invading microbes. Once bound, these proteins can destroy the invaders. In healthy, uninfected animals these pathways are inactive. However, they can be activated either by the presence of antibodies on the surface of an organism or simply by the presence of the complex carbohydrates found on the surface of infectious agents. Because the complement system is so potent, it must be carefully regulated and controlled. This in turn makes for significant complexity.

The complement system can be activated by at least three different pathways, referred to as the alternative, the lectin, and the classical pathways (Figure 5-2). The alternative and lectin pathways are activated directly by microbial carbohydrates—typical examples of the pathogen-associated molecular patterns that trigger innate immunity. The classical pathway, in contrast, is an evolutionary recent pathway activated by antibodies bound to the surface of an organism and thus works only in association with acquired immune responses.

5.2 COMPLEMENT PROTEINS

The proteins that form the complement system are either labeled numerically with the prefix C (e.g., C1, C2, C3) or designated by letters of the alphabet (B, D,

FIGURE 5-1 The functions of the complement system. Complement may either alter microbial membranes or alternatively trigger inflammation. Either way, it hastens the elimination of microbial invaders and is thus a key component of the innate immune system.

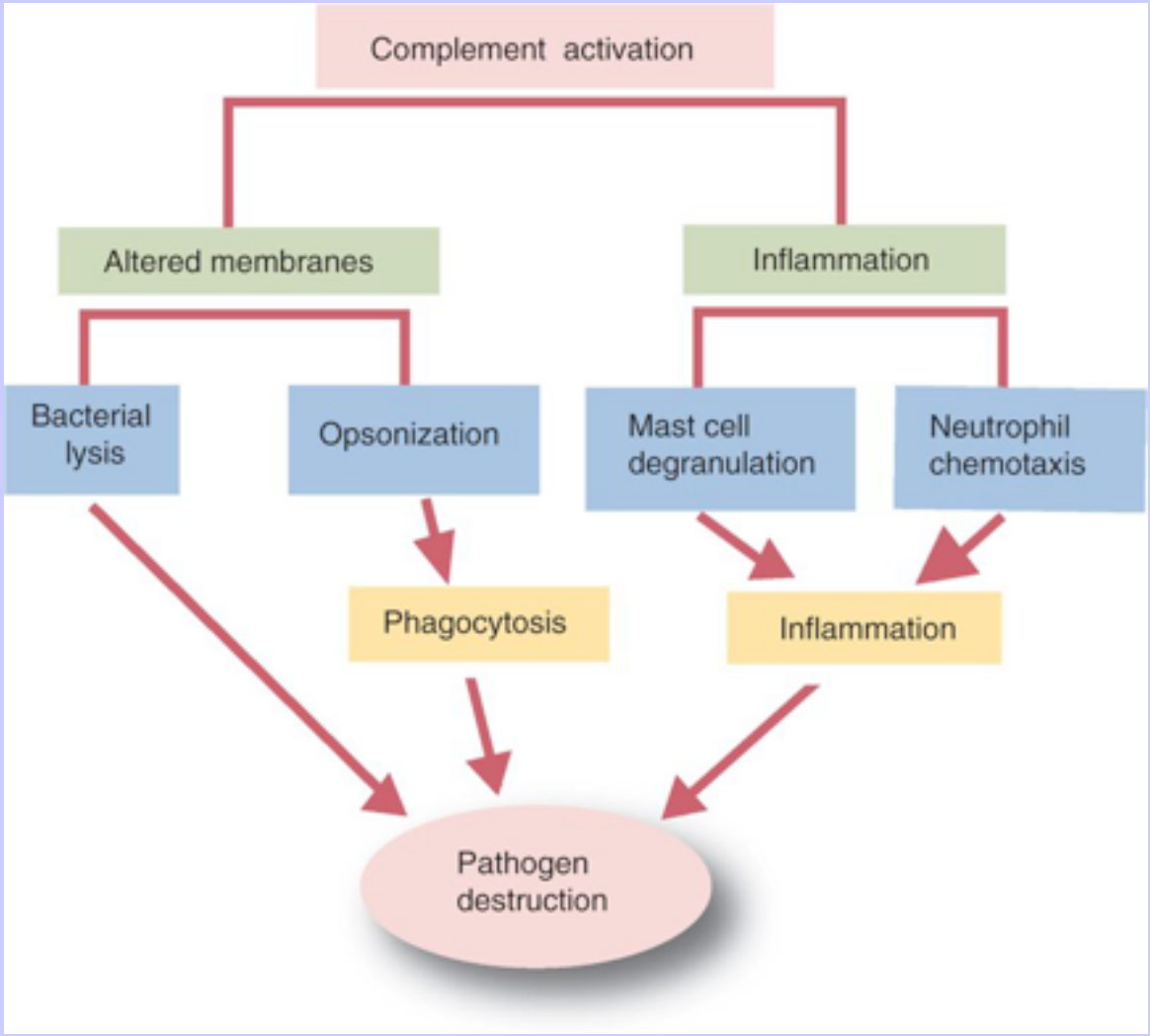
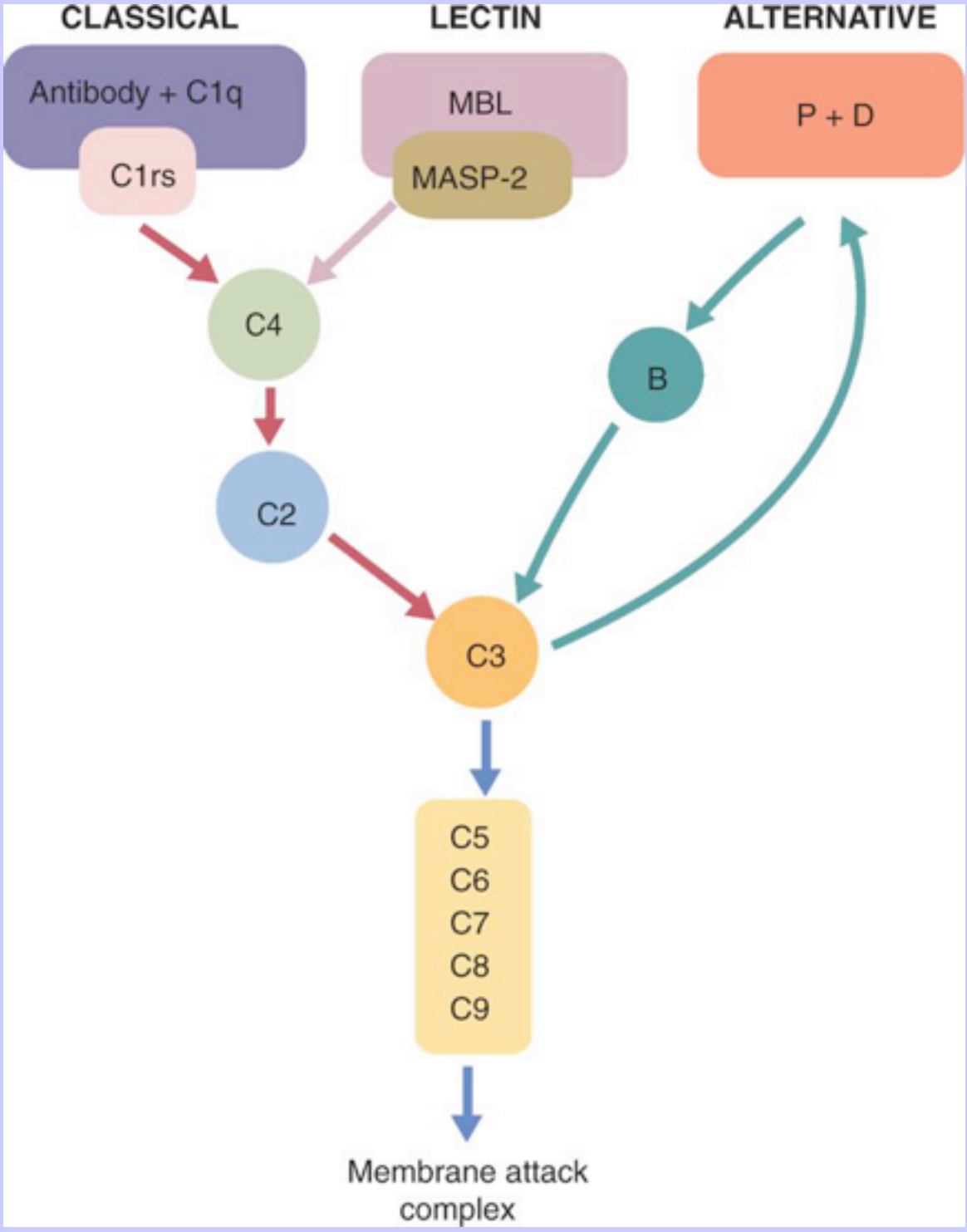


FIGURE 5-2 The three pathways by which the complement system can be activated.



P, and so forth). There are at least 30 such proteins. Some are found free in serum; others are cell-bound receptors. Complement proteins account for about 15% of the globulin fraction of serum. The molecular weights of complement components vary from 24 kDa for factor D to 460 kDa for C1q. Their serum concentrations in humans vary between 20 mg/ml of C2 and 1300 mg/ml of C3 (Table 5-1). Complement components are synthesized at various sites throughout the body. Most C3, C6, C8, and B are made in the liver, whereas C2, C3, C4, C5, B, D, P, and I are made by macrophages. Neutrophils can store large quantities of C6 and C7. As a result, these components are readily available for defense at sites where macrophages and neutrophils accumulate.

5.3 ACTIVATION PATHWAYS

5.3.1 The Alternative Pathway

The alternative pathway of complement activation is an evolutionary ancient pathway that is even found in some invertebrates. It is triggered when microbial cell walls come into contact with complement components in the bloodstream and thus is a key component of innate immunity.

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The most important complement protein is called C3. C3 is a disulfide-linked heterodimer with α and β chains. It is synthesized by liver cells and macrophages and is the complement component of highest concentration in serum.

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Table 5-1 Complement Components

Name	MW (kDa)	Serum conc. (μg/ml)
Classical Pathway		
C1q	460	80
C1r	83	50
C1s	83	50
C4	200	600
C2	102	20
C3	185	1300
Alternate Pathway		
D	24	1
B	90	210
Terminal Components		
C5	204	70
C6	120	65
C7	120	55
C8	160	55
C9	70	60
Control Proteins		
C1-INH	105	200
C4BP	550	250
H	150	480
I	88	35
Ana INH	310	35
P	4 × 56	20
S	83	500

C3 possesses a hidden thioester chemical group. This is a highly reactive group that, when activated, binds to acceptor groups on many pathogens and marks them for destruction by immune cells. Unfortunately, similar acceptor groups are found on many normal tissues. Thus the activation of the thioester group must be very carefully regulated to ensure that the complement system does not attack normal tissues. In unactivated C3 the thioester group is kept hidden inside the folded molecule. In healthy normal animals, C3 breaks down slowly but spontaneously into two fragments called C3a and C3b (Figure 5-3). This breakdown opens up C3b to reveal the thioester group that then generates a reactive carbonyl group. This highly reactive carbonyl group then irreversibly binds the C3b to nearby surfaces (Figure 5-4). It also exposes binding sites for factor H. When factor H binds to these sites, a protease called factor I cleaves the C3b, shutting off further activity and producing iC3b

and C3c. iC3b is the ligand of receptors found on circulating leukocytes (Figure 5-5). It stimulates these cells to engulf pathogens and activate inflammatory cells. The final breakdown product, C3dg, targets pathogens to surface receptors on B cells and so promotes antibody production. Thus C3b is destroyed immediately after being deposited on a nearby surface. This destruction depends on the activity of factor H, which depends in turn on the nature of the target surface. When factor H interacts with normal cell

FIGURE 5-3 The alternative complement pathway. Surface-bound C3b may either be destroyed, as normally happens, or be activated by the presence of an activating surface.

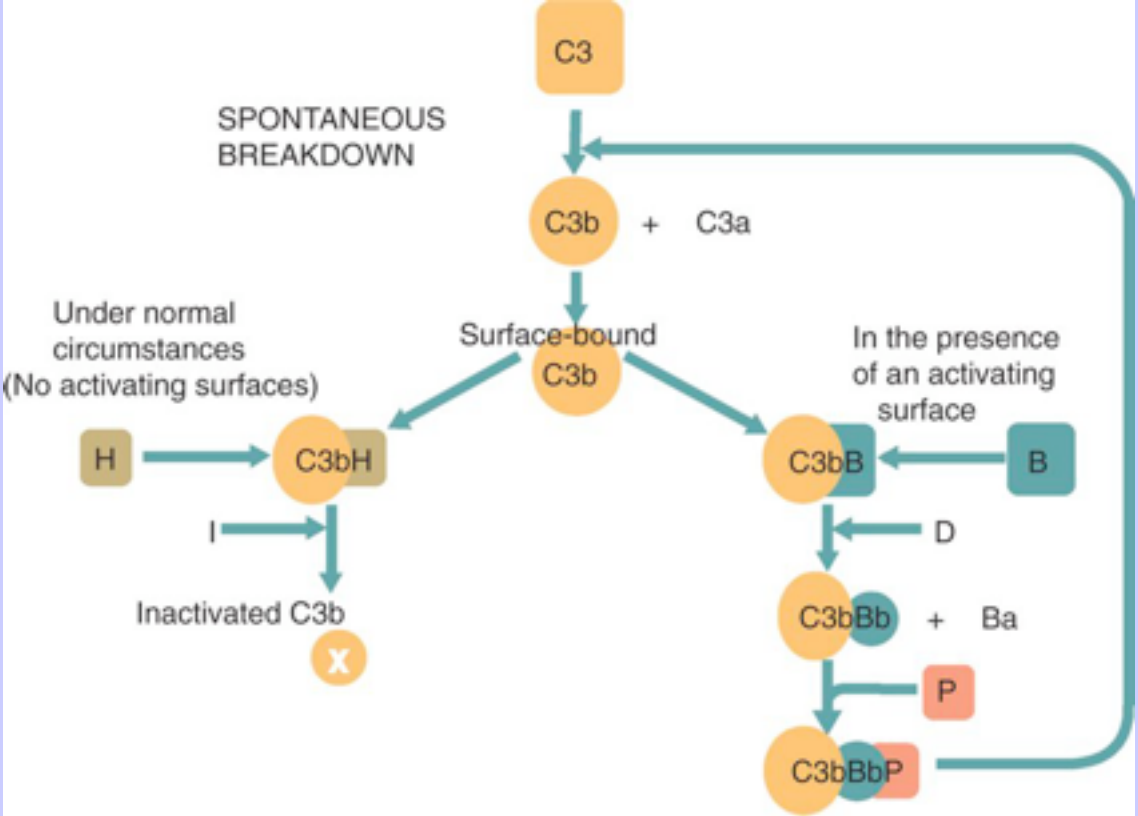

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FIGURE 5-4 Activation of C3 involves its cleavage by C3 convertase. This exposes a thioester bond between a cysteine and a glutamine. This bond breaks to form a reactive carbonyl group that enables the molecule to bind covalently (and hence irreversibly) to target cell surfaces. Removal of C3a also reveals the binding sites for factor H and factor B.

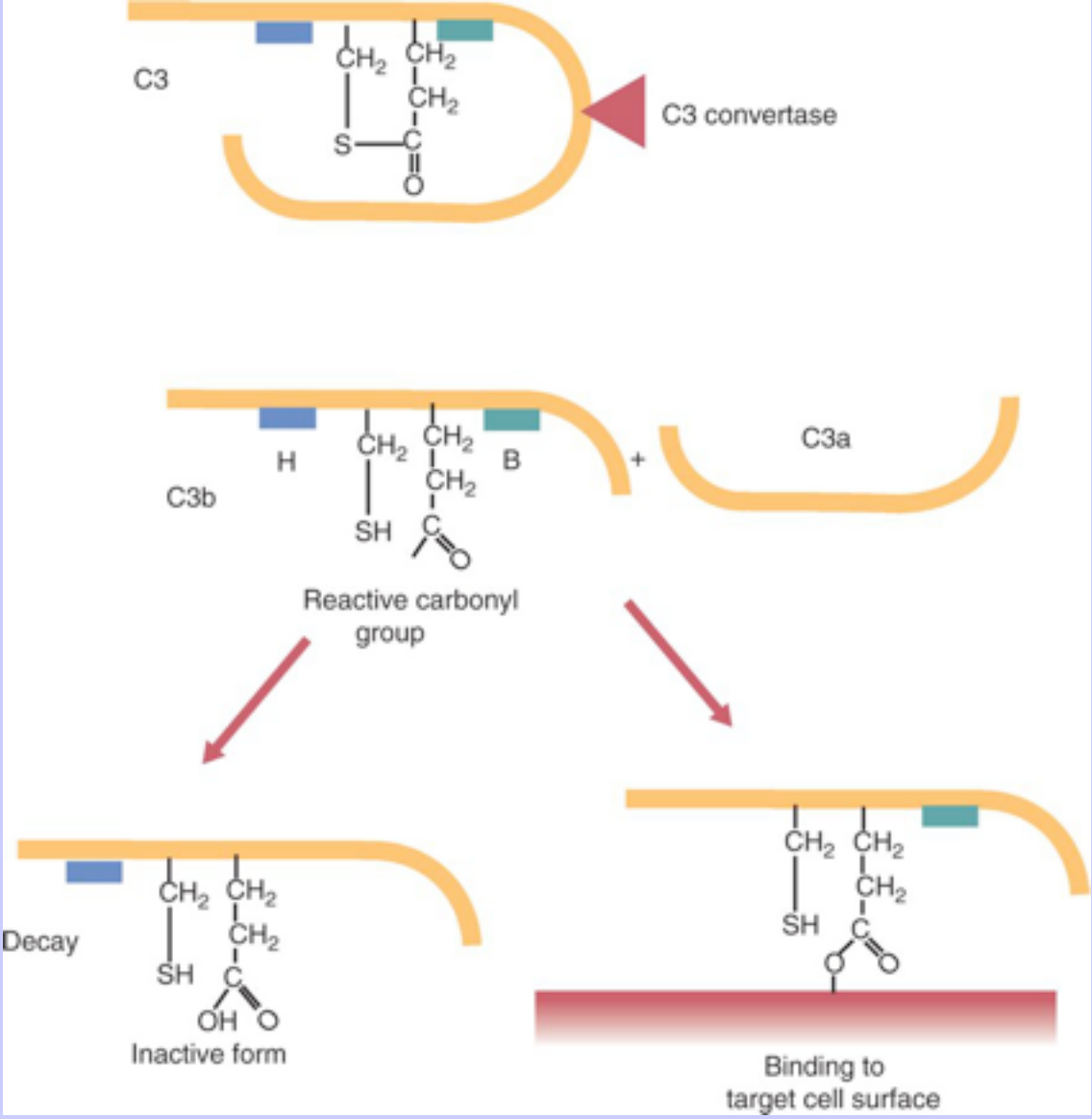
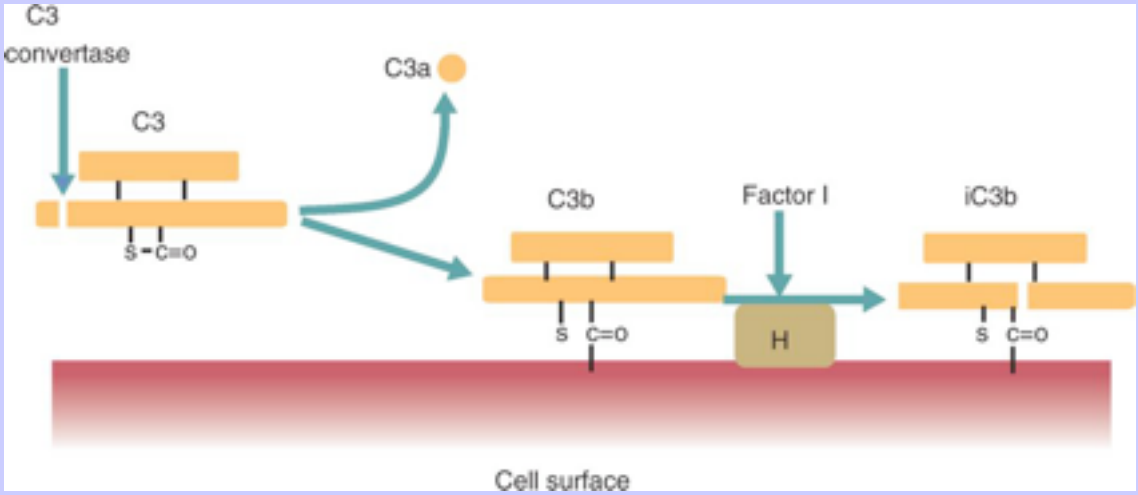


FIGURE 5-5 Activated C3 binds to a cell surface. This C3b is normally inactivated by the actions of factors H and I. However, factor H must first be activated by binding to the surface. In the absence of factor H, factor I will not work. In this case C3b persists and activates the terminal complement pathway.



surfaces, glycoproteins rich in sialic acid and other neutral or anionic polysaccharides enhance its binding to C3b, factor I is activated, and the C3b is destroyed. Thus in a healthy individual, factors H and I destroy C3b as fast as it is generated. On the other hand, on bacterial cell walls, lipopolysaccharides and other carbohydrates lack sialic acid. As a result, factor H cannot bind to C3b, factor I is inactivated, and the C3b persists.

The opening up of C3b also exposes binding sites for another complement protein called factor B to form a complex called C3bB. The bound factor B is then cleaved by a protease called factor D, releasing a soluble fragment called Ba and leaving C3bBb attached to the bacterial wall. This bound C3bBb is a potent protease whose preferred substrate is C3. (It is therefore called the alternative C3 convertase.) Factor D can act only on factor B after it is bound to C3b. This constraint is called substrate modulation, and it occurs at several points in the complement pathways. It presumably ensures that the activities of enzymes such as factor D are confined to the correct molecules.

The alternative C3 convertase, C3bBb, can split C3 and so generate more C3b. However, C3bBb has a half-life of only 5 minutes. If another protein called factor P (or properdin) binds to the complex to form C3bBbP, its half-life is extended to 30 minutes. Since C3b thus serves to generate more C3bBbP, the net effect of all this is that a positive loop is generated where increasing amounts of C3b are irreversibly bound to the surface of the invading organism.

Surface-bound C3b also binds another protein called C5 (Figure 5-6). Once C5 is bound to C3b, substrate modulation occurs and the C5 can also be cleaved by C3bBb (Figure 5-7). This enzyme splits off a small peptide called C5a, leaving a large fragment, C5b, attached to the C3b. This cleavage also exposes a site on C5b that can bind two new proteins, C6 and C7, to form a multimolecular complex called C5b67 (Figure 5-8). The C5b67 complex can then insert itself into the microbial cell membrane. Once inserted in the surface of an organism, the complex will bind a molecule of C8. Twelve to 18 C9 molecules then aggregate with the C5b678 complex to

form a tubular structure called the membrane attack complex (MAC). The MAC inserts itself into a microbial cell membrane and effectively punches a hole in the invader. If sufficient MACs are formed on an organism, it will be killed by osmotic lysis. These MACs can be seen by electron microscopy as ring-shaped structures on the microbial surface with a central electron-dense area surrounded by a lighter ring of poly C9 (Figure 5-9).

5.3.2 The Lectin Pathway

The second method of activating the complement system involves the binding of microbial carbohydrates to serum lectins. These bound lectins then activate proteases that trigger complement activa-tion. Like the alternative pathway, this is an innate defense mechanism triggered simply by the presence of bacterial cell walls within the bloodstream (Figure 5-10).

Mannose-binding lectin (MBL) in serum can bind to mannose or N-acetylglucosamine on microbial cell

FIGURE 5-6 The two C3 convertases, C4b2b and C3bBb, act on C5 when it is linked to C3b and cleave off a small peptide called C5a. In so doing they reveal a site that binds C6 and C7.

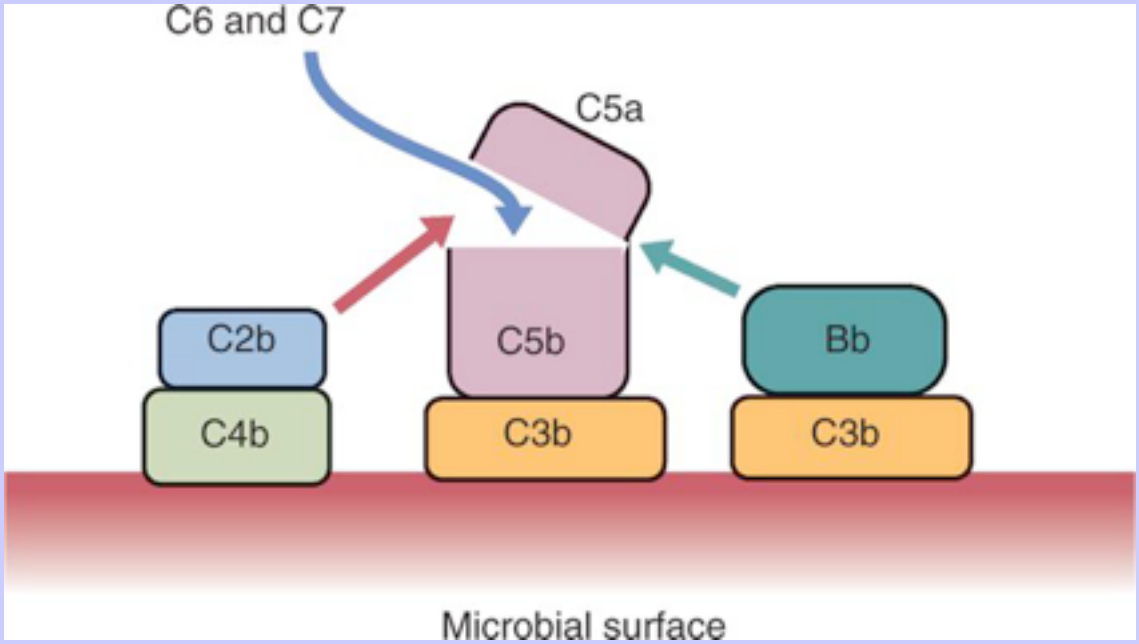


FIGURE 5-7 Substrate modulation is one way in which the complement system is regulated. The target for a protease cannot be cleaved unless it is first bound to another protein. Examples of substrate modulation include the cleavage of factors C2, B, and C5 only after they have bound to C4, C3, and C3, respectively.

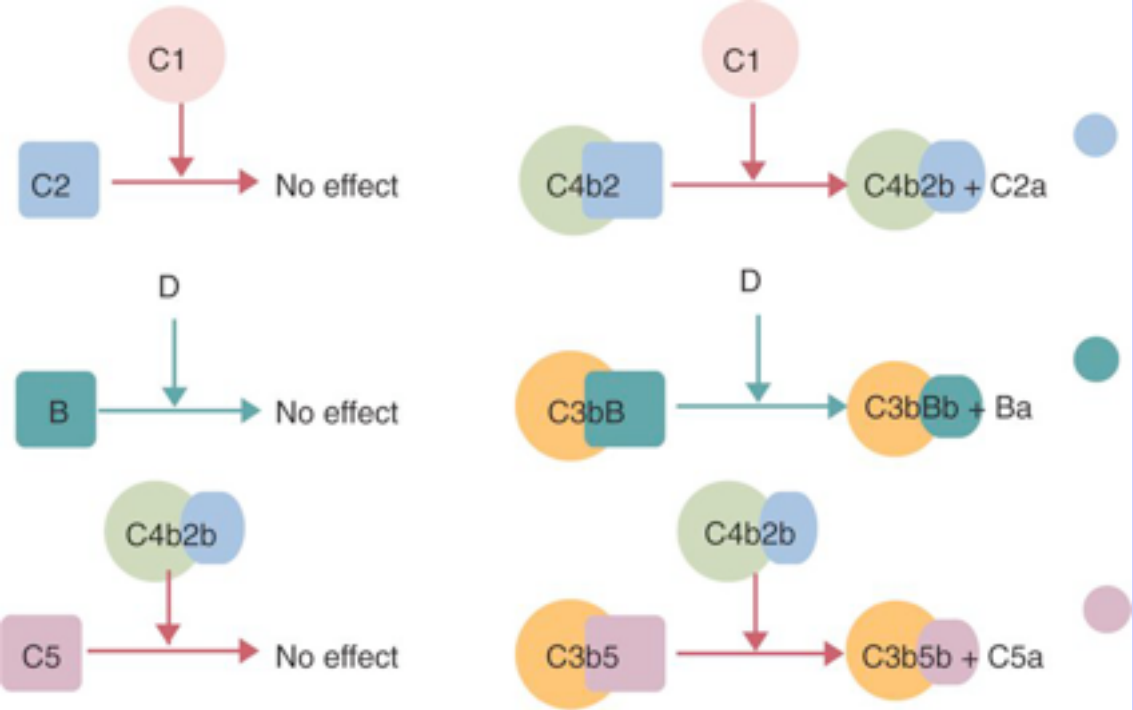


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FIGURE 5-8 The terminal complement pathway. The progressive aggregation of the terminal complement components eventually leads to the polymerization of C9 and the assembly of a membrane attack complex.

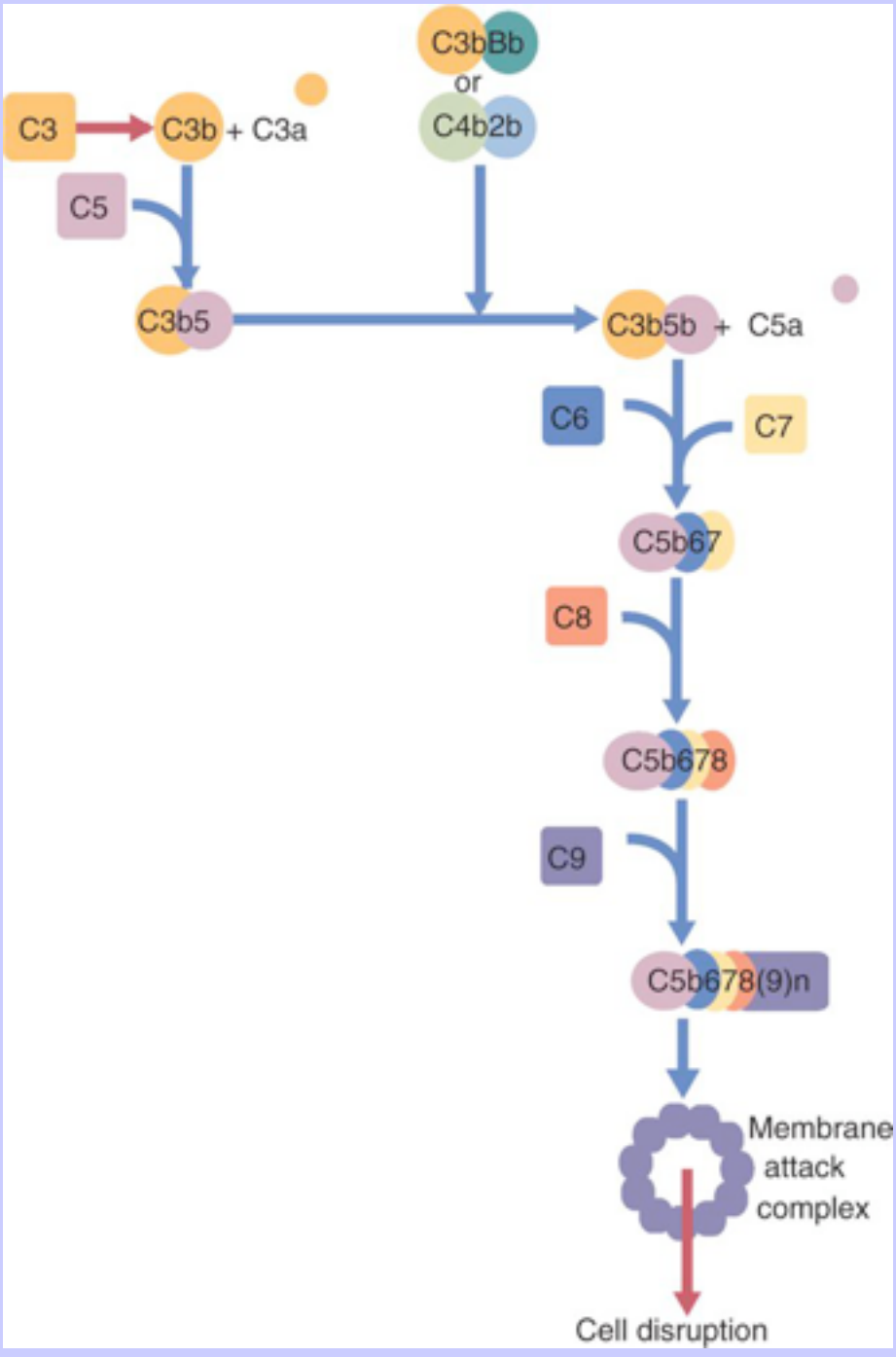
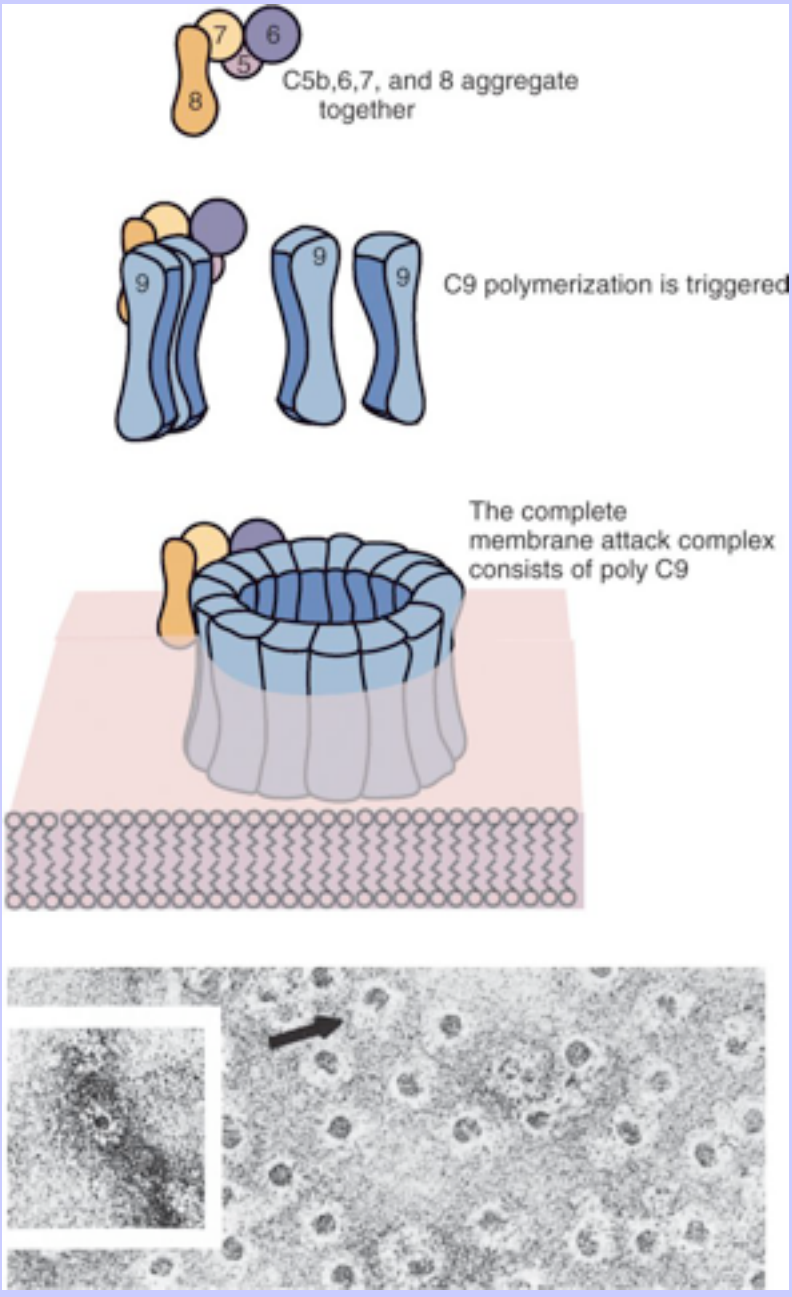


FIGURE 5-9 Formation of poly C9 by the terminal complement pathway and an electron micrograph of poly C9 complement lesions on an erythrocyte membrane. The insert shows a mouse complement lesion. The arrow points to a possible C5b678 complex. Compare these lesions to the T cell polyperforins in Figure 17-9. (From Podack ER, Dennert G: *Nature* 307:442, 1983.)



walls. (Carbohydrates such as galactose or sialic acid found on mammalian glycoproteins do not bind MBL.) Thus MBL can bind to the surface of bacteria, fungi, parasitic protozoa, and viruses (see Chapter 2). Ficolins are another family of lectins that can activate the lectin pathway through MBL-associated serine proteases (MASPs).

Once it has bound to microbial surfaces, the MBL will bind and then activate the serum protease MASP-2. It is believed that binding of MBL to carbohydrates on the microbial surface results in conformational changes that activate MASP-2. Activated MASP-2, in turn, acts on the protein C4, splitting it into C4a and C4b. Removal of C4a exposes a thioester group on the C4b and generates a reactive carbonyl group that covalently attaches the C4b to the microbial surface (see Figure 5-4). C2 is a glycoprotein that binds to C4b to form a complex, C4b2. C2 is then also cleaved by MASP-2 to generate C4b2b.

Cell-bound C4b2b acts on the a chain of C3 to generate C3a and C3b. As in the activation of C4, C3 exposes its thioester group when C3a is split off. As a result, C3b molecules also bind covalently to surfaces carrying C4b2b. The activation of C3b by C4b2b is a major step because each C4b2b complex can activate as many as 200 C3 molecules, which are then irreversibly attached to nearby surfaces. Since the reactions of the complement system are usually confined to the microenvironment close to microbial surfaces, C3 will bind to these organisms. The bound C3b can bind C5 and cleave it to C5a and C5b. The complement pathway then can proceed to completion, causing the destruction of the organism by MACs as described above.

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FIGURE 5-10 Complement activation by the lectin pathway.

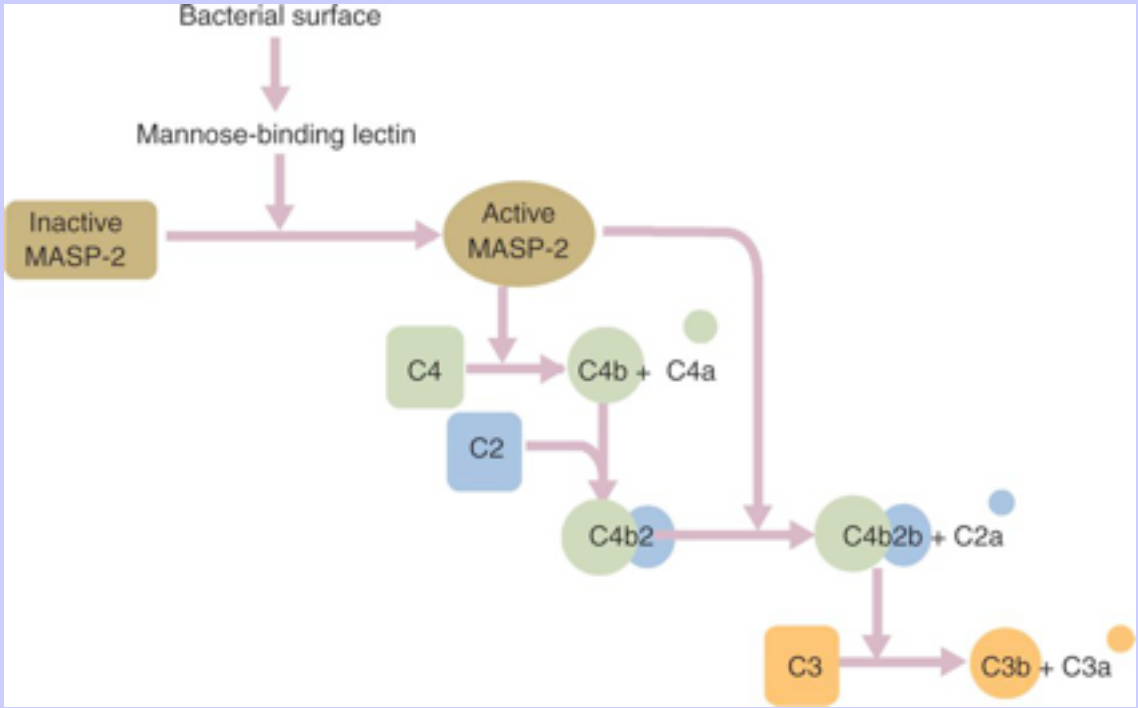
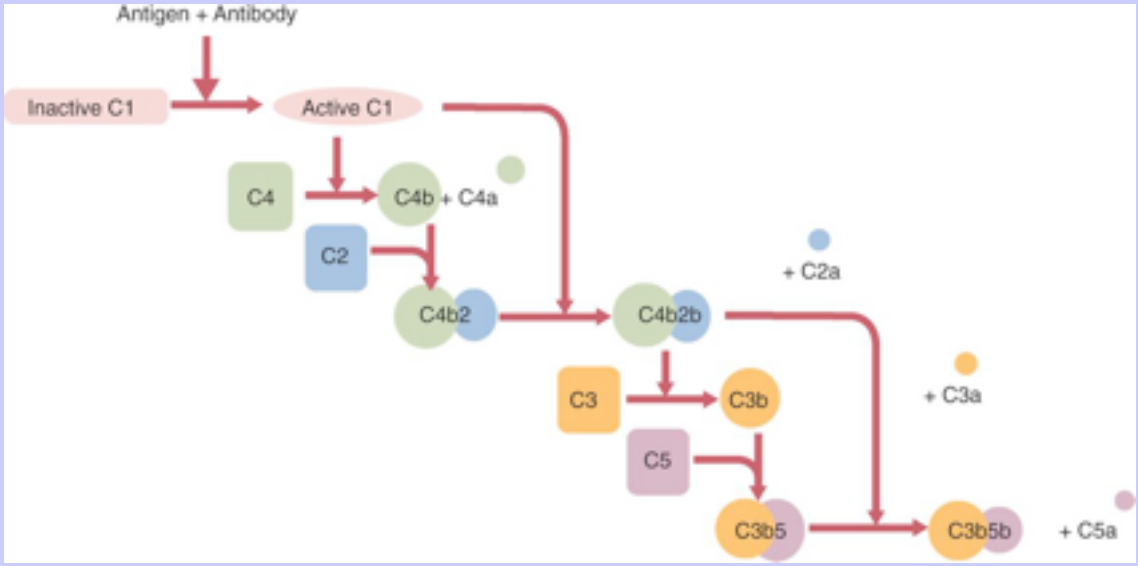


FIGURE 5-11 The basic features of the classical complement pathway.



The MBL–MASP-2 pathway is ancient, having existed for at least 300 million years. Although in many ways it duplicates the alternative pathway, it provides yet another example of duplication of mechanisms to "guarantee" protection.

5.3.3 The Classical Pathway

The classical complement pathway (Figure 5-11) is usually triggered by antibodies bound to the surface of a foreign organism. It is thus part of the acquired immune system. Because of this, it cannot be triggered until antibodies are made, which may occur as late as 7 to 10 days after infection. Nevertheless, once activated it is a very efficient complement-activating pathway. When antibody molecules bind to an antigen, they change their molecular shape and expose active sites on their Fc regions. If several antibody molecules are bound to an organism, multiple active sites will be exposed within a small area. These multiple ac-tive sites trigger classical complement pathway activation.

The first component of the classical complement pathway is a multimolecular protein complex called C1. C1 consists of three proteins (C1q, C1r, and C1s) bound together by calcium. C1q looks like a six-stranded whip when viewed by electron microscopy (Figure 5-12). Two molecules of C1r and two of C1s form a figure-of-eight structure located between the C1q strands. C1q is activated when the tips

FIGURE 5-12 The structure of C1 and its role in interacting with antibodies to initiate the classical complement pathway.

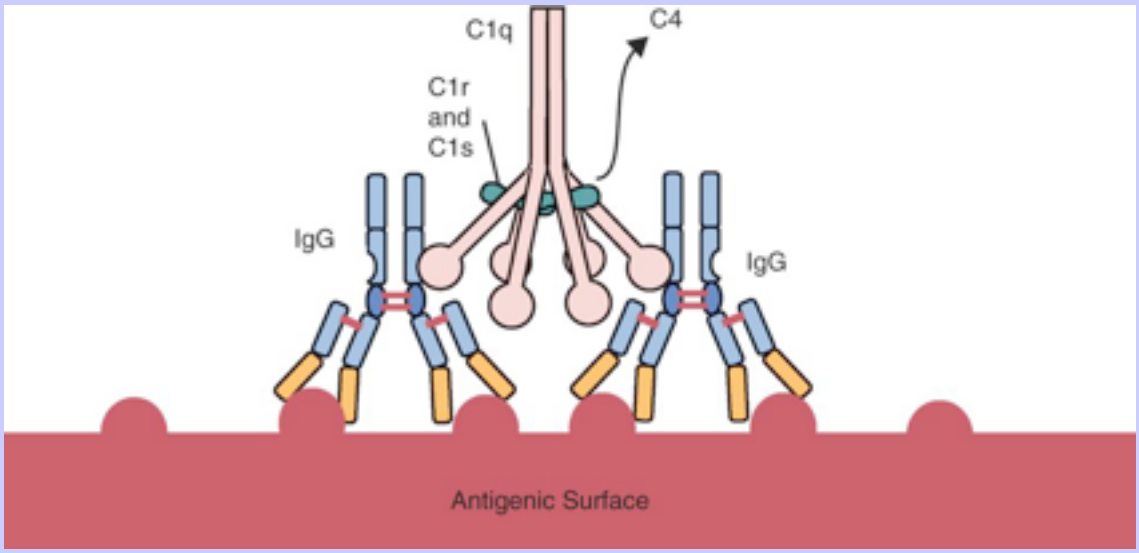
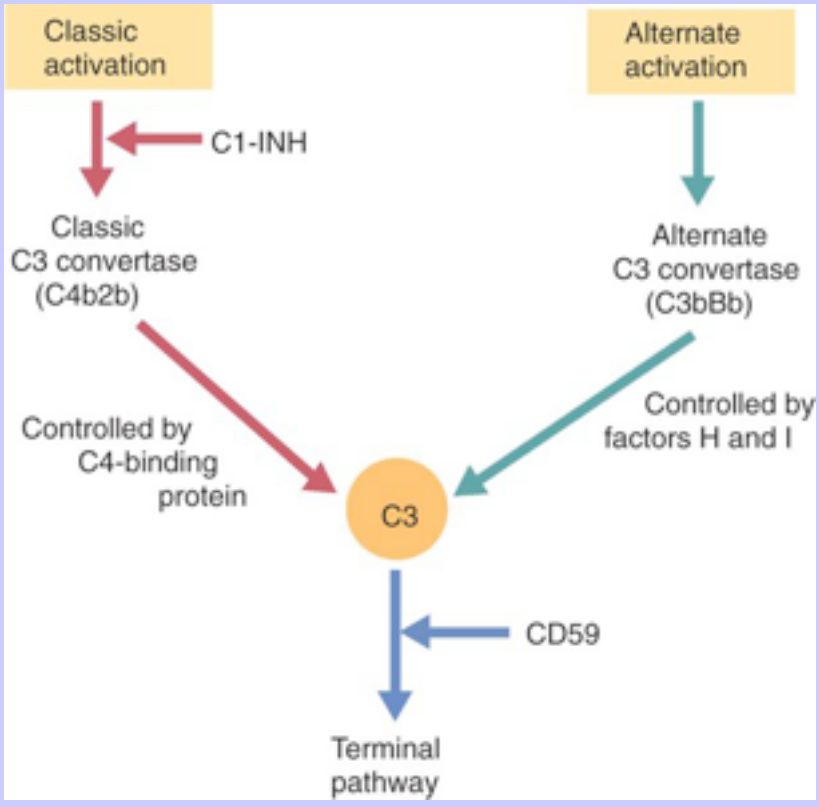


FIGURE 5-13 Basic control mechanisms of the complement system.



of at least two strands bind to complement-activating sites on immunoglobulin Fc regions. Binding to the immunoglobulin causes a conformational change in C1q that is transmitted to C1r. As a result, C1r reveals an active proteolytic site that cleaves a peptide bond in C1s to convert that molecule to an enzymatically active form. Single antigen-bound molecules of immunoglobulin M (IgM) or paired antigen-bound molecules of IgG are needed to activate C1. The polymeric IgM structure readily provides two closely spaced complement-activating sites. In contrast, two IgG molecules must be located very close together to have the same effect. As a result, IgG is much less efficient than IgM in activating the classical pathway. C1 may also be activated directly by some viruses or by bacteria such as *Escherichia coli* and *Klebsiella pneumoniae*.

Activated C1s cleaves C4 into C4a and C4b. C2 then binds to C4b to form C4b2. Activated C1s then splits the bound C2 generating a small peptide, C2a, and C4b2b. C1s cannot act on soluble C2; the C2 must first be bound to C4b before it can be cleaved (another example of substrate modulation). The C4b2b complex, as described above, is a potent protease that cleaves C3 and is therefore called classical C3 convertase. C3b generated in this way binds and activates C5. Subsequent reactions lead to formation of the MAC and microbial killing.

The close relationship between the lectin pathway and the classical pathway is shown by the observation that some lectins can also activate the classical pathway. For example, a lectin called specific intracellular adhesion molecule-grabbing nonintegrin (SIGN)-R1 found on the surface of macrophages binds to bacteria such as *Streptococcus pneumoniae* and thus acquires the ability to activate C1 and trigger the classical pathway directly.

5.4 REGULATION OF COMPLEMENT

The consequences of complement activation are so significant and potentially dangerous that all of the activation pathways must be carefully controlled by regulatory proteins (Figure 5-13).

The most important regulator of the classical pathway is C1-inactivator (C1-INH). C1-INH blocks the activities of active C1r and C1s. Other regulatory proteins control the activities of the C3 and C5 convertases. For example, CD55, or decay accelerating factor, is a glycoprotein expressed on the surface of red blood cells, neutrophils, lymphocytes, monocytes, platelets, and endothelial cells. CD55 binds to the convertases and accelerates their decay. Its function is to protect normal cells from complement attack. Other proteins that accelerate degradation of the convertases include factor H and C4-binding protein (C4BP) found in plasma and CD35 (CR1) and CD46 found on cell membranes. Control of the C56789 complex is mediated by three glycoproteins: vitronectin, clusterin, and, most im-portantly, CD59 (protectin). They all inhibit C5b678 insertion and C9 polymerization in normal cell membranes.

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5.4.1 Complement Receptors

Five cell surface receptors for C3 or its fragments have been identified. These are called CR1 (CD35), CR2 (CD21), CR3 (CD11a/CD18), CR4 (CD11c/CD18), and CRIg.

CR1 binds C3b and C4b as well as the C3b breakdown product, iC3b. CR1 is found on primate red cells, neutrophils, eosinophils, monocytes, macrophages, B cells, and some T cells. Red cell CR1 accounts for 90% of all CR1 in the blood. In primates, CR1 removes immune complexes from the circulation. (Immune complexes bind to CR1 on red cells, and the coated red cells are then removed in the liver and spleen [see Chapter 27].) Deficiencies of complement components or their receptors may allow circulating immune complexes to accumulate in organs such as kidney and cause tissue damage. For example, some patients with the autoimmune disease systemic lupus erythematosus have a CR1 deficiency and are thus unable to remove these immune complexes effectively. C3-deficient dogs develop immune complex–mediated kidney lesions for the same reason.

CR2 (CD21), found on most B cells, binds a breakdown fragment of C3 called C3d. This cell surface receptor forms a complex with CD19 that regulates B cell responses (see Chapter 13, Figure 13-10). To respond optimally to antigens, B cells require stimulation by C3d acting through CR2.

CR3 (CD11a/CD18) is an integrin that binds iC3b. It is found on macrophages, neutrophils, and natural killer cells. A genetic deficiency of CR3 (leukocyte adherence deficiency) has been described in humans, cattle, and dogs in which affected individuals experience severe recurrent infections (see Chapter 34).

CR4 (CD11c/CD18) is another integrin found on neutrophils, T cells, natural killer cells, a few platelets, and macrophages. It binds breakdown fragments of C3.

CRIg is expressed on tissue macrophages including Kupffer cells in the liver. It has an affinity for C3b and iC3b. It is a receptor for the C3-dependent opsonization of blood-borne pathogens.

5.5 OTHER CONSEQUENCES OF COMPLEMENT ACTIVATION

While microbial killing due to lysis mediated by MACs is the most obvious activity of the complement system, its protective effects go far beyond this, contributing to the body's defenses in many ways.

5.5.1 Opsonization

C3b and C4b bound covalently to a microbial surface effectively tag it as foreign and serve as very potent and effective opsonins. Phagocytic cells possess CR1, whereas tissue macrophages possess CRIg. Thus C3b-coated organisms will bind strongly to these cells and undergo type II phagocytosis (see Chapter 3). If for some reason these organisms cannot be ingested, then neutrophils may secrete their lysosomal enzymes and oxidants into the surrounding tissue fluid. These molecules then cause inflammation and tissue damage—a reaction classified as type III hypersensitivity (see Chapter 27).

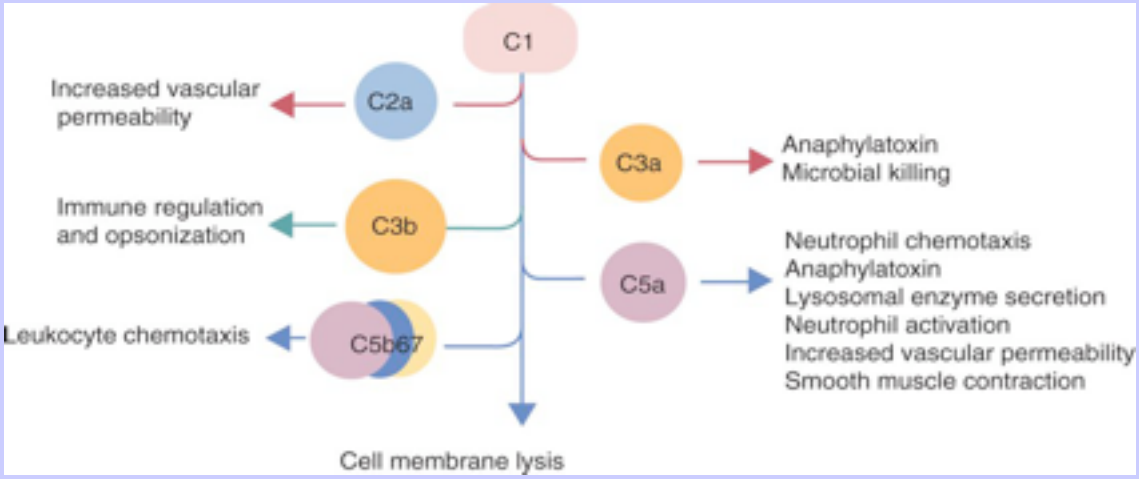
5.5.2 Chemotaxis

The complement system is a major contributor to acute inflammation. For example, activation of the complement system by any of its pathways generates several potent chemotactic peptides, including C5a and C5b67 (Table 5-2). C5b67 is chemotactic for neutrophils and eosinophils, whereas C5a attracts not only neutrophils and eosinophils but also macrophages and basophils. When C5a attracts neutrophils, it stimulates their respiratory burst and upregulates CR1 and integrin expression.

5.5.3 Inflammation

The small peptides C3a and C5a cause acute inflammation when injected into the skin. These molecules have been called anaphylatoxins because they degranulate mast cells and stimulate platelets to release the vasoactive molecules histamine and serotonin. They

FIGURE 5-14 Some of the biological consequences of complement activation.



increase vascular permeability, causing lysosomal enzyme release from neutrophils and thromboxane release from macrophages (Figure 5-14). C3a and its inactivated derivative C3a-des Arg are also antibacterial peptides. Thus C3a is an efficient killer of *E. coli, Pseudomonas aeruginosa, Enterococcus faecalis,* and *Streptococcus pyogenes*. The C3a appears to act by disrupting bacterial membranes. It therefore resembles the defensins and other antimicrobial peptides and provides yet another mechanism by which the complement system contributes to innate immunity.

Table 5-2 Complement-Derived Chemotactic Factors

Factor	Target
C3a	Eosinophils
C5a	Neutrophils, eosinophils, macrophages
C567	Neutrophils, eosinophils
Bb	Neutrophils
C3e	Promotes leukocytosis

5.5.4

Immune Regulation

Complement regulates antibody formation through C3d bound to antigen. When an antigen molecule binds to a B cell receptor, any C3d on its surface will bind to CD21/CD19 complexes on the B cell surface. (Remember that several hundred C3 molecules may attach to an antigen as a result of C3 convertase activity.) Activation of the CD21/CD19 complex sends a signal that significantly potentiates B cell receptor signaling and is an important co-stimulatory pathway for mature B cells. Thus depletion of C3 is associated with reduced primary antibody responses.

Coating of antigens with C3d also permits antigens to bind to CR2 on dendritic cells and so influences antigen processing. In the absence of C3, immune complexes will not localize on follicular dendritic cells in germinal centers.

5.6 COMPLEMENT GENES

The genes coding for complement proteins are mainly scattered throughout the genome. However, two major gene clusters have been identified. The genes coding for C4, C2, and factor B are clustered within the major histocompatibility complex class III region; the genes for C4BP, CD55, CD35, CD21, CD46, and factor H are linked in the RCA (regulation of complement activation) cluster.

Complement components, like other proteins, may occur in different allelic forms. The precise number varies between components and species. For example, bovine factor H has three allotypes, equine C3 has six, and canine C3 has two. Canine C6 has seven allotypes, and porcine C6 has 14. Eleven allotypes of canine C7 have been identified, while canine C4 has at least five. There is an association among the C4-4 allotype, low serum C4 levels, and the development of autoimmune polyarthritis in dogs. Feline and equine C4 each have at least four allotypes.

5.7 COMPLEMENT DEFICIENCIES

5.7.1 Canine C3 Deficiency

Because the complement system is an essential defensive mechanism, complement deficiencies increase susceptibility to infections. The most severe of these diseases occurs in individuals deficient in C3. For example, a colony of Brittany Spaniels with an autosomal recessive C3 deficiency has been described (Figure 5-15). Dogs that are homozygous for this trait have no detectable C3, whereas heterozygous animals have C3 levels that are approximately half normal. Heterozygous animals are clinically normal. The homozygous-deficient animals have lower IgG levels than normal, and their ability to make antibodies against defined antigens is reduced. The dogs tend to make more IgM and less IgG. They experience recurrent sepsis, pneumonia, pyometra, and wound infections. The organisms involved include *Clostridium, Pseudomonas, E. coli,* and *Klebsiella*. Some affected dogs develop

FIGURE 5-15 Inheritance of a C3 deficiency in a colony of Brittany Spaniels. The number below each circle or square represents the animal's C3 level as a percentage of a standard reference serum. The mean level in healthy spaniels was 126. (Squares denote males, circles denote females.) (From Winkelstein JA, Cork LC, Griffin DE, et al: *Science* 212:1169-1170, 1981.)

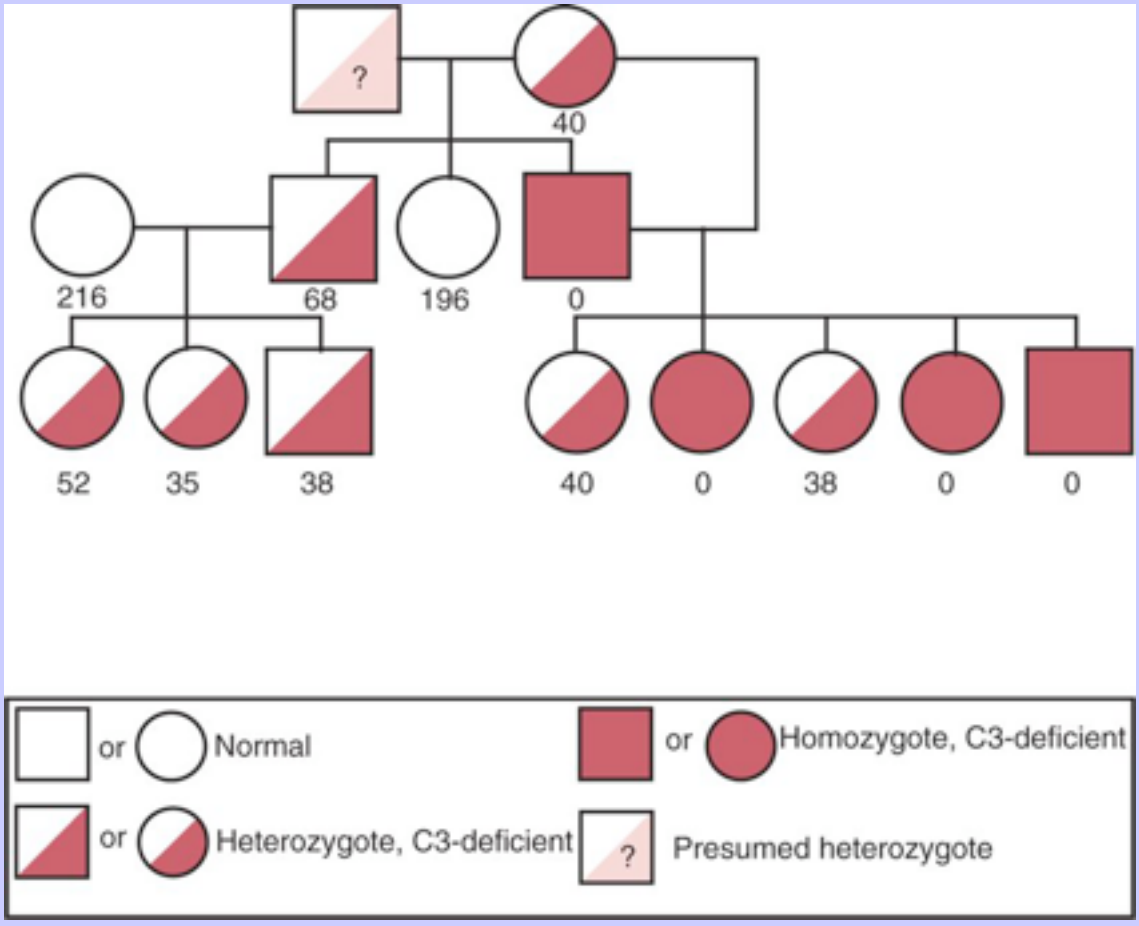
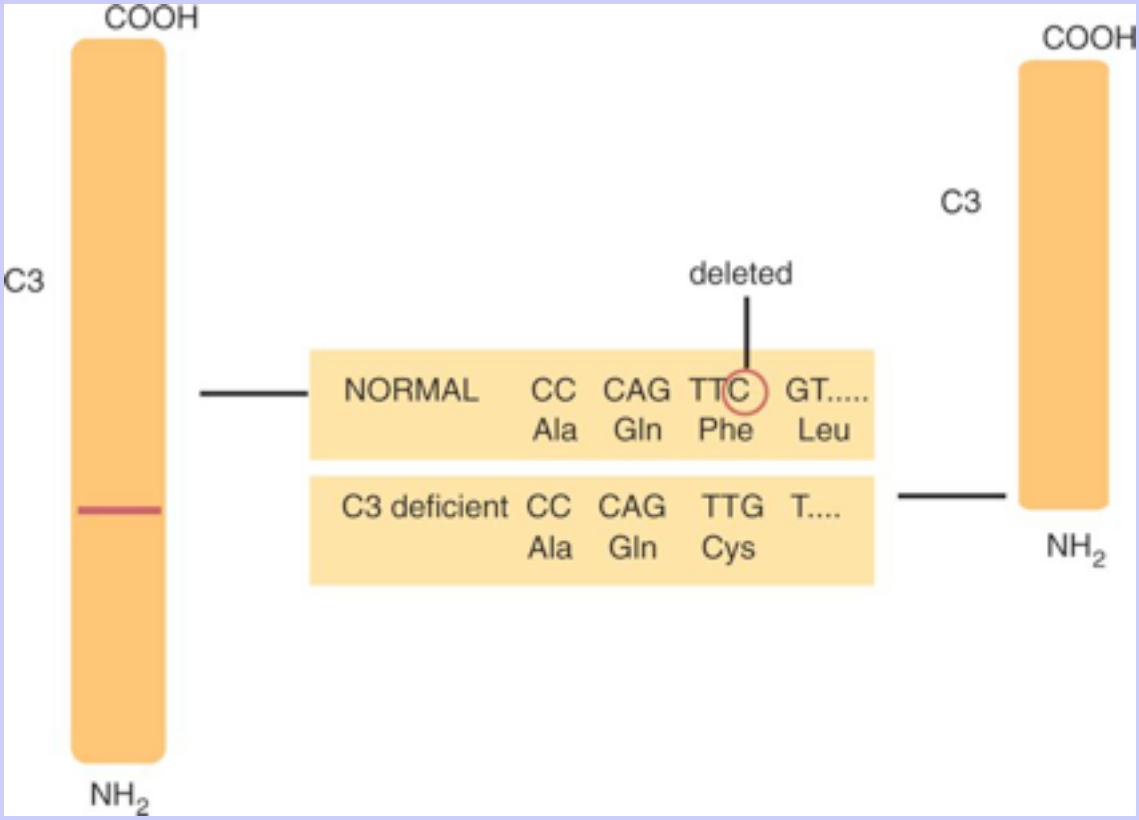


FIGURE 5-16 The mutation that results in canine C3 deficiency.



amyloidosis, and many develop an immune complex–mediated kidney disease (see Chapter 27). The mutation responsible for this deficiency (deletion of a cytosine residue) shortens the C3 chain as a result of a frameshift and the generation of a premature stop codon (Figure 5-16).

5.7.2 Porcine Factor H Deficiency

Factor H is a critical component of the alternative complement pathway. It normally inactivates C3b as soon as it is generated and so prevents excessive alternative pathway activation. If an animal fails to make factor H, C3b will be generated in an uncontrolled fashion. Factor H deficiency has been identified as an autosomal recessive trait in Yorkshire pigs. Affected piglets are healthy at birth and develop normally for a few weeks. However, eventually they fail to thrive, stop growing, become anemic, and die of renal failure.

On autopsy, multiple petechial hemorrhages are seen on the surface of the kidneys, accompanied by

FIGURE 5-17 **A,** A thin section of the glomerulus of a piglet with factor H deficiency. Note the thickened basement membrane and increased numbers of mesangial cells, hence the name *membranoproliferative glomerulonephritis*. **B,** An immunofluorescence photomicrograph of another glomerulus from a factor H-deficient piglet. This is stained with fluorescent anti-C3. The bright fluorescence indicates the presence of C3 deposited in this glomerulus. Compare this figure with Figure 27-10 in Chapter 27. (**A,** Courtesy Johan H. Jansen; **B,** from Jansen JH, Hogasen K, Mollnes TE: *Am J Pathol* 143:1356-1365, 1993.)

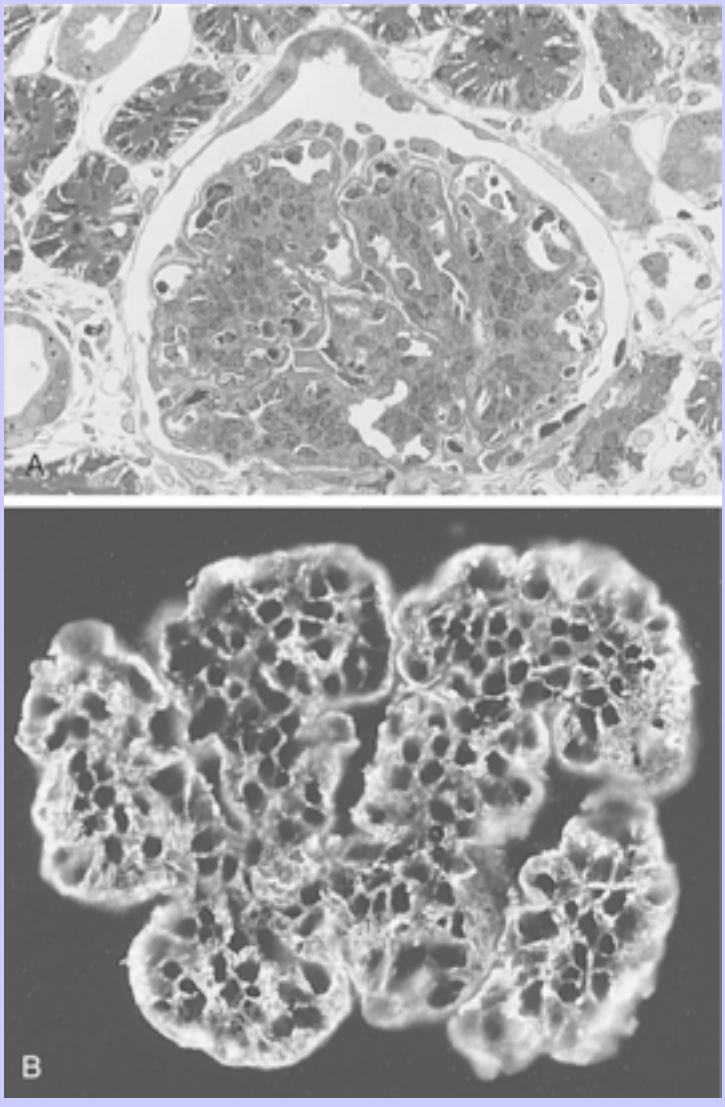
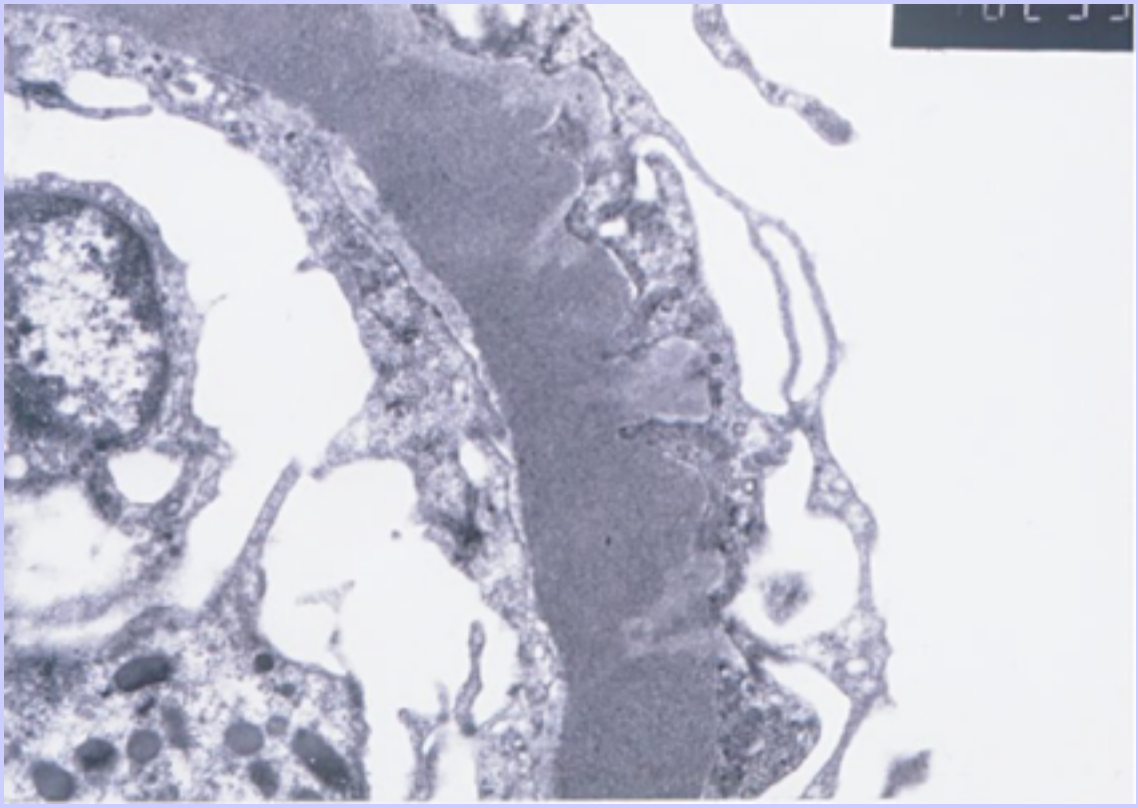


FIGURE 5-18 Electron micrograph showing dense intramembranous deposits in the glomerulus of a piglet with factor H deficiency. (From Jansen JH: APMIS 101:281-289, 1993.)



atrophy of the renal papillae. On light microscopy, alterations are seen in the renal glomeruli, i.e., mesangial cell proliferation and capillary basement membrane thickening (Figure 5-17). Electron microscopy reveals extensive intramembranous electron-dense deposits within the glomerular basement membranes (Figure 5-18). This is typical of type II membranoproliferative glomerulonephritis or dense-deposit disease (see Chapter 27). Indirect immunofluorescence demonstrates massive deposits of C3 but no immunoglobulins in the basement membranes. C3 can be found in the glomeruli before birth, but the morphological changes (mesangial proliferation and intramembranous dense deposits) are never seen before 5 days of age. These pigs have no plasma C3. Nephritic piglets are almost totally deficient in factor H (2% of normal levels), whereas heterozygotes have half the normal levels. If factor H is replaced by plasma transfusions, the progress of the disease can be slowed and piglet survival enhanced. Since heterozygotes can be readily detected by measurement of plasma C3, this disease can be eradicated from affected herds.

5.7.3 Other Complement Deficiencies

MBL deficiency has been described in children, where it results in increased susceptibility to infection. It has not yet been described in domestic animals. In contrast to the severe effects of a C3 deficiency, congenital deficiencies of other complement components in laboratory animals or humans are not necessarily lethal. Thus

individuals with C6 or C7 deficiencies have been described who are quite healthy. Apparently healthy C6-deficient pigs have been described. The lack of discernible effect of these deficiencies suggests that the terminal portion of the complement pathway leading to lysis may not be biologically essential.

5.8 SOURCES OF ADDITIONAL INFORMATION

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