Lecture X

Immunity against infection

Vaccines

MECHANISMS OF HUMORAL AND CELL-MEDIATED IMMUNE RESPONSES TO VIRUSES

RESPONSE TYPE	EFFECTOR MOLECULE OR CELL	ACTIVITY
Humoral	Antibody (especially secretory IgA)	Blocks binding of virus to host cells, thus preventing infection or reinfection
	IgG, IgM, and IgA antibody	Blocks fusion of viral envelope with host-cell plasma membrane
	IgG and IgM antibody	Enhances phagocytosis of viral particles (opsonization)
	IgM antibody	Agglutinates viral particles
	Complement activated by IgG or IgM antibody	Mediates opsonization by C3b and lysis of enveloped viral particles by membrane-attack complex
Cell-mediated	IFN-γ secreted by T_H or T_C cells	Has direct antiviral activity
	Cytotoxic T lymphocytes (CTLs)	Kill virus-infected self-cells
	NK cells and macrophages	Kill virus-infected cells by antibody-dependent cell-mediated cytotoxicity (ADCC)

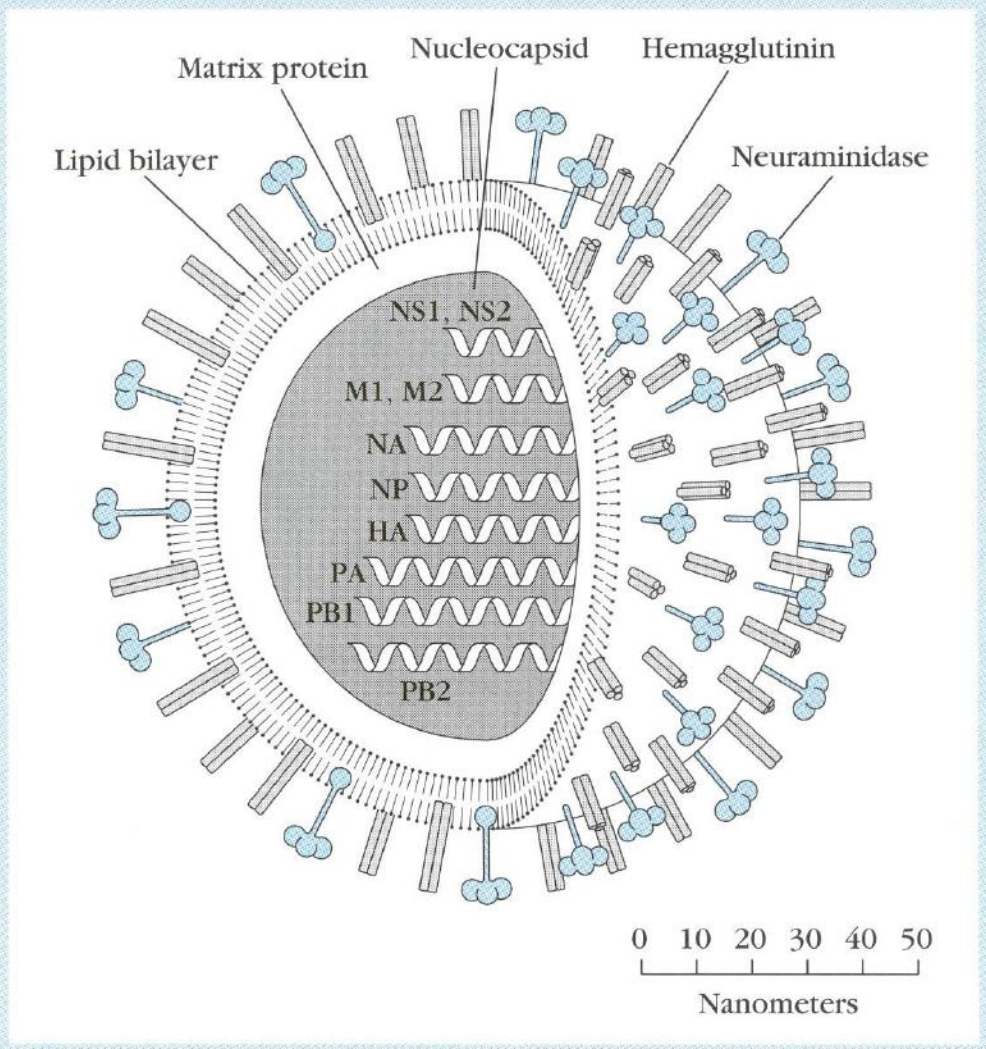


FIGURE 19-2

Schematic representation of influenza structure. The envelope is covered with neuraminidase and hemagglutinin spikes. Inside is an inner layer of matrix protein surrounding the nucleocapsid, which consists of eight ssRNA strands associated with nucleoprotein. The eight RNA strands encode ten proteins: PB1, PB2, PA, HA (hemagglutinin), NP (nucleoprotein), NA (neuraminidase), M1, M2, NS1, and NS2.

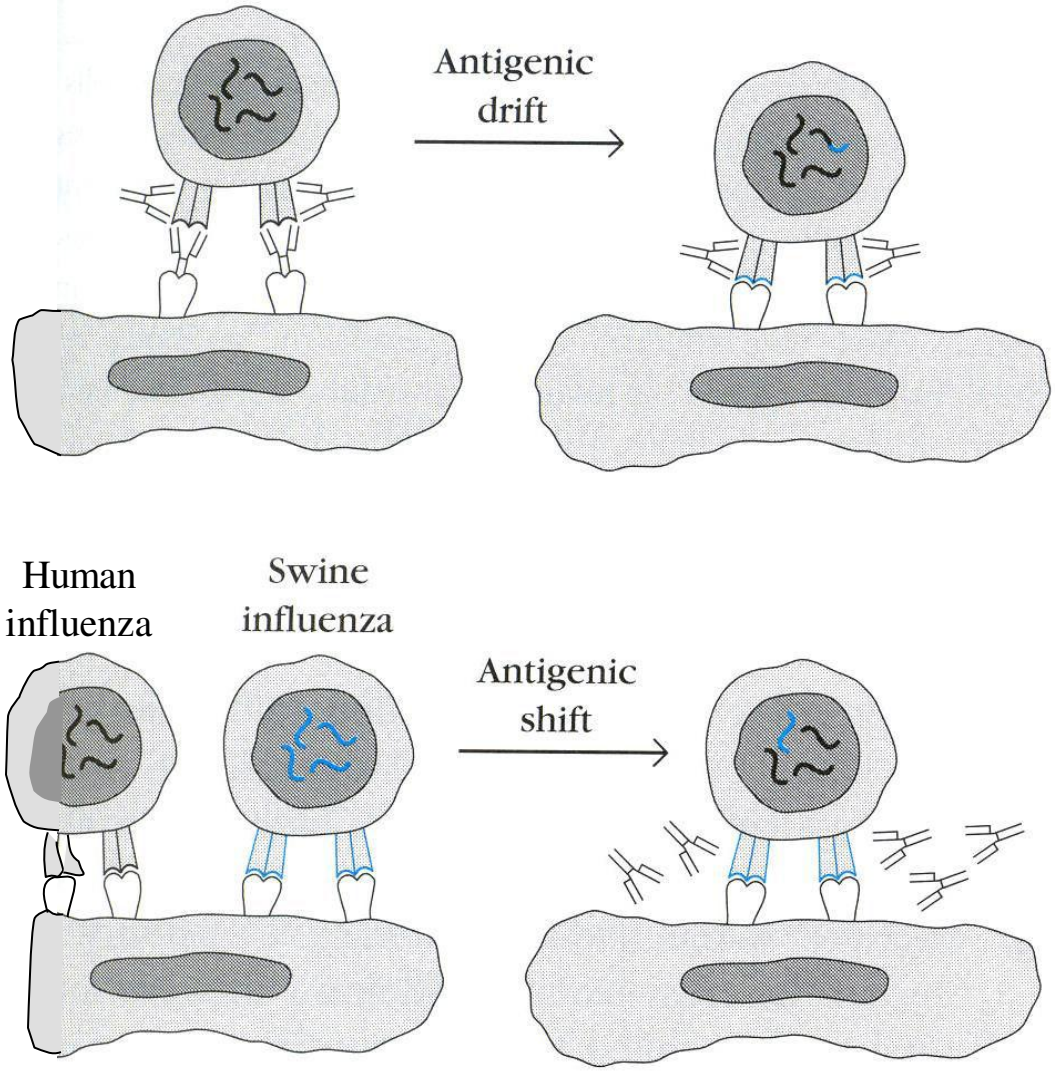


FIGURE 19-4
Two mechanisms generate variations in influenza surface antigens.
a) In antigenic drift, the accumulation of point mutations eventually yields a variant protein that is no longer recognised by antibody to original antigen.
b) Antigenic shift my occur via reassortment of an entire ssRNA between human and animal virions coinfecting the same cell. Only four of the eight RNA strands are depicted.

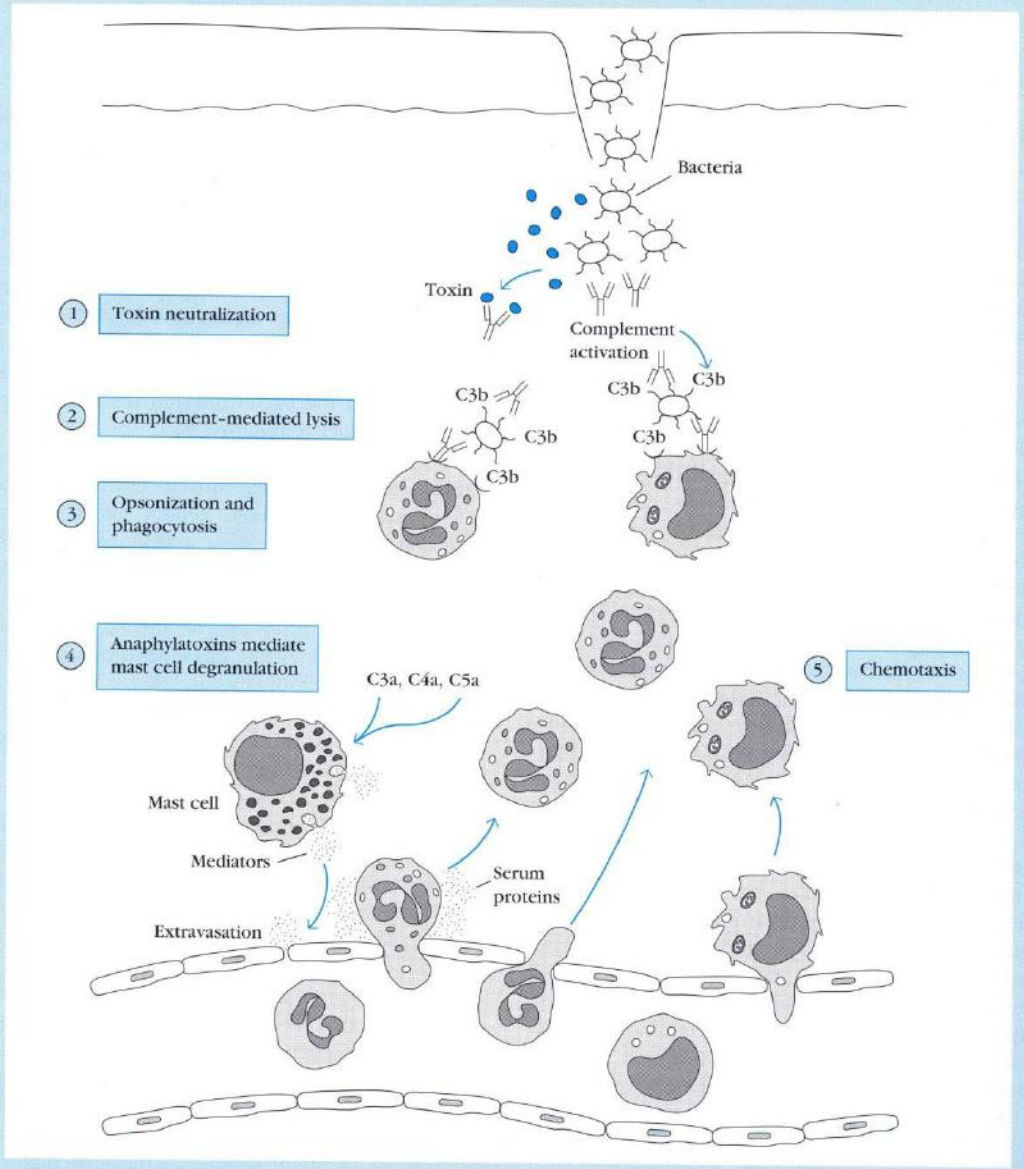


FIGURE 19-6

Antibody-mediated mechanisms for combating infection by extracellular bacteria. (1) Antibody neutralizes bacterial toxins (blue circles). (2) Complement activation on bacterial surfaces leads to complement-mediated lysis of bacteria. (3) Antibody and the complement split product C3b bind to bacteria, serving as opsonins to increase phagocytosis. (4) C3a and C5a, generated by antibody-initiated complement activation, induce local mast cell degranulation, releasing substances that mediate vasodilation and extravasation of lymphocytes and neutrophils. (5) Other complement split products are chemotactic for neutrophils.

HOST IMMUNE RESPONSES TO BACTERIAL INFECTION AND BACTERIAL EVASION MECHANISMS

INFECTION PROCESS	HOST DEFENSE	BACTERIAL EVASION MECHANISMS
Attachment to host cells	Blockage of attachment by secretory IgA antibodies	Secretion of proteases that cleave secretory IgA dimers *(Neisseria meningitidis, N. gonorrhoeae, Haemophilus influenzae)*
		Antigenic variation in attachment structures (pili of *N. gonorrhoeae*)
Proliferation	Phagocytosis (Ab- and C3b-mediated opsonization)	Production of surface structures (polysaccharide capsule, M protein, fibrin coat) that inhibit phagocytic cells
		Intracellular mechanisms for surviving within phagocytic cells
		Induction of apoptosis in macrophages *(Shigella flexneri)*
	Complement-mediated lysis and localized inflammatory response	Generalized resistance to complement-mediated lysis by gram-positive bacteria
		Insertion of membrane-attack complex prevented by long side chain in cell-wall LPS (some gram-negative bacteria)
		Secretion of elastase that inactivates C3a and C5a *(Pseudomonas)*
Invasion of host tissues	Ab-mediated agglutination	Secretion of hyaluronidase, which enhances bacterial invasiveness
Toxin-induced damage to host cells	Neutralization of toxin by antibody	

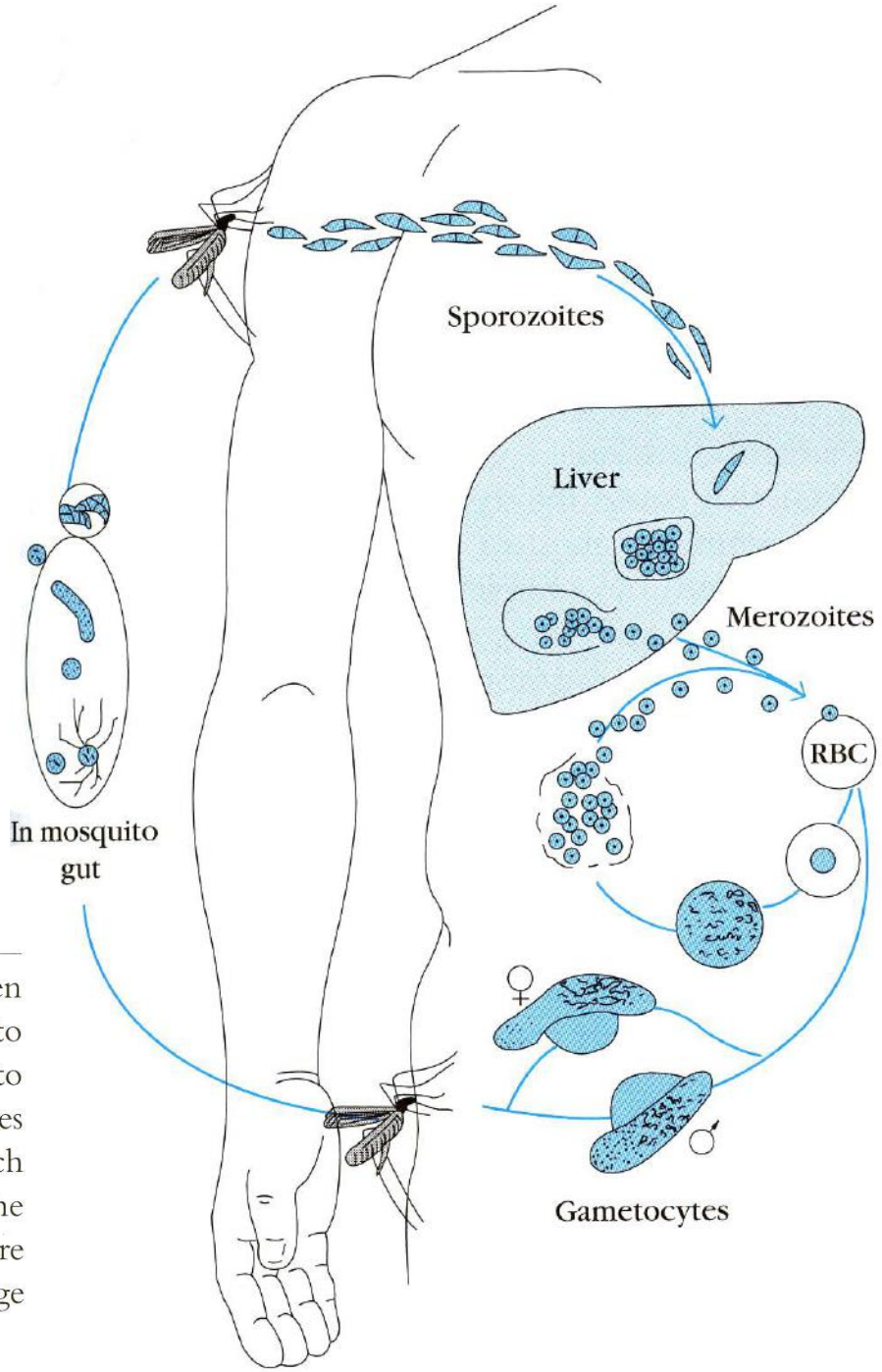


FIGURE 19-11

The life cycle of *Plasmodium*. Sporozoites enter the bloodstream when an infected mosquito takes a blood meal. The sporozoites migrate to the liver where they multiply, transforming liver hepatocytes into giant multinucleate schizonts, which release thousands of merozoites into the bloodstream. The merozoites infect red blood cells, which eventually rupture, releasing more merozoites. Eventually some of the merozoites differentiate into male and female gametocytes, which are ingested by a mosquito and differentiate into the sporozoite stage within the salivary gland of the mosquito.

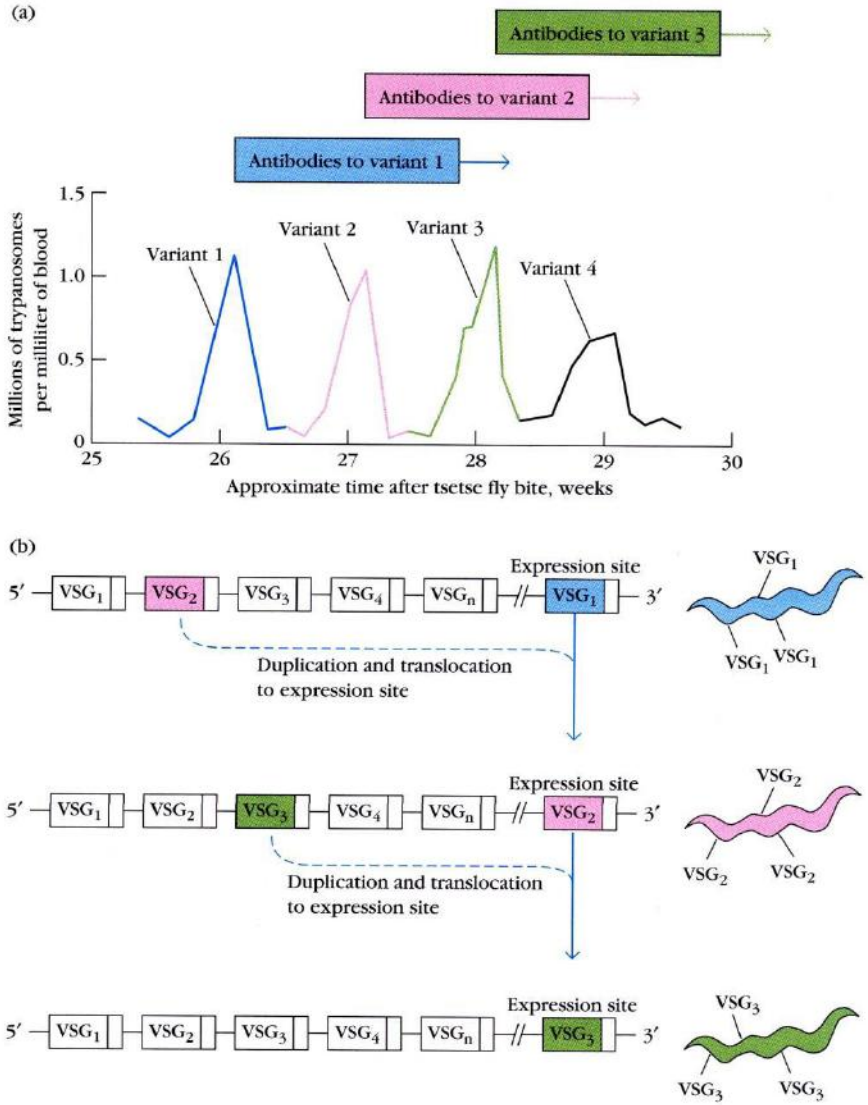
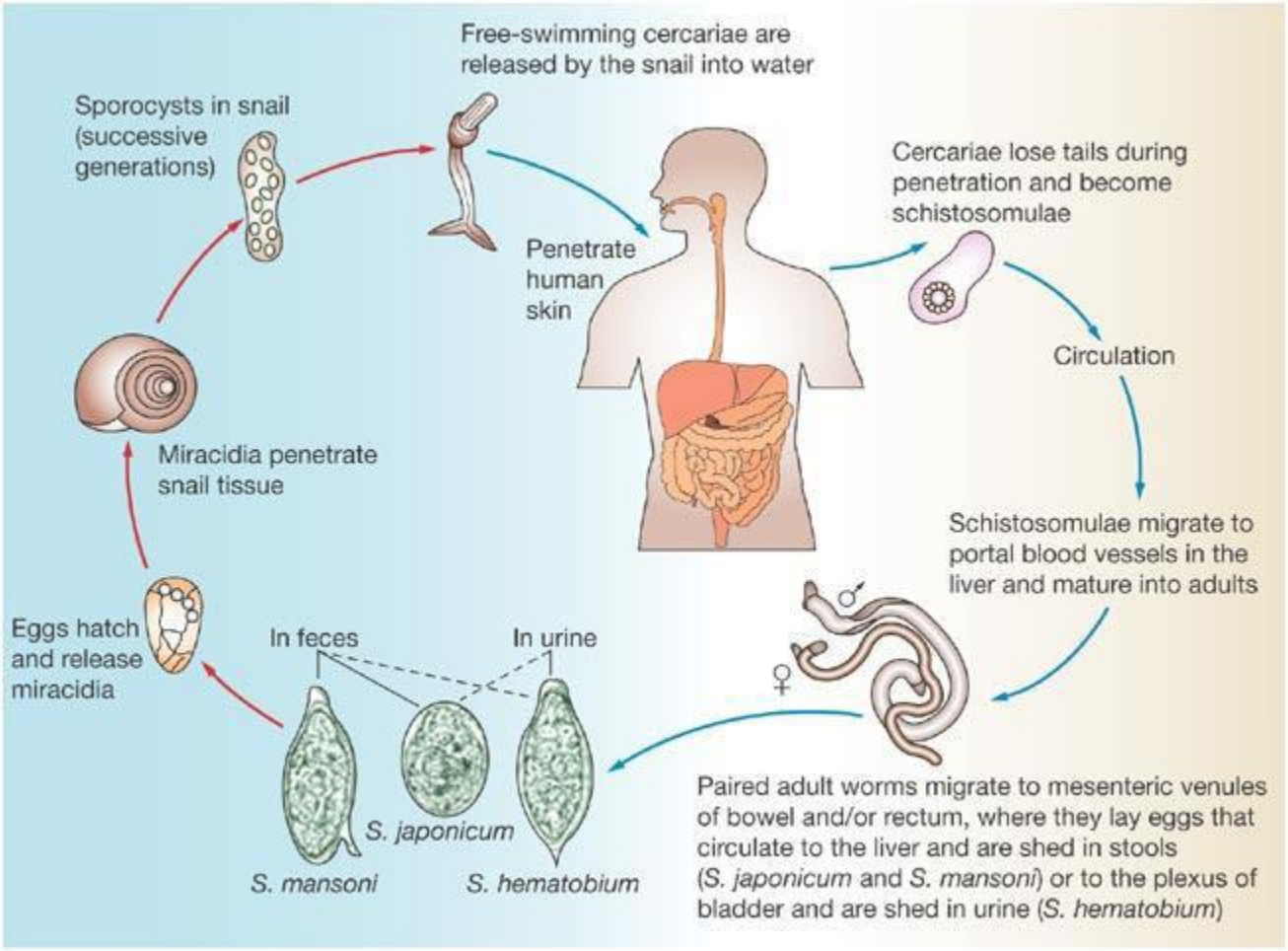


FIGURE 19-12

(a) Successive waves of parasitemia following infection with *Trypanosoma* result from antigenic shifts in the parasite's variable surface glycoprotein (VSG). Each variant that arises is unaffected by the humoral antibodies induced by the previous variant. (b) Antigenic shifts in trypanosomes occur by the duplication of gene segments encoding variant VSG molecules and their translocation to an expression site located close to the telomere. [Part (a) adapted from John Donelson, 1988, *The Biology of Parasitism*, Alan R. Liss.]


Free-swimming cercariae are released by the snail into water
Sporocysts in snail (successive generations)
Penetrate human skin
Cercariae lose tails during penetration and become schistosomulae
Circulation
Schistosomulae migrate to portal blood vessels in the liver and mature into adults
Paired adult worms migrate to mesenteric venules of bowel and/or rectum, where they lay eggs that circulate to the liver and are shed in stools (S. japonicum and S. mansoni) or to the plexus of bladder and are shed in urine (S. hematobium)
In feces
In urine
S. japonicum
S. mansoni
S. hematobium
Eggs hatch and release miracidia
Miracidia penetrate snail tissue

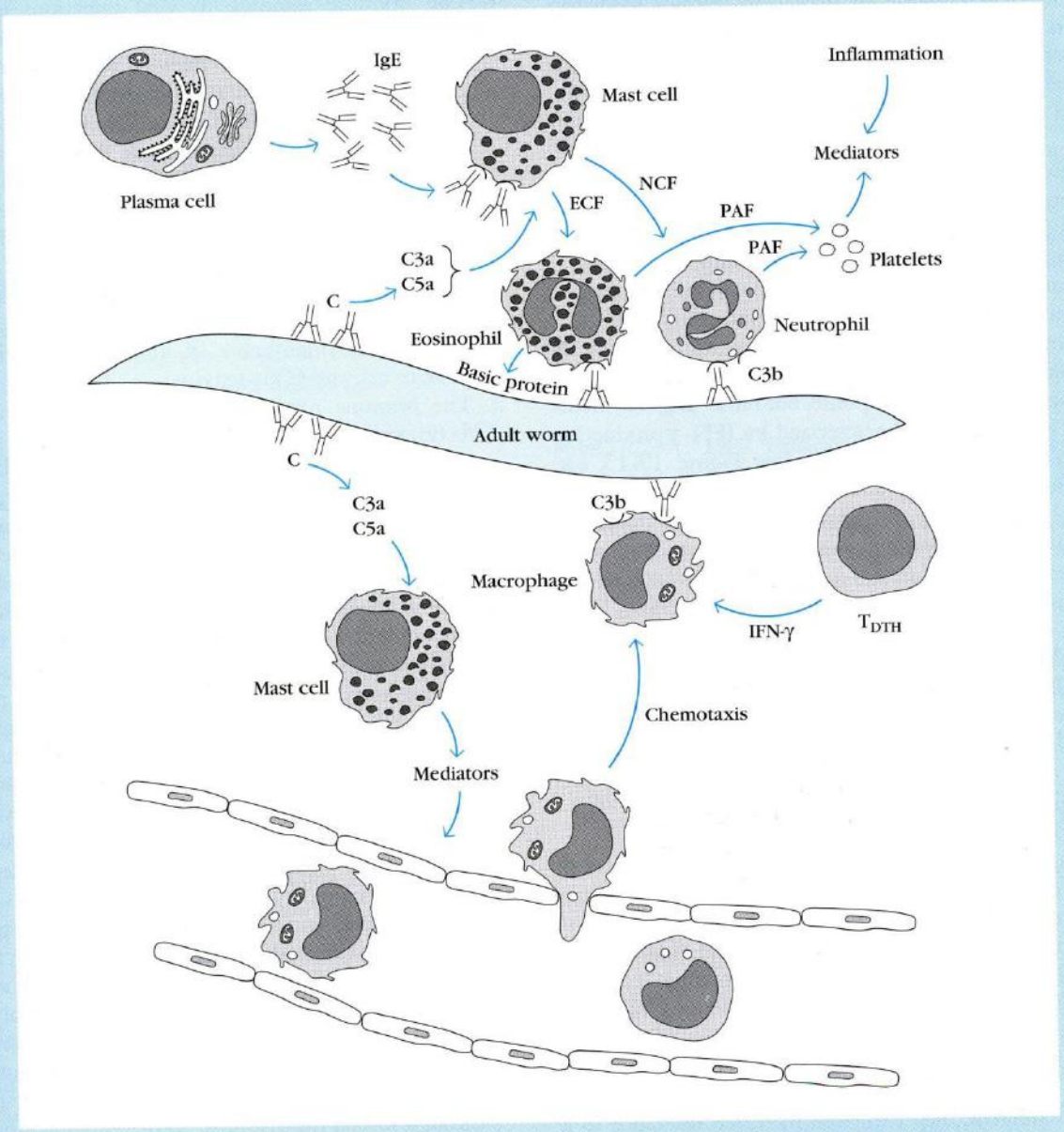


FIGURE 19-13

Overview of the immune response generated against *Schistosoma mansoni*. The response includes an IgE humoral component (*top*) and cell-mediated component involving T_{DTH} cells (*bottom*). C = complement; ECF = eosinophil chemotactic factor; NCF = neutrophil chemotactic factor; PAF = platelet-activating factor.

AQUISITION OF IMMUNITY THROUGH PASSIVE AND ACTIVE IMMUNIZATION

TYPE	ACQUIRED THROUGH
Passive immunization	Natural maternal antibody Artificial immune serum
Active immunization	Natural infection Artificial infection: Attenuated organisms Inactivated organisms Purified microbial macromolecules Cloned microbial antigens (alone or in vectors) Synthetic peptides Anti-idiotype antibodies Multivalent complexes

COMPARISON OF ATTENUATED (LIVE) AND INACTIVATED (KILLED) VACCINES

CHARACTERISTIC	ATTENUATED VACCINE	INACTIVATED VACCINE
Production	Selection for avirulent organisms: virulent pathogen is grown under adverse culture conditions or prolonged passage of a virulent human pathogen in different hosts	Virulent pathogen is inactivated by chemicals or irradiation with γ-rays
Booster requirement	Generally requires only a single booster	Requires multiple boosters
Relative stability	Less stable	More stable (advantageous for Third World countries where refrigeration is limited)
Type of immunity induced	Produces humoral and cell-mediated immunity	Produces mainly humoral immuni[illegible]
Reversion tendency	May revert to virulent form	Cannot revert to virulent form

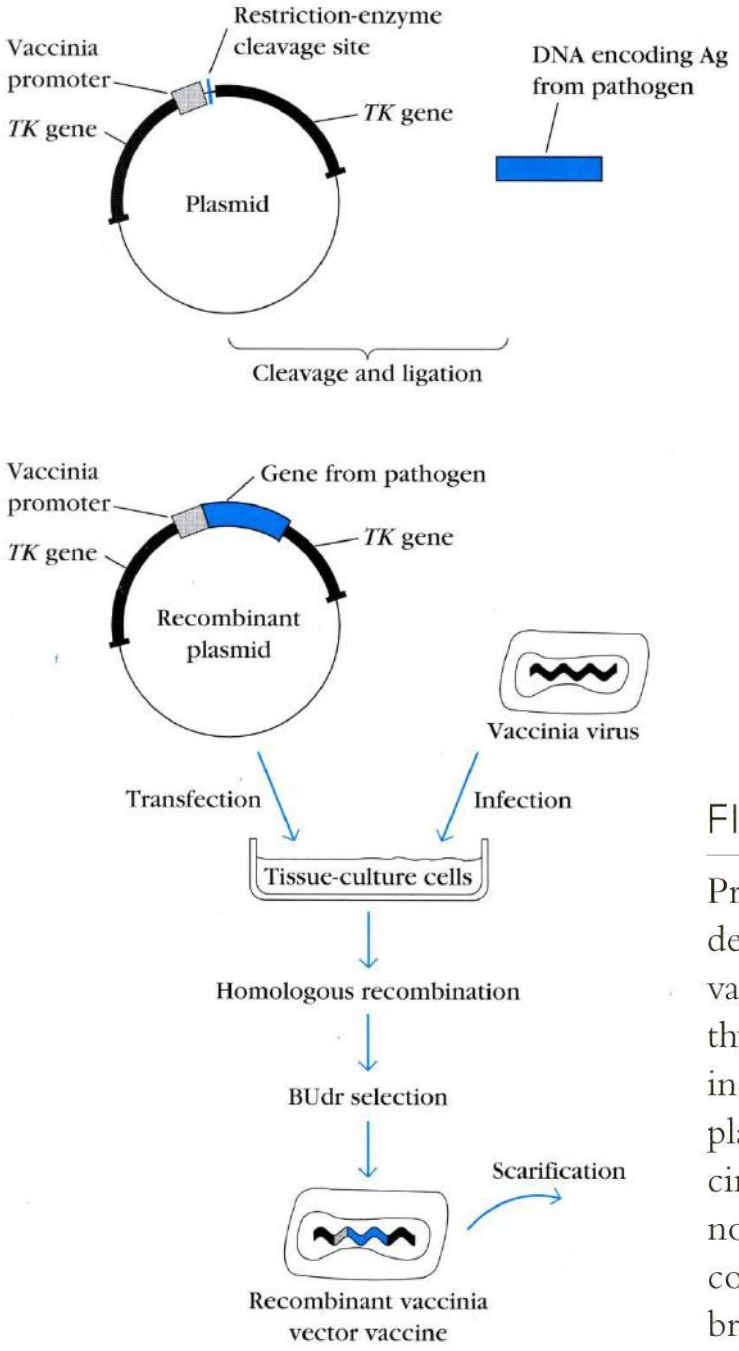


FIGURE 18-4

Production of vaccinia vector vaccine. The gene encoding the desired antigen (blue) is inserted into a plasmid vector adjacent to a vaccinia promoter (gray) and flanked on either side by the vaccinia thymidine kinase (*TK*) gene (black). When tissue-culture cells are incubated simultaneously with vaccinia virus and the recombinant plasmid, the antigen gene and promoter are inserted into the vaccinia virus genome by homologous recombination at the site of the nonessential *TK* gene, resulting in a TK^- recombinant virus. Cells containing the recombinant vaccinia virus are selected by addition of bromodeoxyuridine (BUdr), which kills TK^+ cells. [Adapted from B. Moss, 1985, *Immunol. Today* **6**:243.]

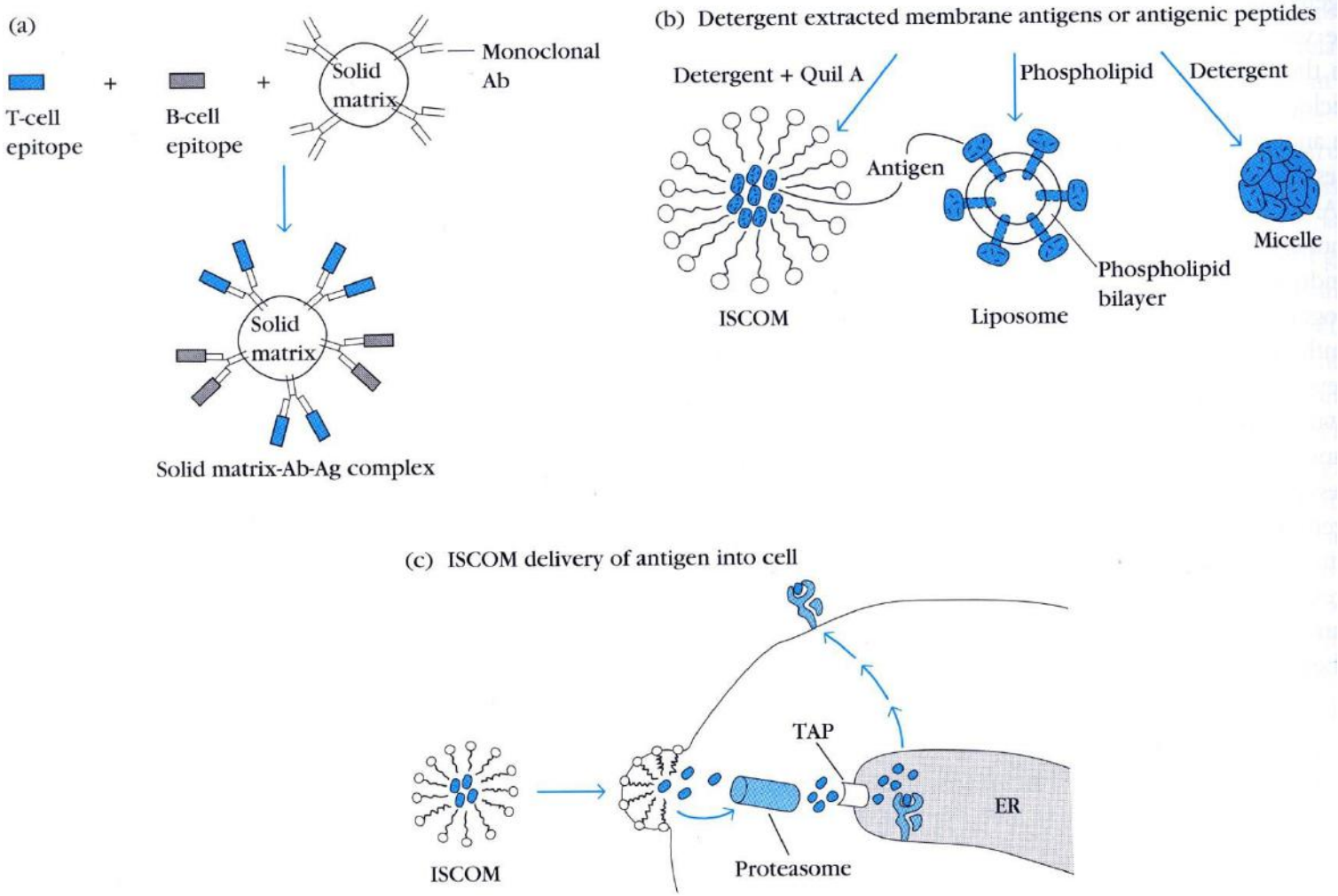


FIGURE 18-5

Multivalent subunit vaccines. (a) Solid matrix-antibody-antigen complexes can be designed to contain synthetic peptides representing both T-cell epitopes (blue) and B-cell epitopes (gray). (b) Protein micelles, liposomes, and immunostimulating complexes (ISCOMs) can all be prepared with extracted antigens or antigenic peptides (blue). In micelles and liposomes, the hydrophilic residues of the antigen molecules are oriented outward. In ISCOMs, the long fatty-acid tails of the external detergent layer are adjacent to the hydrophobic residues of the centrally located antigen molecules. (c) ISCOMs and liposomes can deliver antigens inside cells, so they mimic endogenous antigens. Subsequent processing by the cytosolic pathway and presentation with class I MHC molecules induces a cell-mediated response.

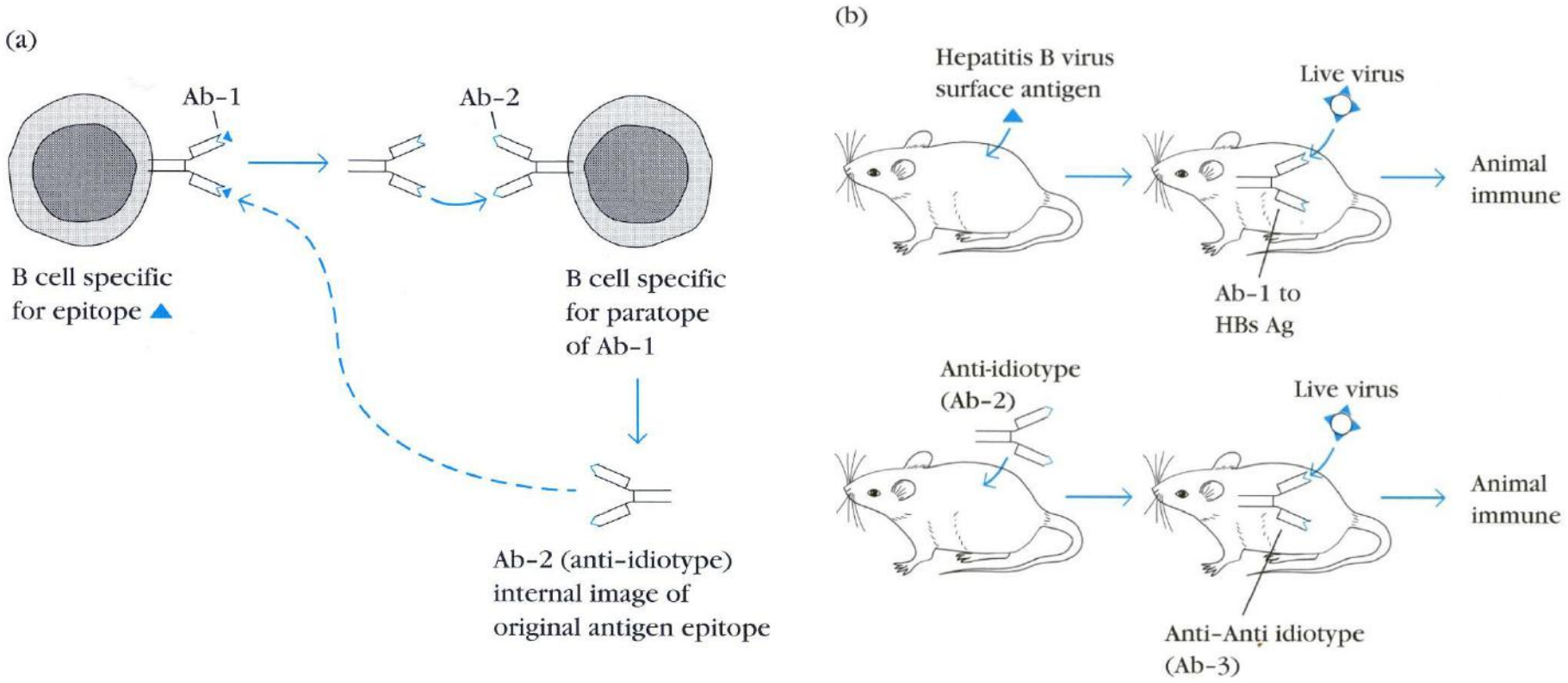


FIGURE 18-6

Use of anti-idiotype antibody as a vaccine. (a) The binding site on some anti-idiotype antibodies (Ab-2) resembles the structure of the epitope on the original antigen. Such anti-paratope antibody can interact with B cells specific for the original antigen, thus inducing production of more antibody against the antigen. (b) Immunization with anti-idiotype antibody has been shown experimentally to protect mice against hepatitis B virus without exposing the animal to the virus. HBsAg = hepatitis B surface antigen.