Lecture III

Antigens

Structure and function of immunoglobulins

POSTULATED MODE OF ACTION OF SOME COMMONLY USED ADJUVANTS

ADJUVANT	POSTULATED MODE OF ACTION			
	PROLONGS ANTIGEN PERSISTENCE	ENHANCES CO-STIMULATORY SIGNAL	INDUCES GRANULOMA FORMATION	STIMULATES LYMPHOCYTES NONSPECIFICALLY
Freund's incomplete adjuvant	+	+	+	–
Freund's complete adjuvant	+	++	++	–
Insoluble aluminum salts (alum)	+	?	+	–
Mycobacterium tuberculosis	–	?	+	–
Bordetella pertussis	–	?	–	+
Bacterial lipopolysaccharide (LPS)	–	+	–	+
Synthetic polynucleotides (poly IC/poly AU)	–	?	–	+

COMPARISON OF ANTIGEN RECOGNITION BY T CELLS AND B CELLS

CHARACTERISTIC	B CELLS	T CELLS
Interaction with antigen	Involves binary complex of membrane Ig and Ag	Involves ternary complex of T-cell receptor, Ag, and MHC molecule
Binding of soluble antigen	Yes	No
Involvement of MHC molecules	None required	Required to display processed antigen
Chemical nature of antigens	Protein, polysaccharide, lipid	Only protein
Epitope properties	Accessible, hydrophilic, mobile peptides containing sequential or nonsequential amino acids	Internal linear peptides produced by processing of antigen and capable of binding to MHC molecules

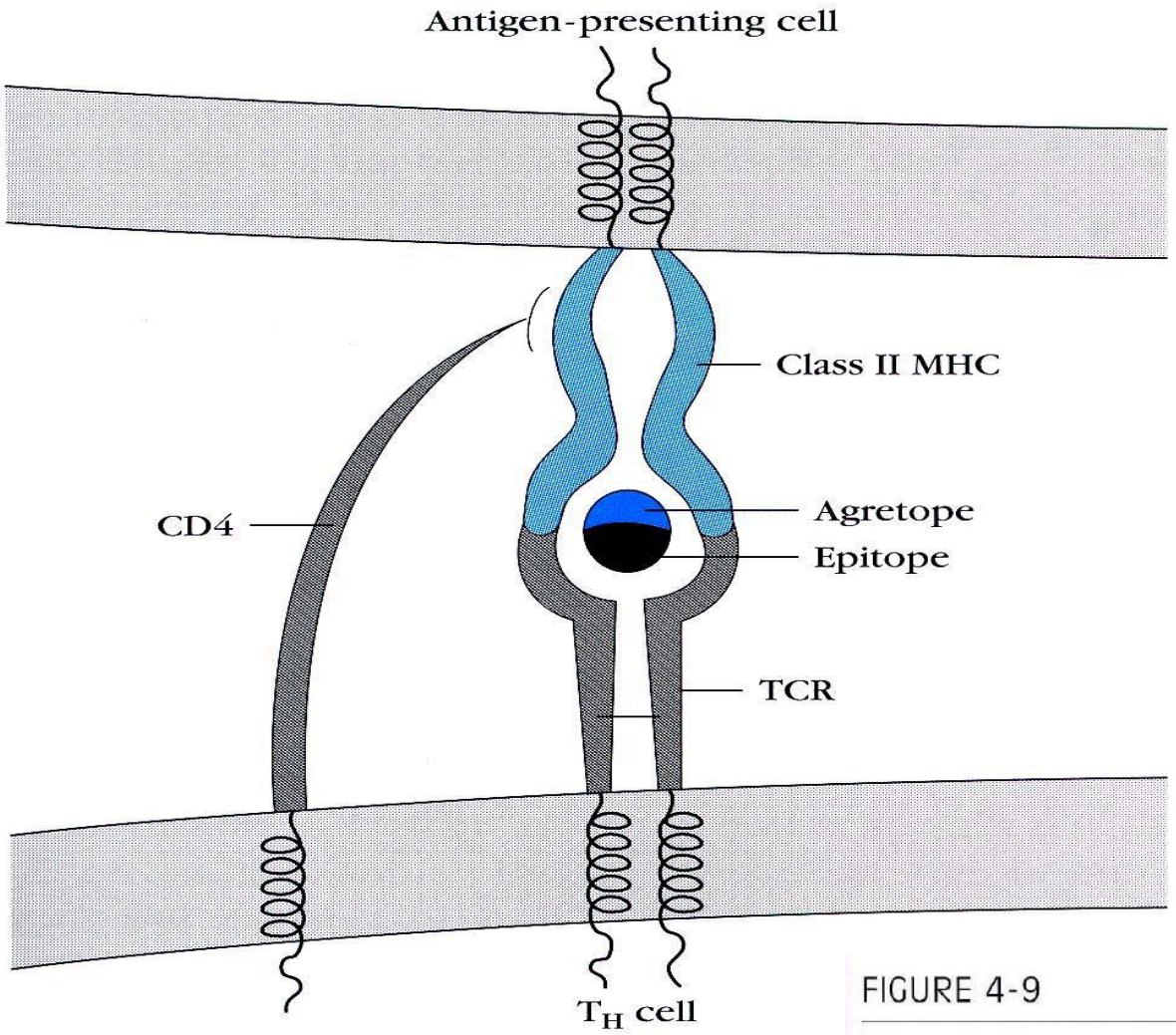
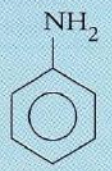
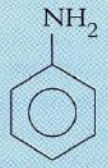
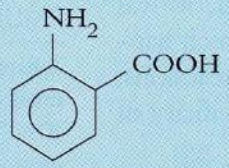
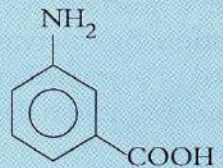


FIGURE 4-9

Schematic diagram of the ternary complex formed between a T-cell receptor (TCR) on a T_H cell, an antigen, and class II MHC molecule. Antigens that are recognized by T cells have two distinct interaction sites: an agretope, which interacts with an MHC molecule, and an epitope, which interacts with the T-cell receptor. As discussed in later chapters, CD4 on T_H cells also interacts with MHC molecules. T_C cells form similar ternary complexes with class I MHC molecules on target cells.

REACTIVITY OF ANTISERA WITH VARIOUS HAPTENS

ANTISERUM AGAINST	REACTIVITY WITH  AMINOBENZENE (ANILINE)	 *o*-AMINOBENZOIC ACID	 *m*-AMINOBENZOIC ACID	 *p*-AMINOBENZOIC ACID
Aminobenzene	+++	0	0	0
o-aminobenzoic acid	0	+++	0	0
m-aminobenzoic acid	0	0	++++	0
p-aminobenzoic acid	0	0	0	+++±

ANTISERUM AGAINST	REACTIVITY WITH  AMINOBENZENE (ANILINE)	 *P*-CHLOROAMINO-BENZENE	 *P*-TOLUIDINE	 *P*-NITROAMINO-BENZENE
Aminobenzene	+ ∴ ++	+	+±	+
p-chloroaminobenzene	+++	++	++	+±
p-toluidine	+±	++	++	+
p-nitroaminobenzene	+	++	+±	+

KEY: 0 indicates no reactivity; +++ and ++++ indicate strong reactivity; +±, and ++ indicate lesser degrees of reactivity

SOURCE: Based on K. Landsteiner, 1962, *The Specificity of Serologic Reaction,* Dover Press.
Modified by J. Klein, 1982, *Immunology: The Science of Self-Nonself Discrimination,* John Wiley Publishers.

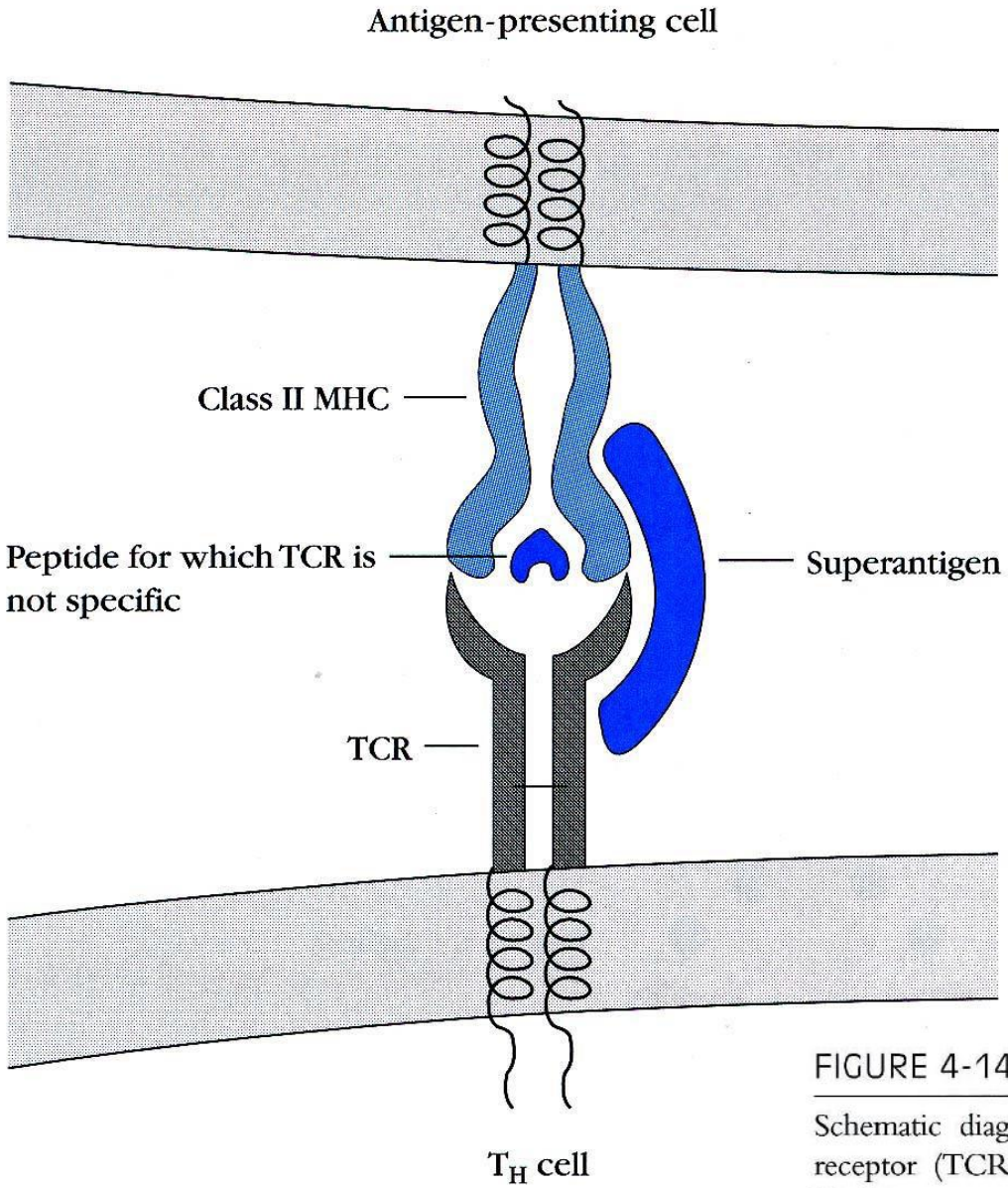


FIGURE 4-14

Schematic diagram of ternary complex formed between a T-cell receptor (TCR), superantigen, and MHC molecule. Superantigens bind to common sequences in class II MHC molecules and T-cell receptors that lie outside the normal antigen-binding sites (see Figure 4-9). T-cell activation by superantigens is not limited by the antigenic specificity of the T cell.

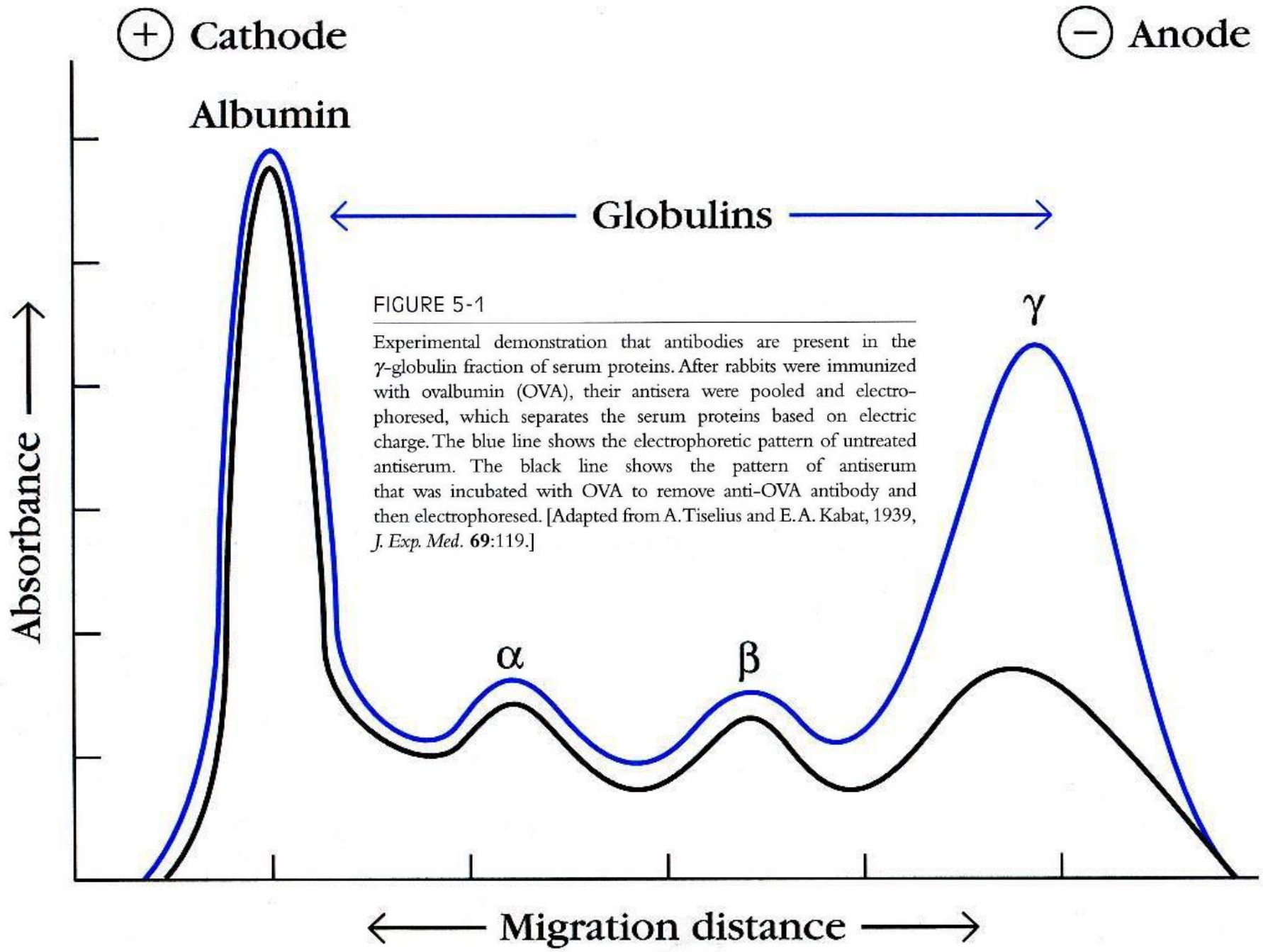


FIGURE 5-1

Experimental demonstration that antibodies are present in the γ-globulin fraction of serum proteins. After rabbits were immunized with ovalbumin (OVA), their antisera were pooled and electrophoresed, which separates the serum proteins based on electric charge. The blue line shows the electrophoretic pattern of untreated antiserum. The black line shows the pattern of antiserum that was incubated with OVA to remove anti-OVA antibody and then electrophoresed. [Adapted from A. Tiselius and E. A. Kabat, 1939, *J. Exp. Med.* **69**:119.]

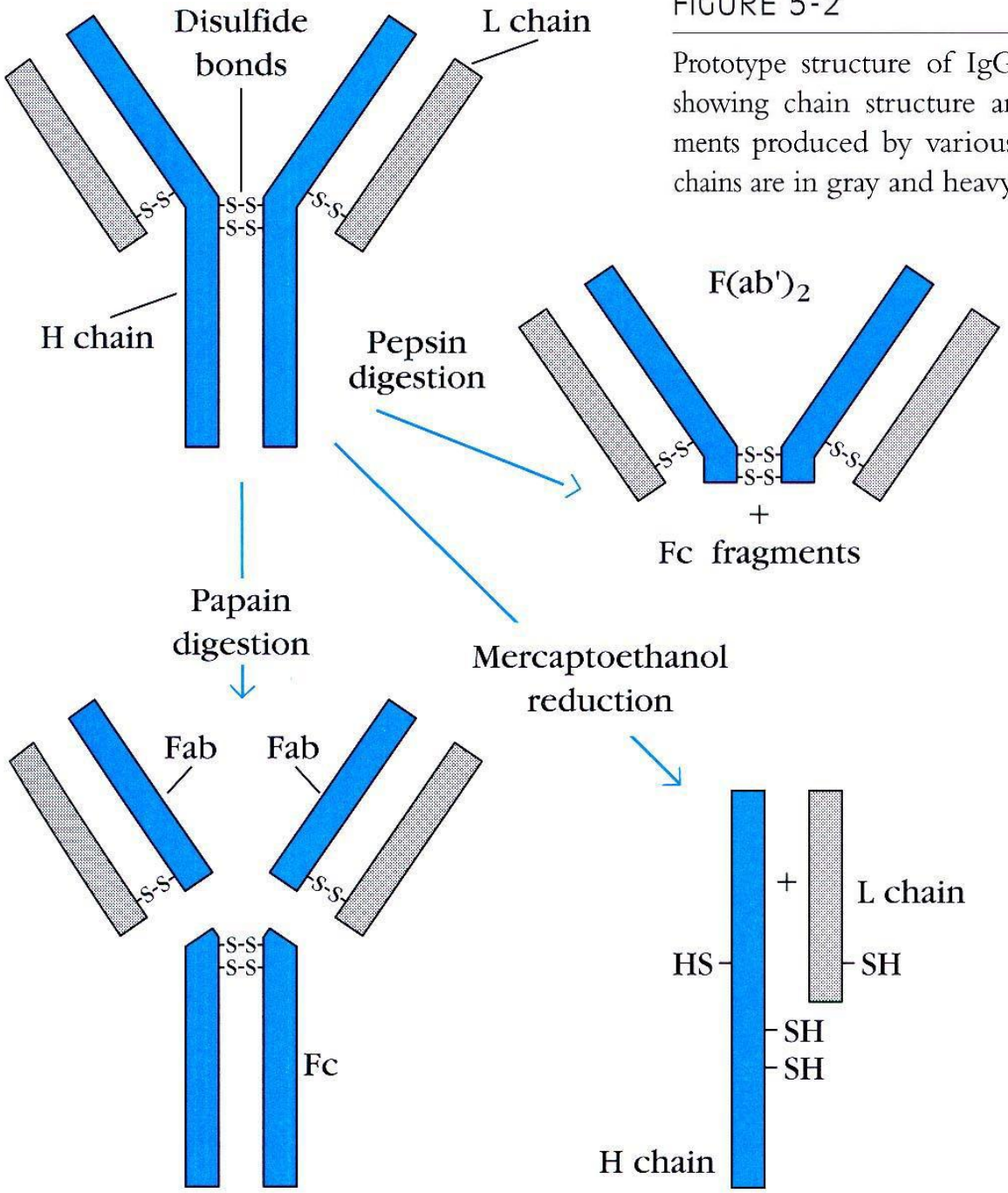


FIGURE 5-2

Prototype structure of IgG, proposed by Rodney Porter in 1962, showing chain structure and interchain disulfide bonds. The fragments produced by various treatments are also indicated. Light (L) chains are in gray and heavy (H) chains in blue.

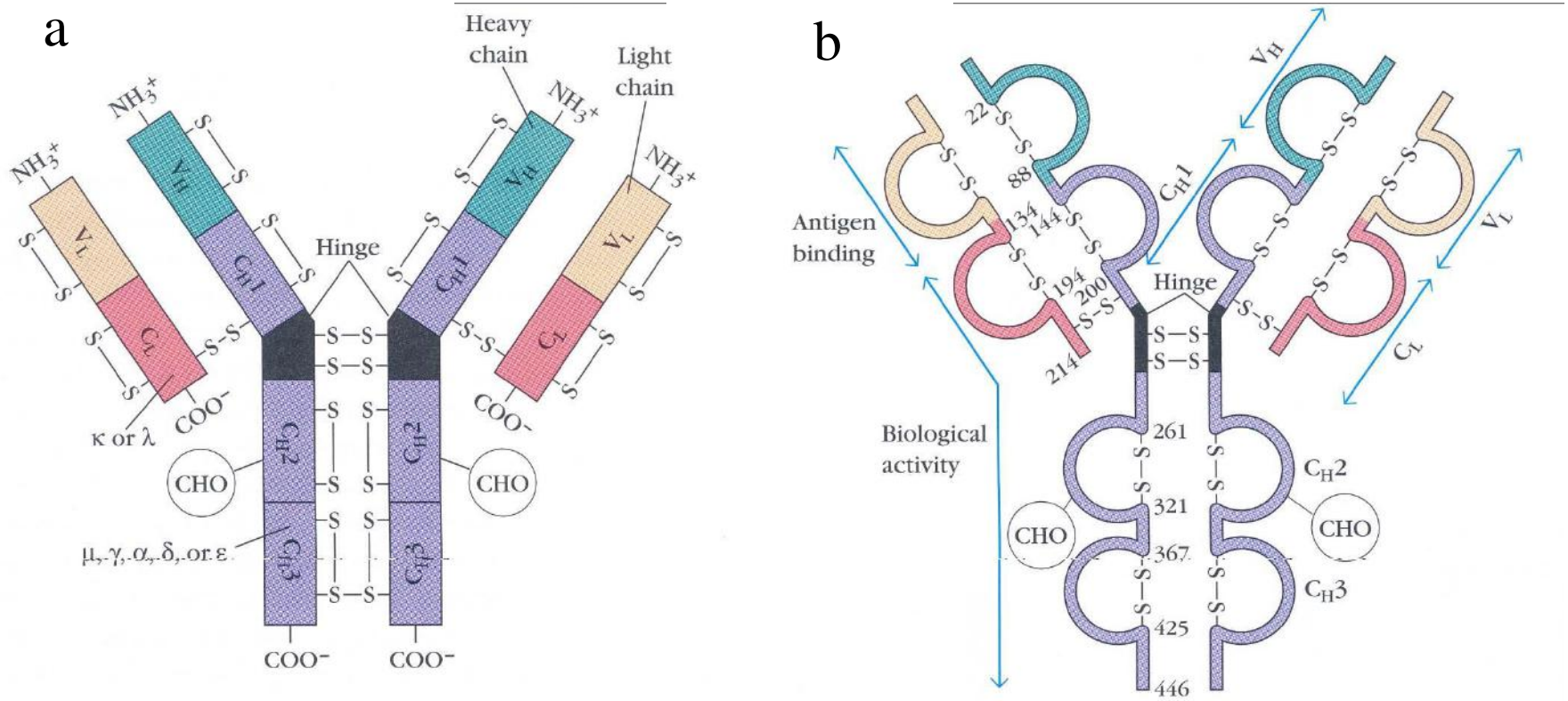


FIGURE 5-3

Schematic diagram of structure of immunoglobulins derived from amino acid sequencing studies. (a) Each heavy and light chain in an immunoglobulin molecule contains an amino-terminal variable (V) region (aqua and tan, respectively) that consists of 100–110 amino acids and differs from one antibody to the next. The remainder of the molecule—the constant (C) region (red and purple)—exhibits limited variation that defines the two light-chain subtypes and the five heavy-chain subclasses. Some heavy chains (γ, δ, and α) also contain a proline-rich hinge region (black). (b) Heavy and light chains are folded into domains, each containing about 110 amino acid residues and an intrachain disulfide bond that forms a 60-amino acid loop. The amino-terminal domains, corresponding to the V regions, function in antigen binding; effector functions are mediated by the other domains. The μ and ε heavy chains, which lack a hinge region (black), contain an additional domain in the central portion of the molecule.

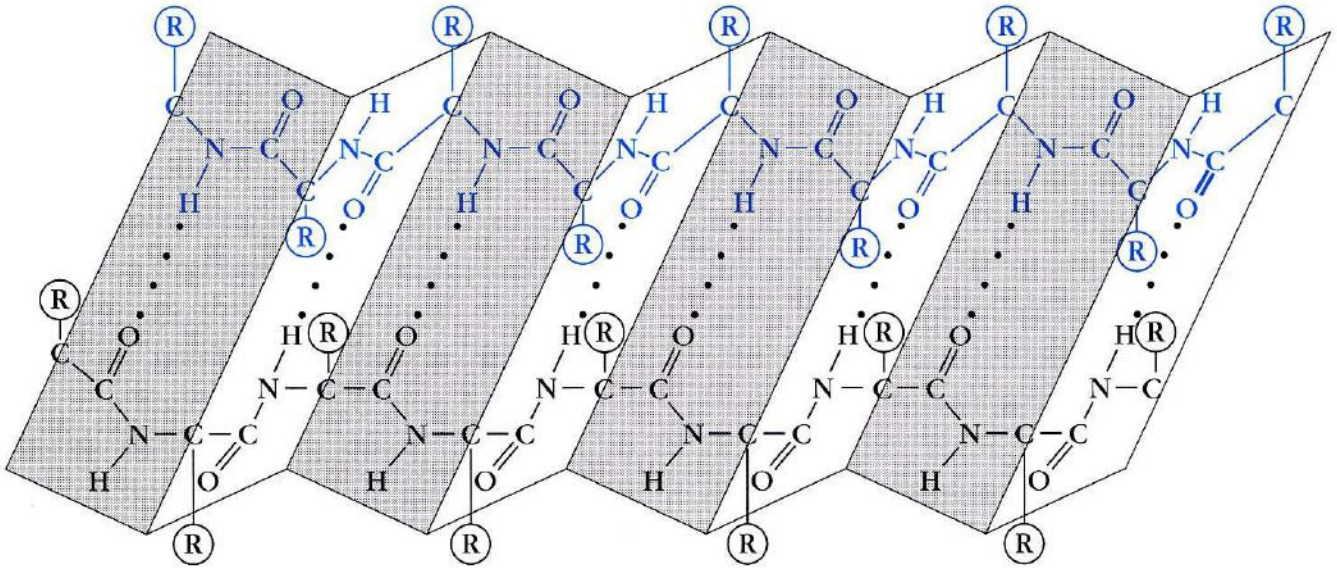


FIGURE 5-4

Structural formula of a β pleated sheet containing two antiparallel β strands. The structure is held together by hydrogen bonds between peptide bonds in neighboring chains. The amino acid side groups (R) are arranged perpendicular to the plane of the sheet. [Adapted from J. Darnell et al., 1990, *Molecular Cell Biology*, page 50, Scientific American Books, New York.]

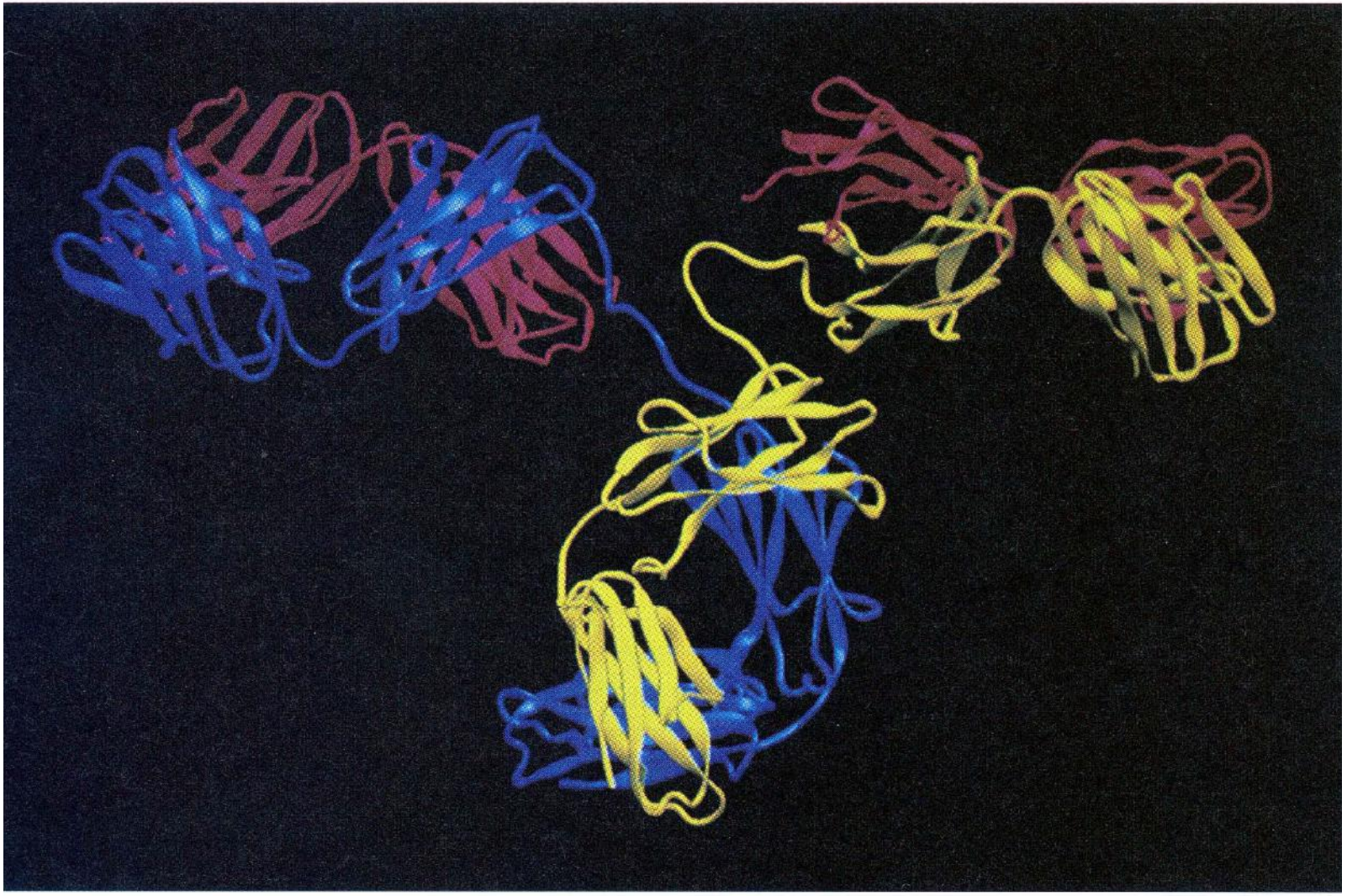


FIGURE 5-5

Ribbon representation of an intact monoclonal antibody depicting the heavy chains (yellow and blue) and light chains (red). The domains of the molecule composed of β pleated sheets are readily visible as is the extended conformation of the hinge region. [The laboratory of A. McPhearson provided this image based on x-ray crystallography data determined by L. J. Harris, 1992, *Nature* **360**:369.]

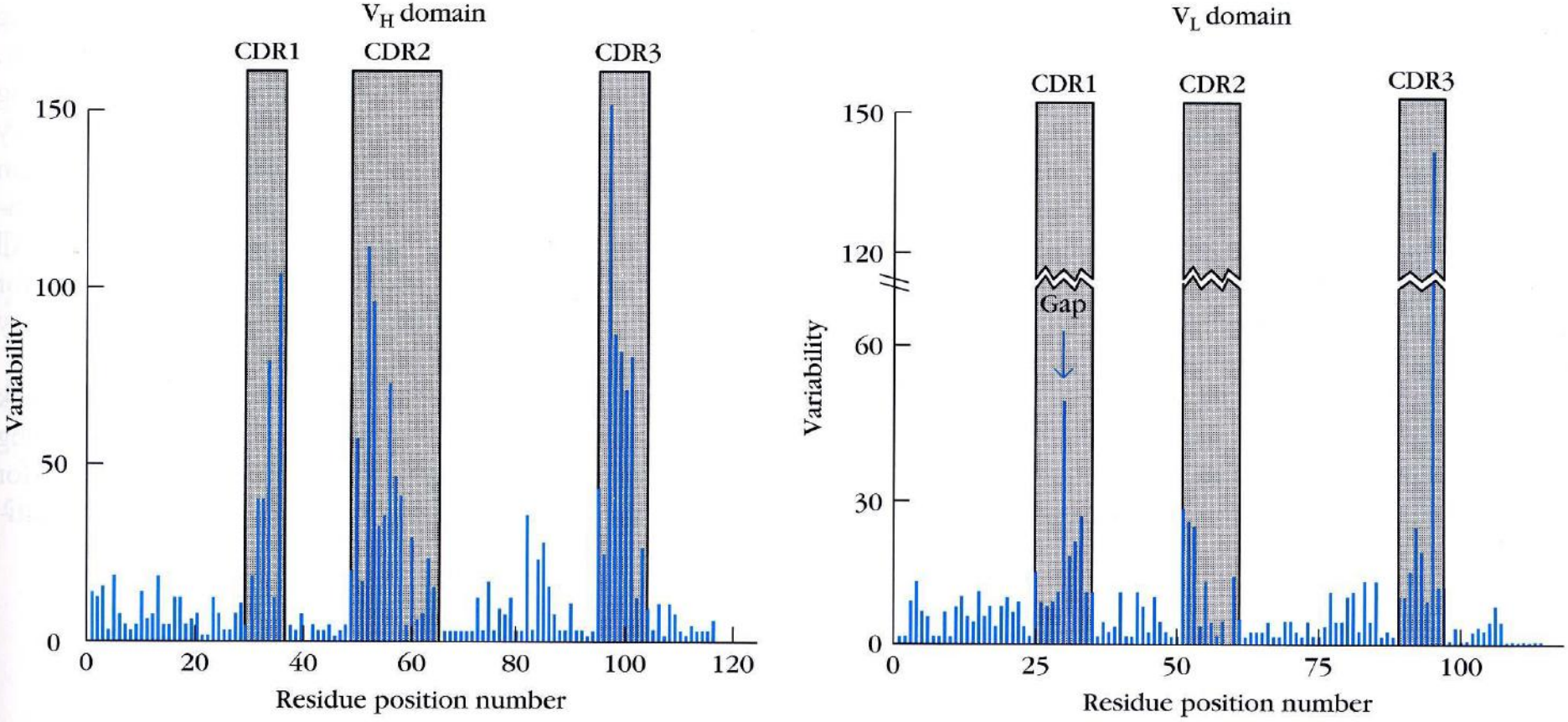


FIGURE 5-8

Relative variability of amino acid residues in the V_L and V_H domains of human antibodies with different specificities. Three hypervariable (HV) regions, also called complementarity-determining regions (CDRs), are present in both heavy- and light-chain V domains (blue). As shown in Figure 5-6 (*right*), the three HV regions in the light-chain V domain are brought into proximity in the folded structure. The same is true of the heavy-chain V domain. [Based on E.A. Kabat et al., 1977, *Sequence of Immunoglobulin Chains*, U.S. Dept. of Health, Education, and Welfare.]

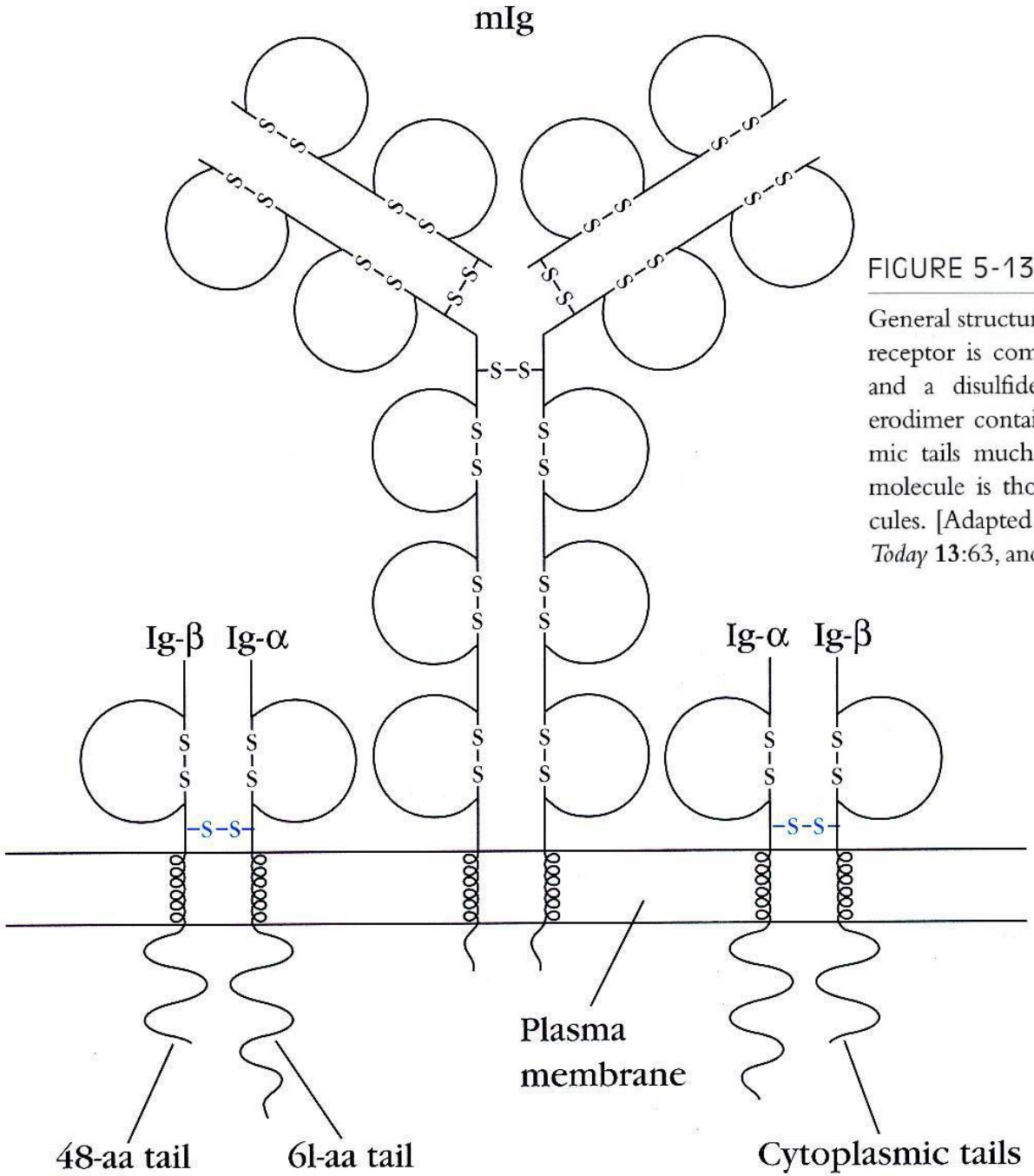


FIGURE 5-13

General structure of the B-cell receptor (BCR). This antigen-binding receptor is composed of membrane-bound immunoglobulin (mIg) and a disulfide-linked heterodimer called Ig-α/Ig-β. The heterodimer contains the immunoglobulin-fold structure and cytoplasmic tails much longer than those in mIg. As depicted, each mIg molecule is thought to be associated with two heterodimer molecules. [Adapted from A. D. Keegan and W. E. Paul, 1992, *Immunol. Today* **13**:63, and M. Reth, 1992, *Annu. Rev. Immunol.* **10**:97.]

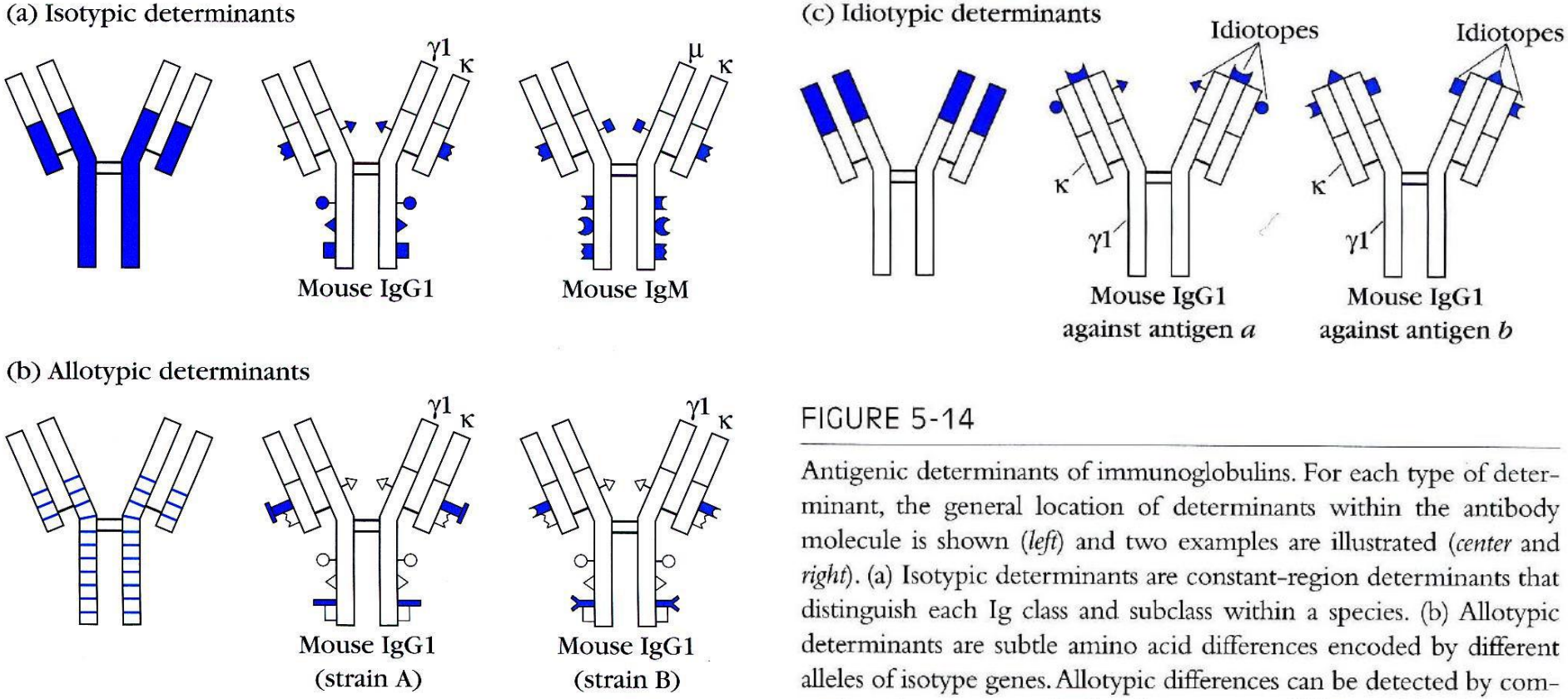


FIGURE 5-14

Antigenic determinants of immunoglobulins. For each type of determinant, the general location of determinants within the antibody molecule is shown (*left*) and two examples are illustrated (*center* and *right*). (a) Isotypic determinants are constant-region determinants that distinguish each Ig class and subclass within a species. (b) Allotypic determinants are subtle amino acid differences encoded by different alleles of isotype genes. Allotypic differences can be detected by comparing the same antibody class among different inbred strains. (c) Idiotypic determinants are generated by the conformation of the amino acid sequences of the heavy- and light-chain variable region specific for each antigen. Each individual determinant is called an idiotope, and the sum of the individual idiotopes is the idiotype.

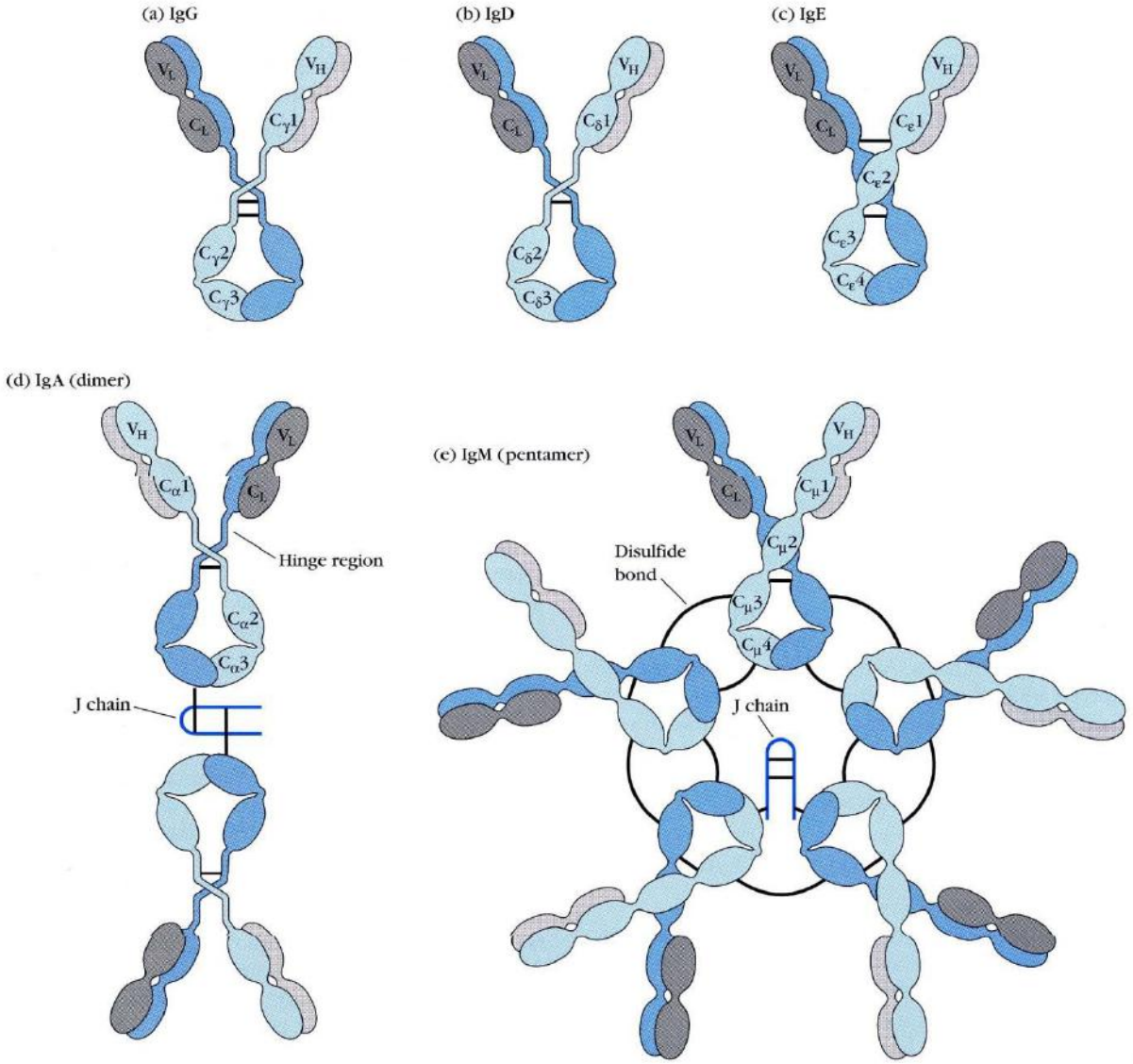


FIGURE 5-15

General structures of the five major classes of secreted antibody. Light chains are shown in shades of gray and heavy chains in shades of blue; disulfide bonds are indicated by thick black lines. Note that the IgG, IgA, and IgD heavy chains contain four domains and a hinge region, whereas the IgM and IgE heavy chains contain five domains but no hinge region. The polymeric forms of IgM and IgA contain a polypeptide, known as the J chain, that is linked by two disulfide bonds to the Fc region in two different monomers. Serum IgM is always a pentamer; most serum IgA exists as a monomer, although some dimers, trimers, and even tetramers sometimes are present. Not shown in these figures are intrachain disulfide bonds and disulfide bonds linking light and heavy chains (see Figure 5-3).

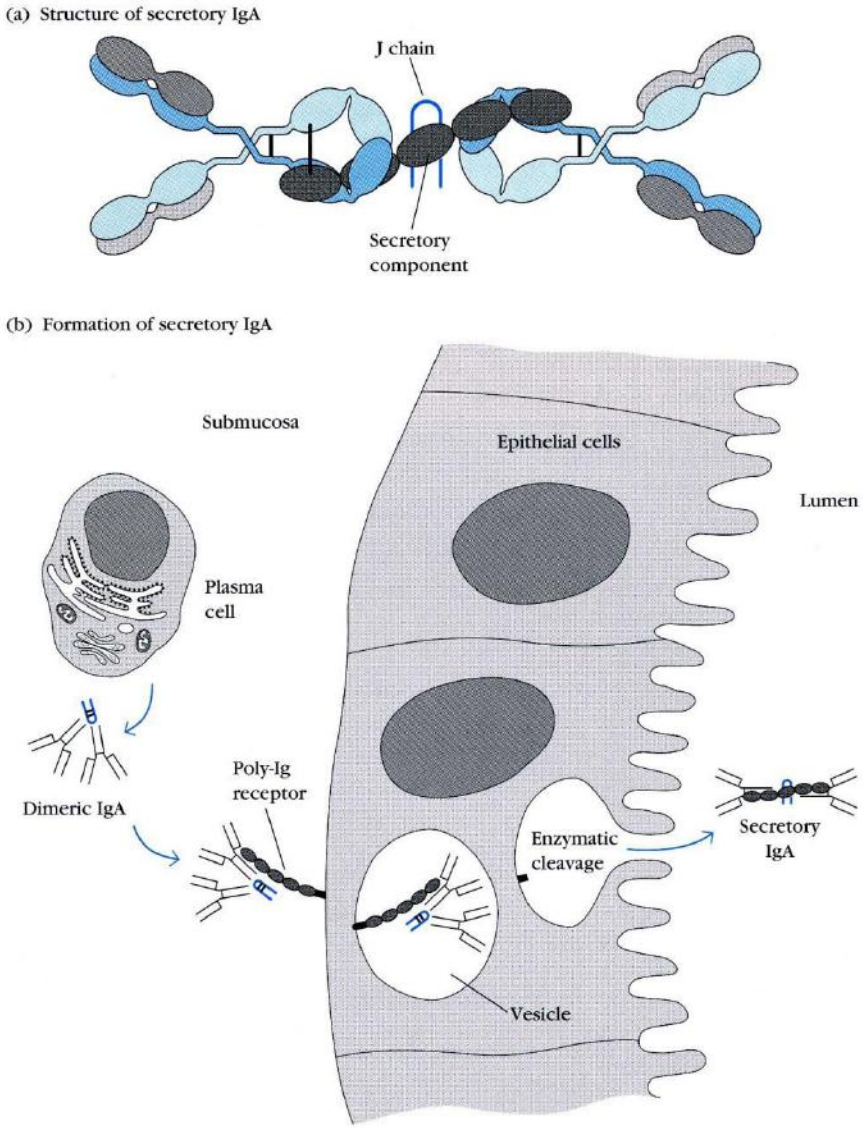


FIGURE 5-17

Structure and formation of secretory IgA. (a) Secretory IgA consists of at least two IgA molecules, which are covalently linked via a J chain and covalently associated with the secretory component. The secretory component contains five Ig-like domains and is linked to dimeric IgA by a disulfide bond between its fifth domain and one of the IgA heavy chains. (b) Secretory IgA is formed during transport through mucous membrane epithelial cells. Dimeric IgA binds to a poly-Ig receptor on the basolateral membrane of an epithelial cell and is internalized by receptor-mediated endocytosis. After transport of the receptor-IgA complex to the luminal surface, the poly-Ig receptor is enzymatically cleaved, releasing the secretory component bound to the dimeric IgA.

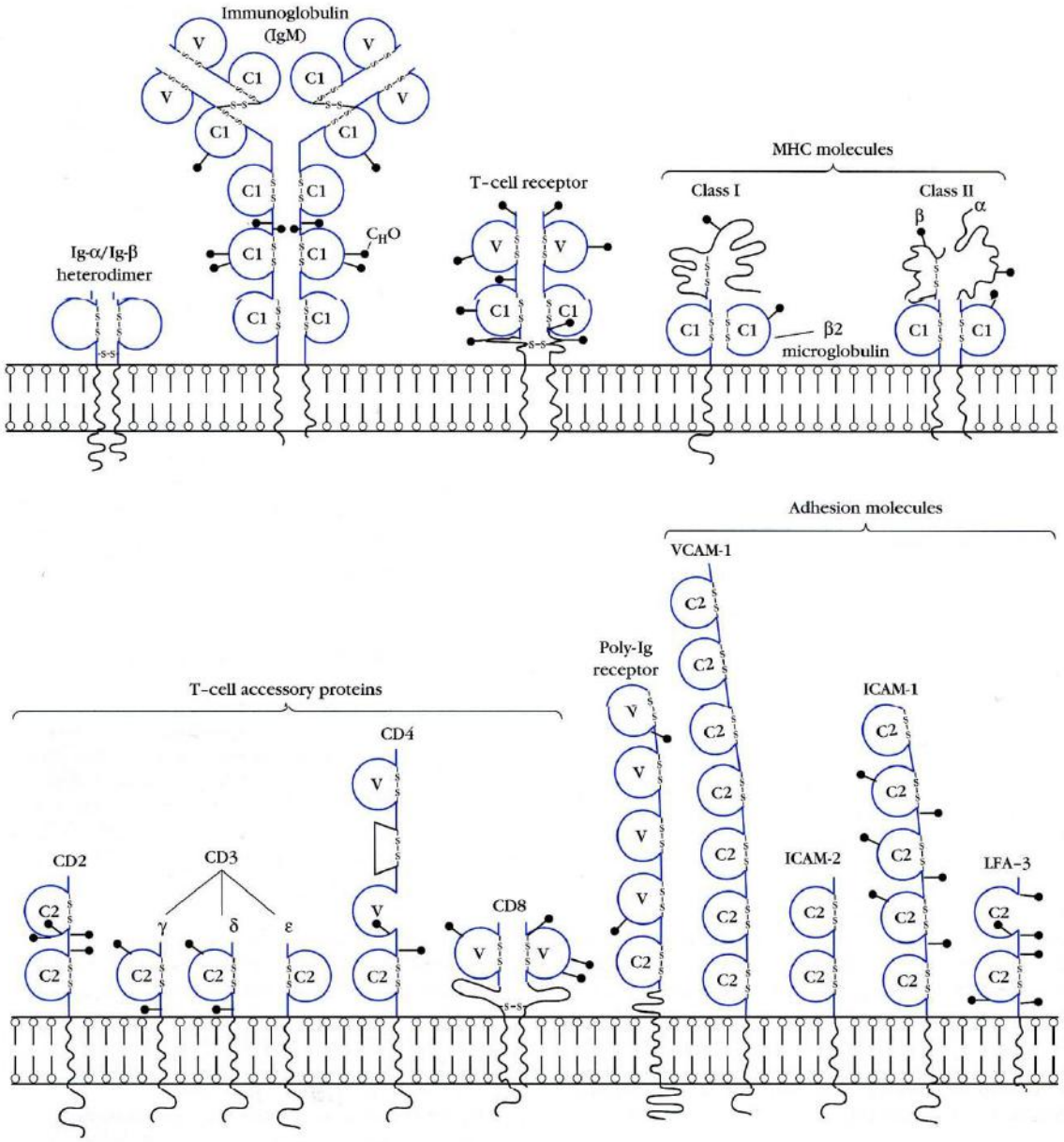


FIGURE 5-19

Some members of the immunoglobulin superfamily, a group of structurally related, usually membrane-bound glycoproteins. The loops shown in blue represent those portions of the molecule with the characteristic Ig-fold structure. In all cases the carboxyl-terminal end of the molecule is anchored in the membrane. Domains labeled C2 are shorter than the classical immunoglobulin constant-region domain (labeled C1) and exhibit equal homology with both variable- and constant-region domains.