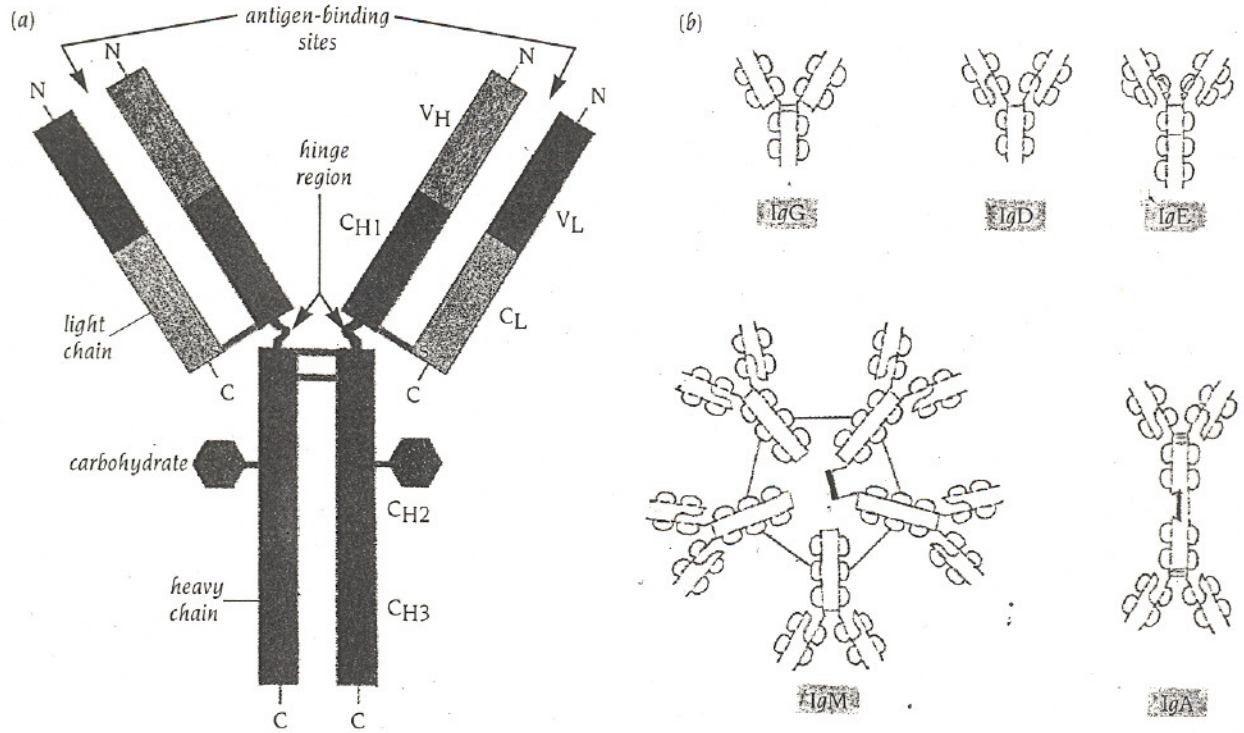


Figure 15.2 (a) The immunoglobulin molecule, IgG, is built up from two copies each of two different polypeptide chains, heavy (H) and light (L). The L chain folds into two domains: V_L with variable sequence between different IgG molecules and C_L with constant sequence. The H chain folds into four domains: one variable V_H and three constant domains, C_{H1}, C_{H2}, and C_{H3}. Disulfide bridges connect the four chains. The antigen-binding sites are at the ends of the variable domains. (b) Schematic polypeptide chain structure of different immunoglobulin molecules. IgM is a pentamer where the heavy chains have one variable domain and four constant domains. An additional polypeptide chain, the J chain, (black bar) is associated with the pentameric molecule. The J chain also links two units to form the dimeric IgA. IgG, IgD, and IgE are monomeric immunoglobulin molecules.

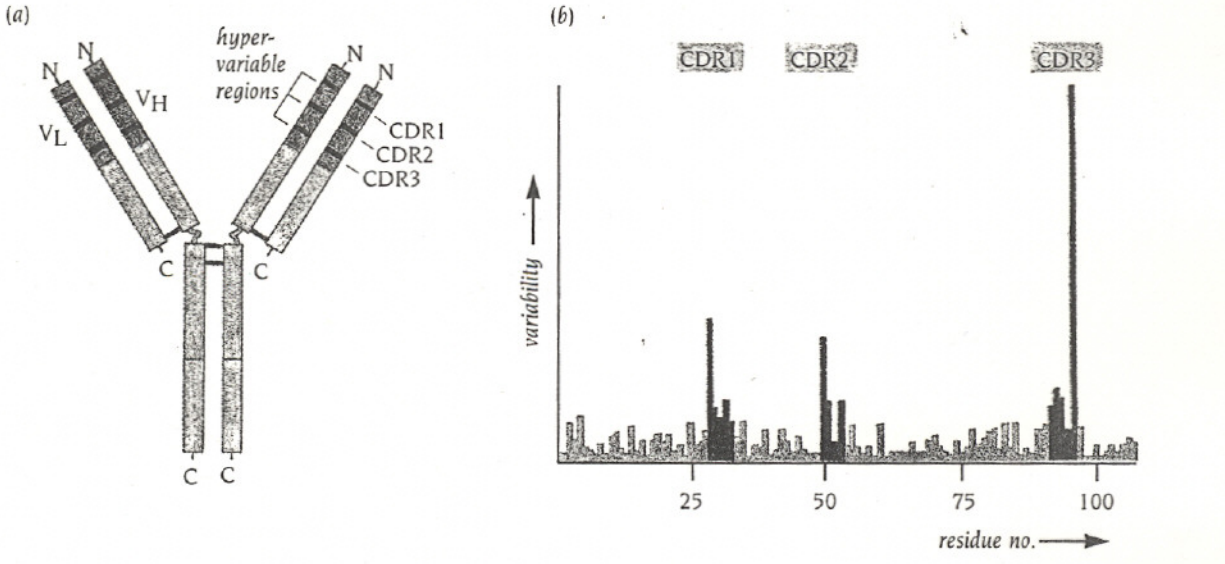
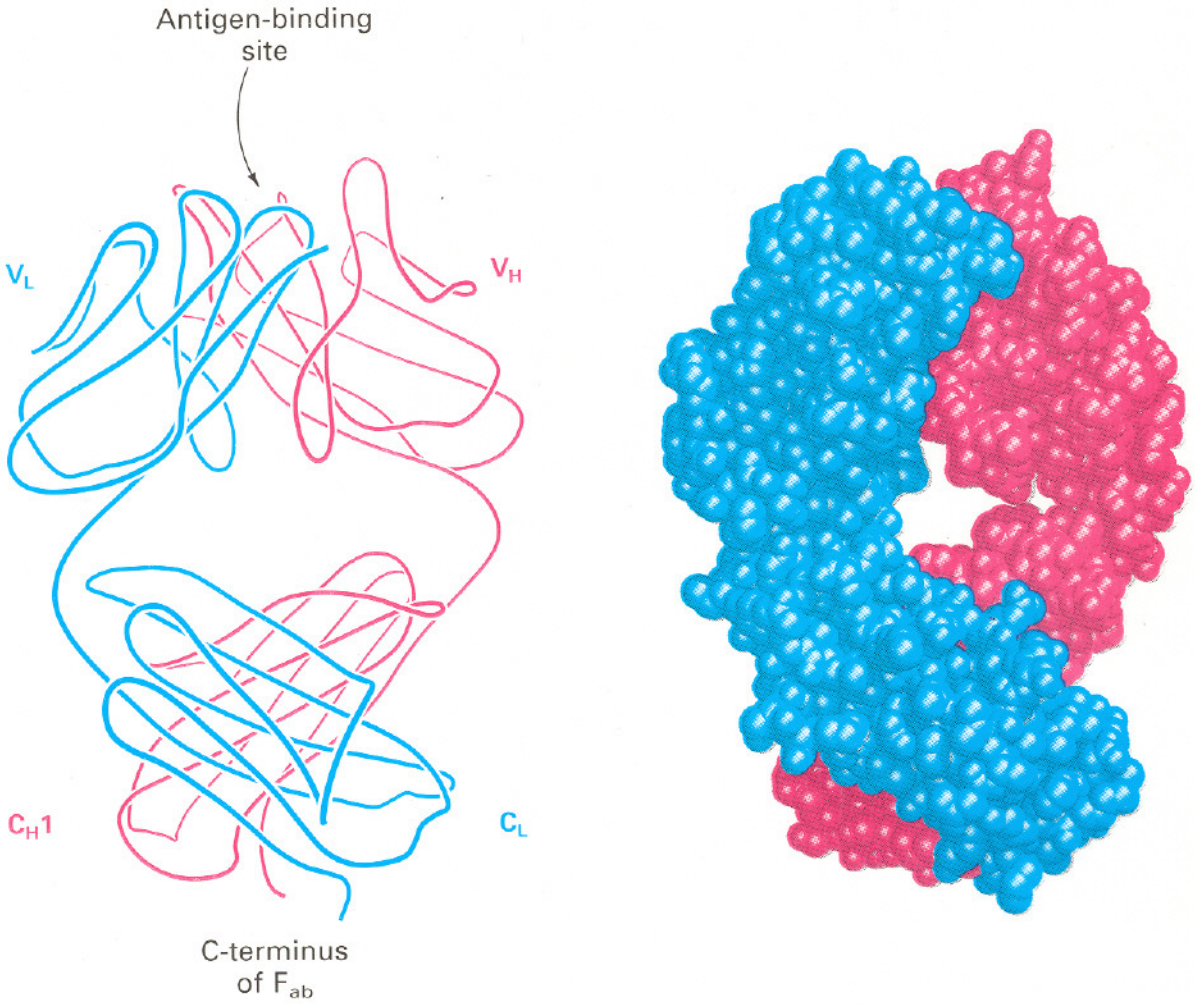
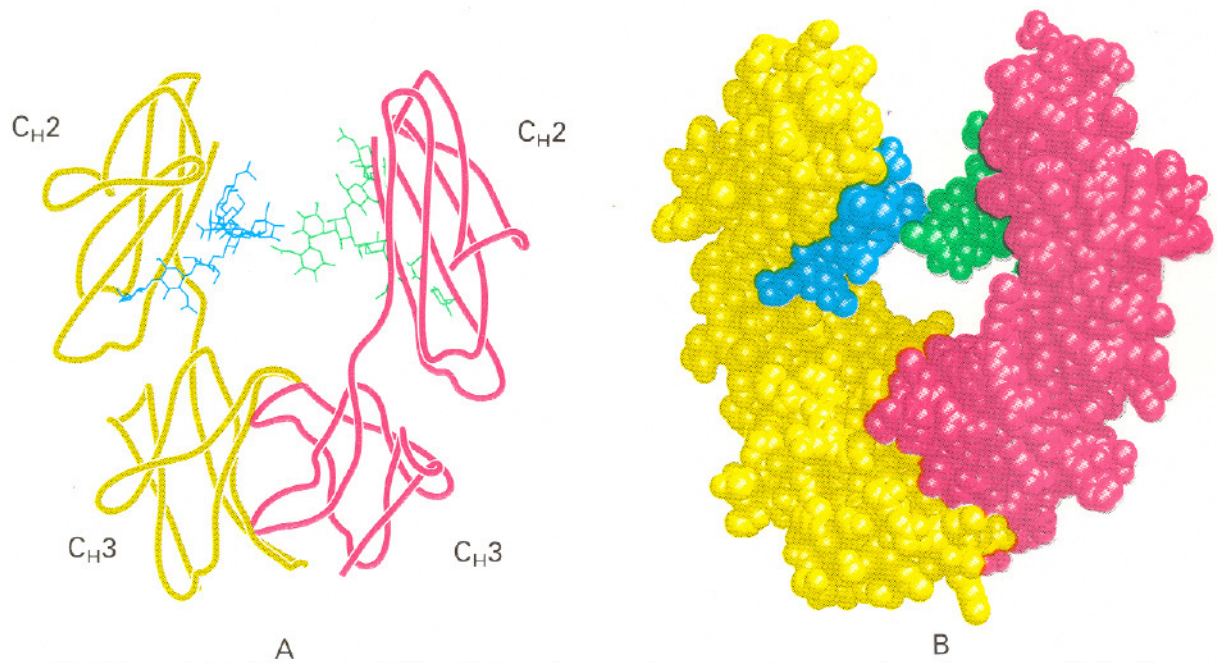


Figure 15.3 Certain regions within the 110 amino acid variable domains show a high degree of sequence variation. These regions determine the antigen specificity and are called hypervariable regions or complementarity determining regions, CDR (a). There are three such regions, CDR1–CDR3, in each variable domain. The sequences of a large number of variable domains in L chains have been compared, and the sequence variability is plotted as a function of residue number along the polypeptide chain in (b). The three large peaks in this diagram correspond to the three hypervariable regions in (a): CDR1–CDR3. [(b) Adapted from T.T. Wu and E.A. Kabat, *J. Exp. Med.* 132: 211–250, 1970.]



Structure of the F_{ab} unit of an antibody molecule



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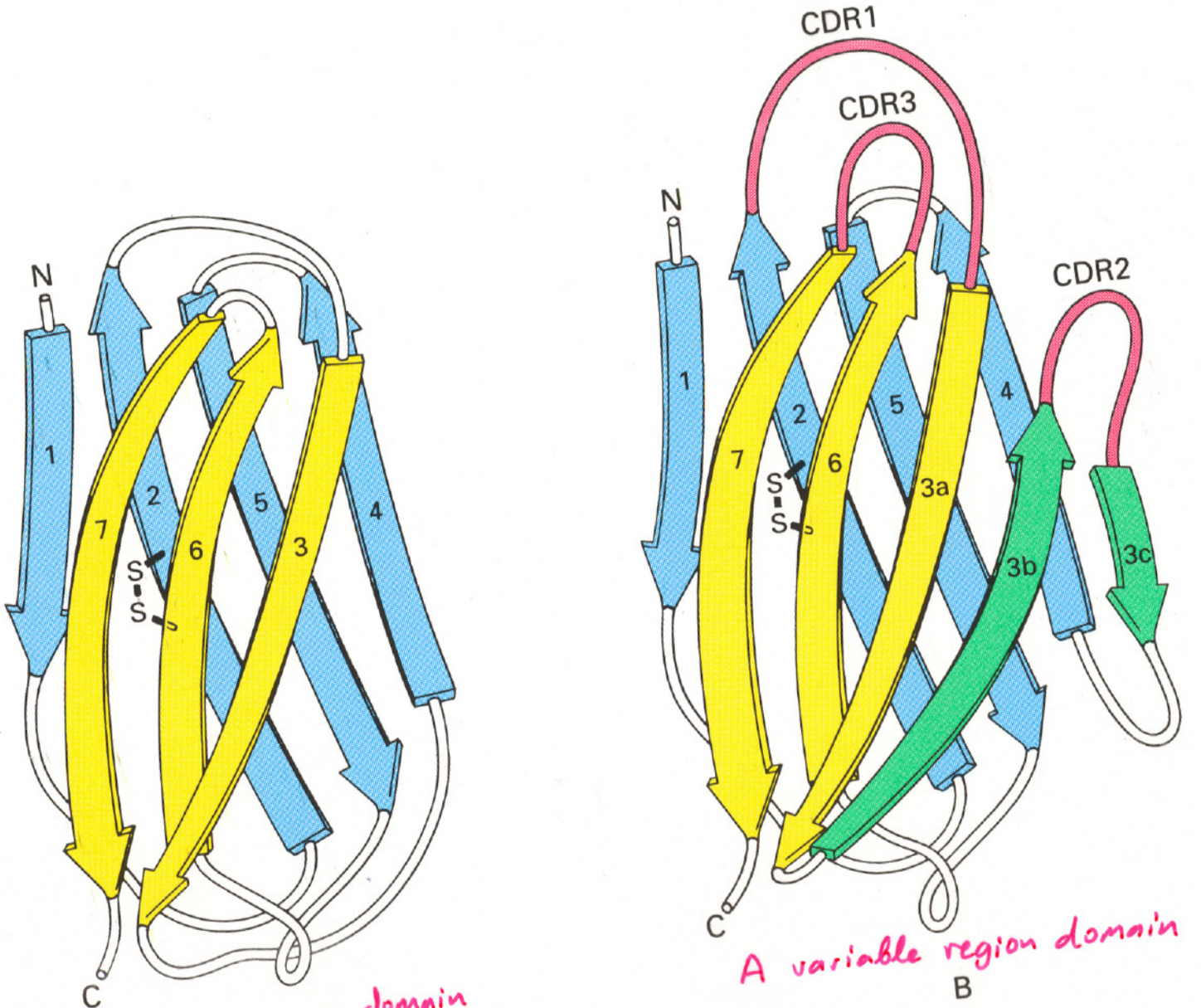
Structure of the F_c unit of an antibody molecule



A constant region domain

A variable region domain

Figure 14-14, page 370

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Immunoglobulin domains consist. of two sheets of antiparallel β strands

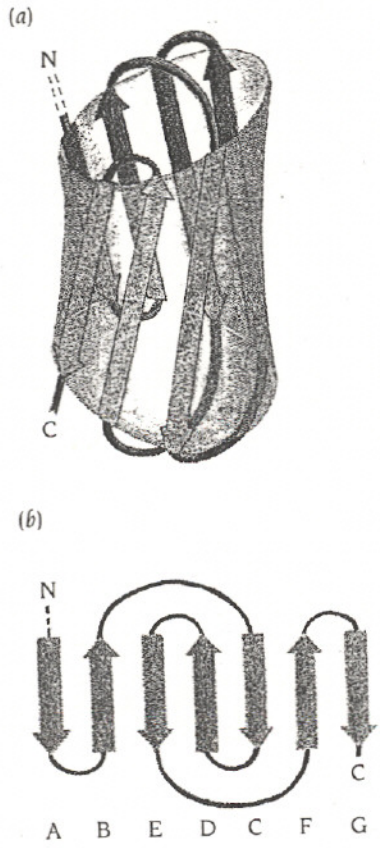


Figure 15.7 The constant domains of immunoglobulins are folded into a compressed antiparallel β barrel built up from one three-stranded β sheet packed against a four-stranded sheet (a). A topological diagram (b) shows the connected Greek key motifs of this fold.

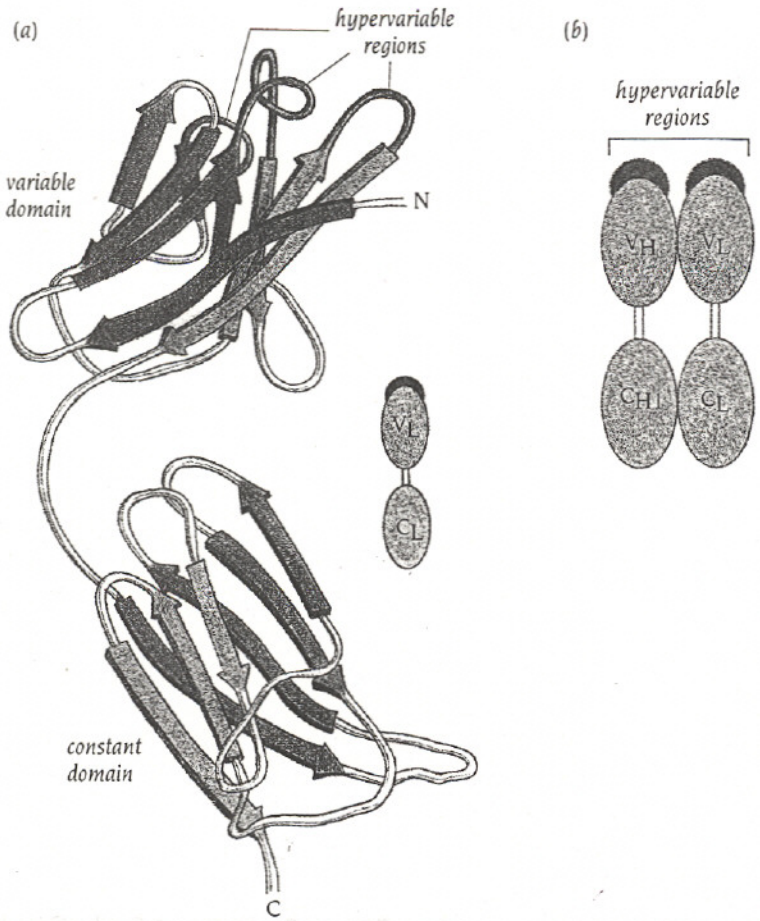
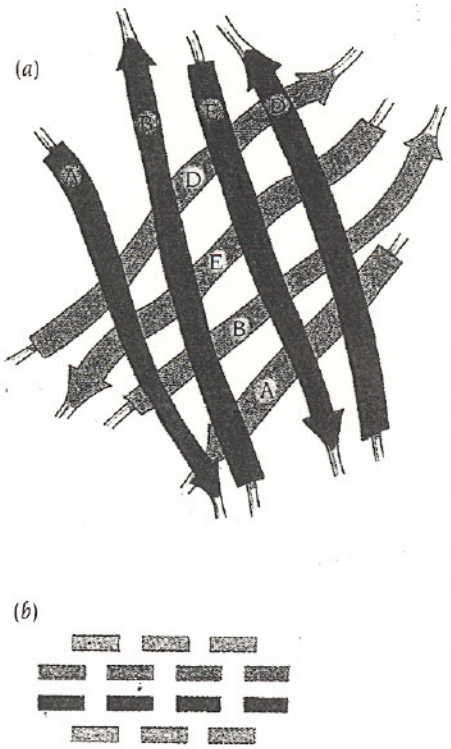


Figure 15.9 (a) The variable and constant domains in the light chain of immunoglobulins are folded into two separate globular units. In both domains the four-stranded β sheet is blue and the other sheet is green. The hypervariable CDR regions are at one end of this elongated molecule. (b) In the Fab fragment, as well as in the intact immunoglobulin molecule, the domains associate pairwise so that V_H interacts with V_L and C_{H1} with C_L. By this interaction the CDR regions of both variable domains are brought close to each other and together form the antigen-binding site.

Figure 15.10 Schematic diagrams of the packing of the four-stranded β sheets of the constant domains C_{H1} and C_L in an Fab fragment of IgG. The sheets are viewed perpendicular to the β strands in (a) and end-on in (b), where the four-stranded β sheets are blue.



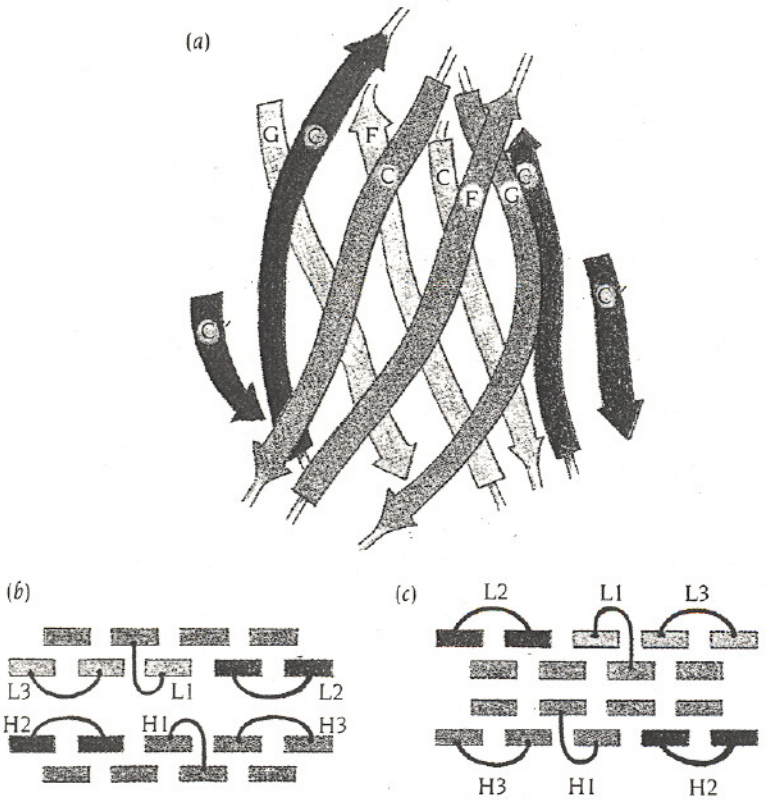


Figure 15.11 The two variable domains V_H and V_L are packed against each other so that the six hypervariable regions are close to each other. (a) Schematic diagram of the packing of the five-stranded β sheets of V_H and V_L in IgG. Only four of the β strands are involved in packing the variable domains against each other. Strand C″ is not involved. (b) Schematic diagram of the strands viewed end-on in the variable domain. Hypervariable loop regions are red. (c) Diagram illustrating a hypothetical packing of the variable domains through their four-stranded sheets. The hypervariable regions would be far apart.

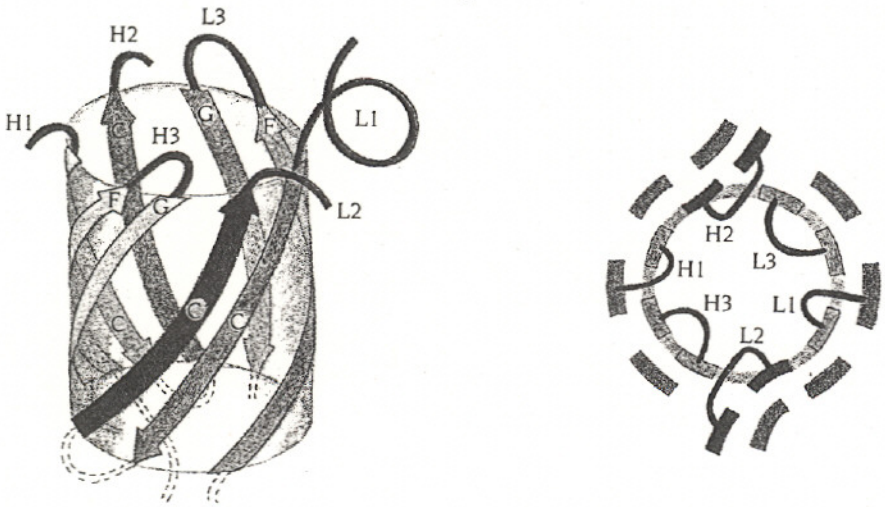


Figure 15.12 Schematic diagram of the barrel arrangement of four β strands from each of the variable domains in Fab. The six hypervariable regions, CDR1–CDR3 from the light chain (L1–L3) and from the heavy chain (H1–H3), are at one end of this barrel. (From J. Novotny et al., *J. Biol. Chem.* 258: 14433–14437, 1983.)

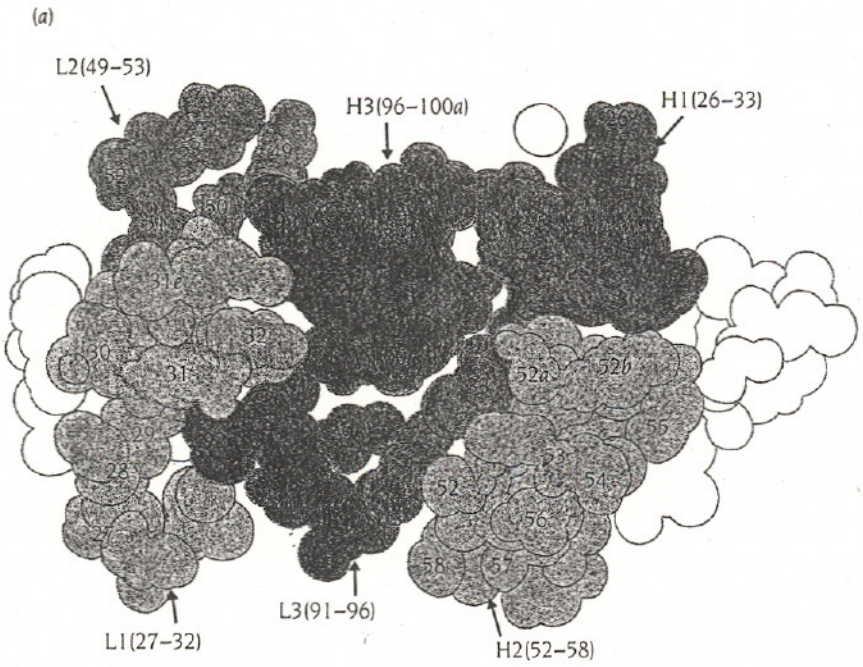
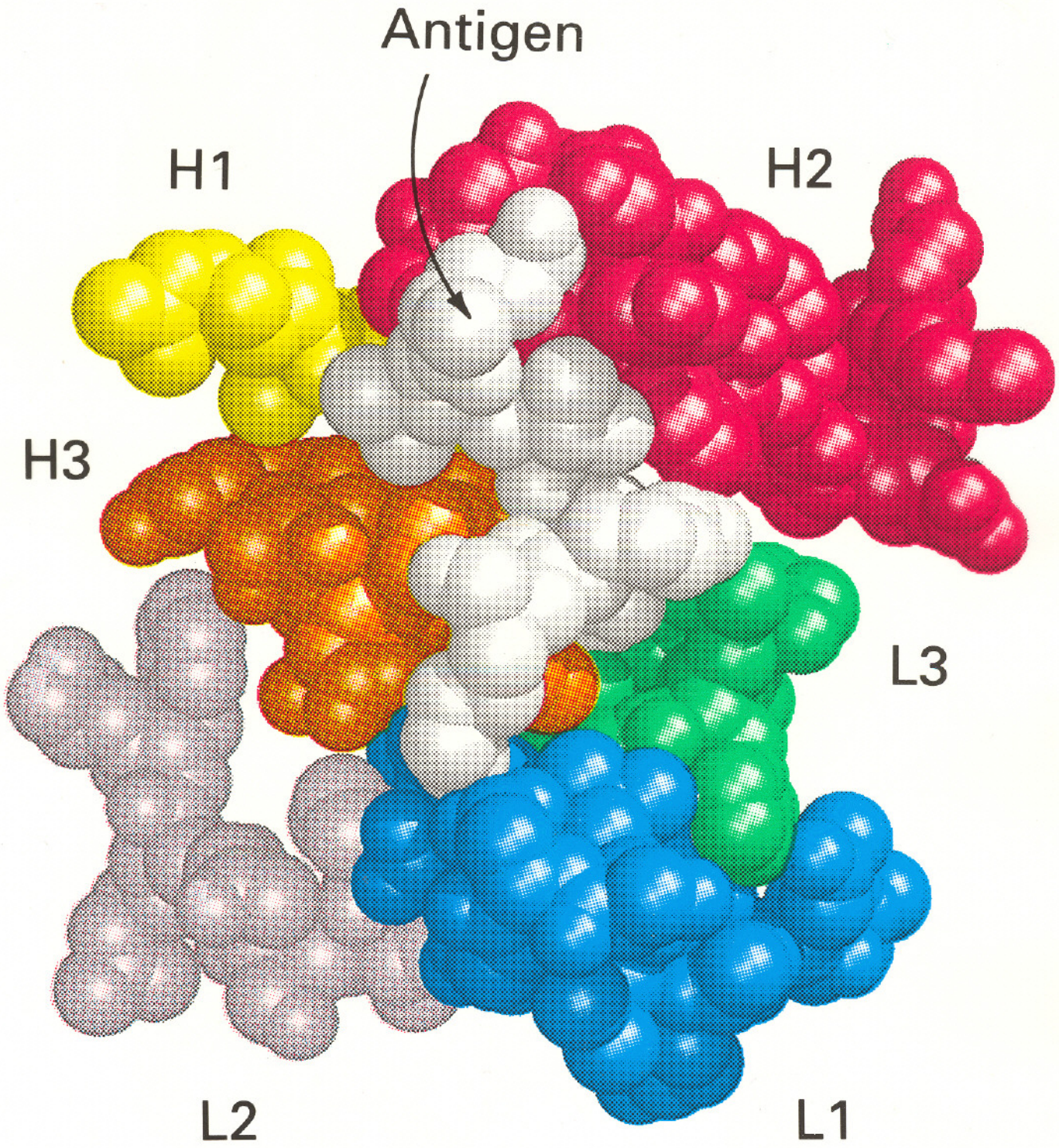


Figure 15.13 (a) Drawing of a space-filling model of the hypervariable regions of an Fab fragment. The superpositions of five sections are shown, cut through a model as shown in (b). It is clearly seen that all six hypervariable regions (L1–L3, H1–H3) contribute to the surface shown here. (From C. Chothia and A. Lesk, *J. Mol. Biol.* 196: 901–917, 1987.)



A peptide antigen makes contact with five of six CDRs in the combining site of an antipeptide antibody

Figure 14-15, page 370

T-86

Set II

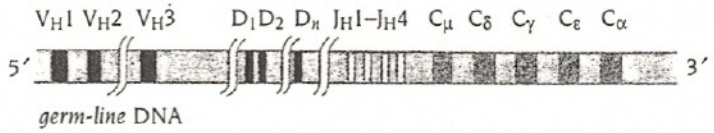


Figure 15.4 Variable domains in immunoglobulins (and T-cell receptors) are made by combinatorial joining of gene segments. Three such segments, V, D, and J, are joined to make the variable domain of a heavy chain. In the mouse the gene-segment pool for an H chain contains about 1000 V segments, 12 D segments, 4 J segments, and a cluster of C segments, each encoding a different class of H chain.

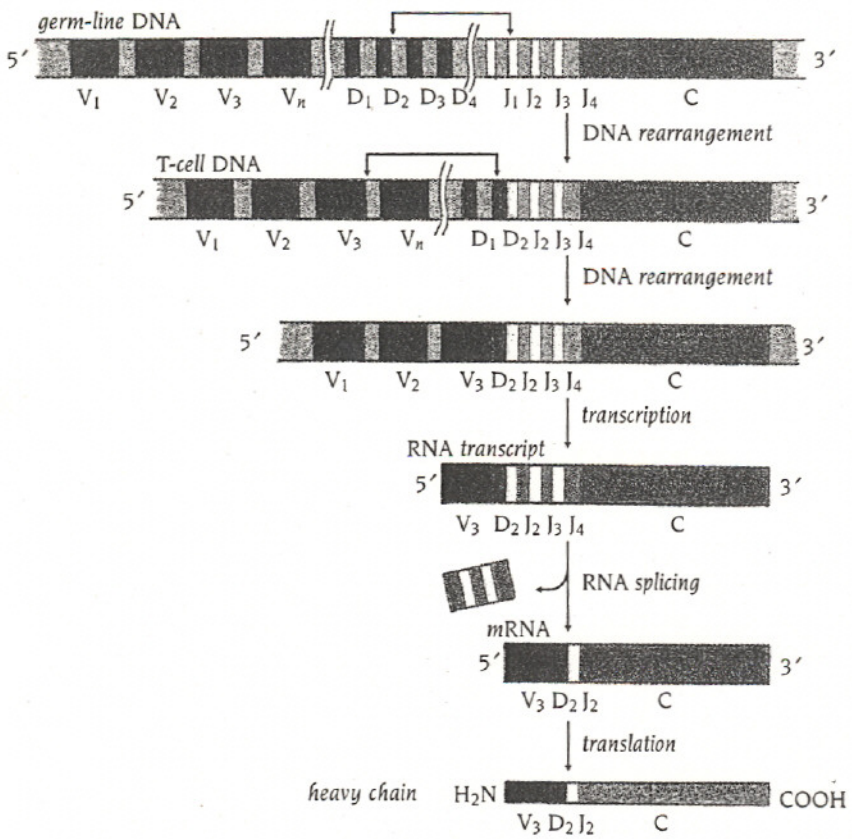
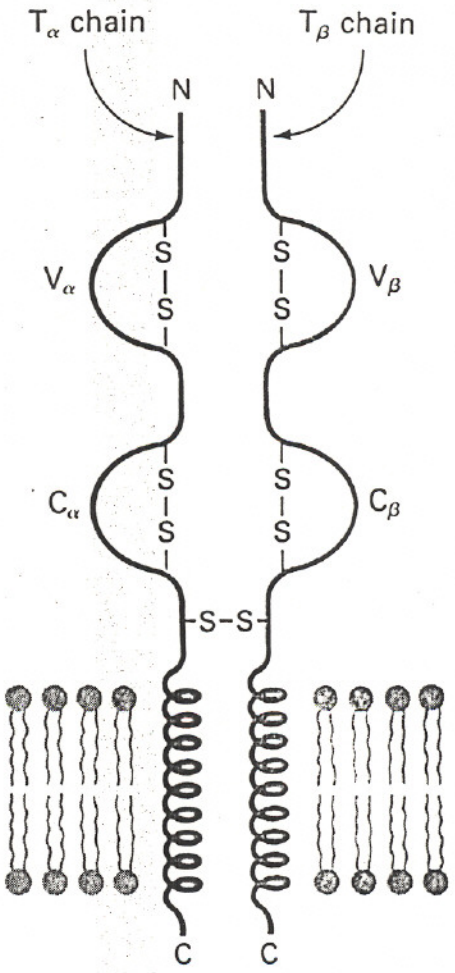


Figure 15.5 The V–D–J joining process involved in making a heavy chain in the mouse. In the germ-line DNA the cluster of about 4 J gene segments and about 10 D segments are separated from the C gene segment by a short intron and from the about 1000 V gene segments by long regions of DNA. During B cell development the chosen V gene segment (V_3) is moved to lie precisely next to the chosen D and J segments (D_2 and J_2). The "extra" J genes (J_3 and J_4) and the intron sequence are transcribed along with the V_3, D_2, J_2, and C segments and then removed by RNA splicing to generate mRNA molecules.

T-cell receptors



- Tα/Tβ chains joined by disulphide bonds

- 43 kDa α / β chains

- homologous in sequence and structure to the V and C Ig domains

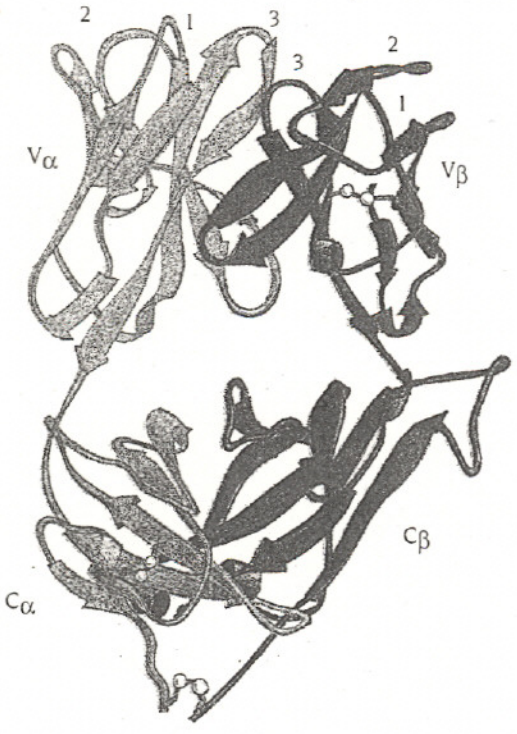


Figure 15.22 T-cell receptor stucture shown as a ribbon diagram. The antigen-binding site is formed by CDR loops (labeled 1 to 3) from the V_α and V_β domain, as for antibodies. A disulfide bond (yellow) links the two peptide chains. (Courtesy of A.I. Wilson.)

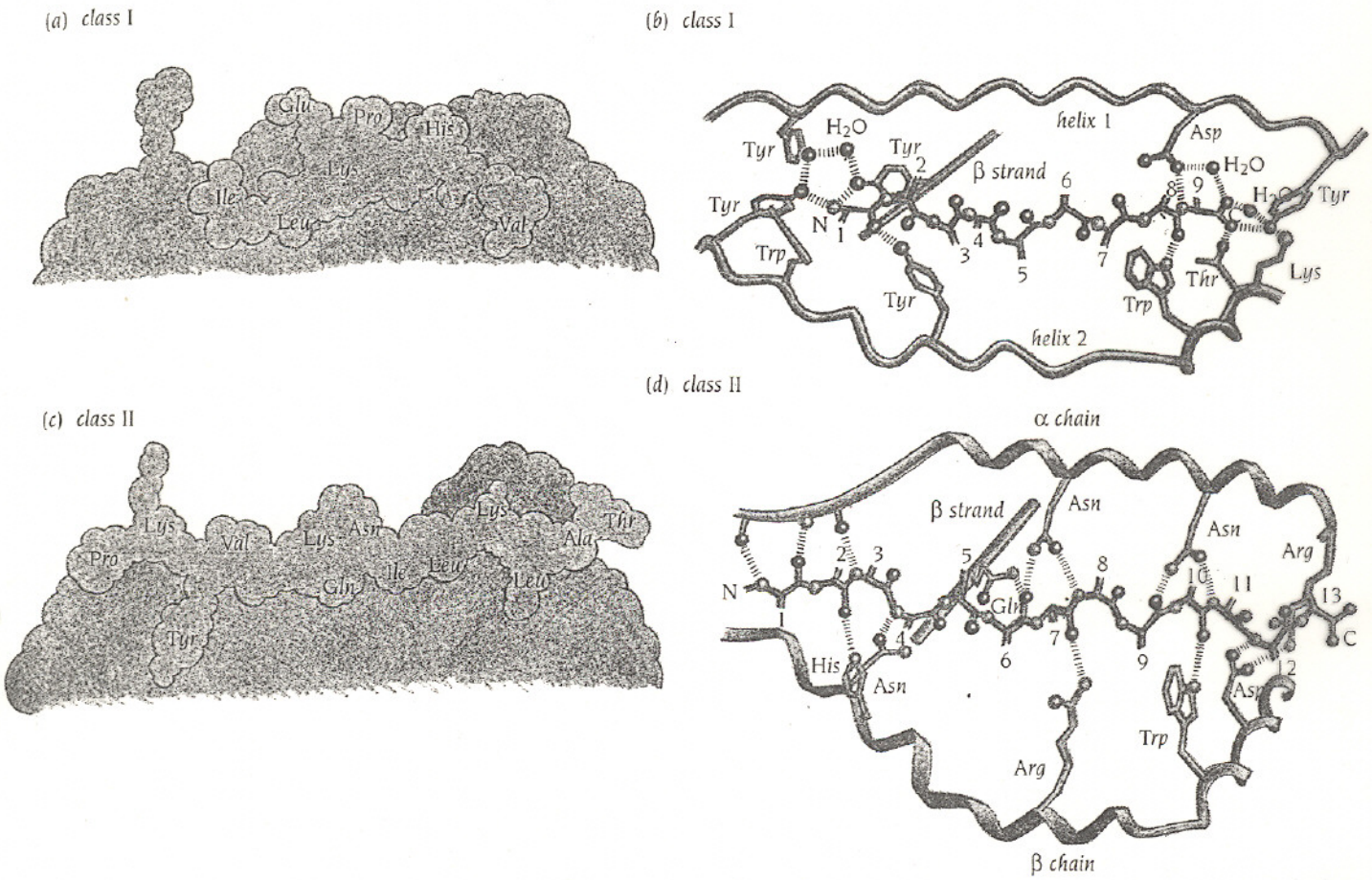
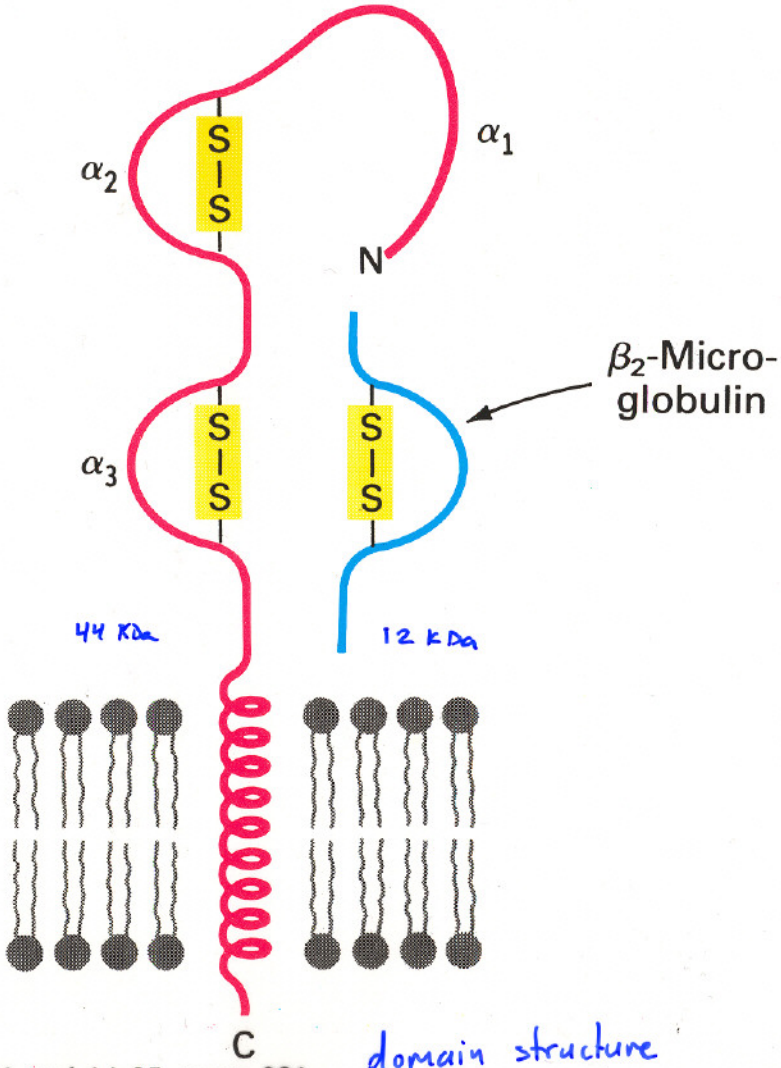
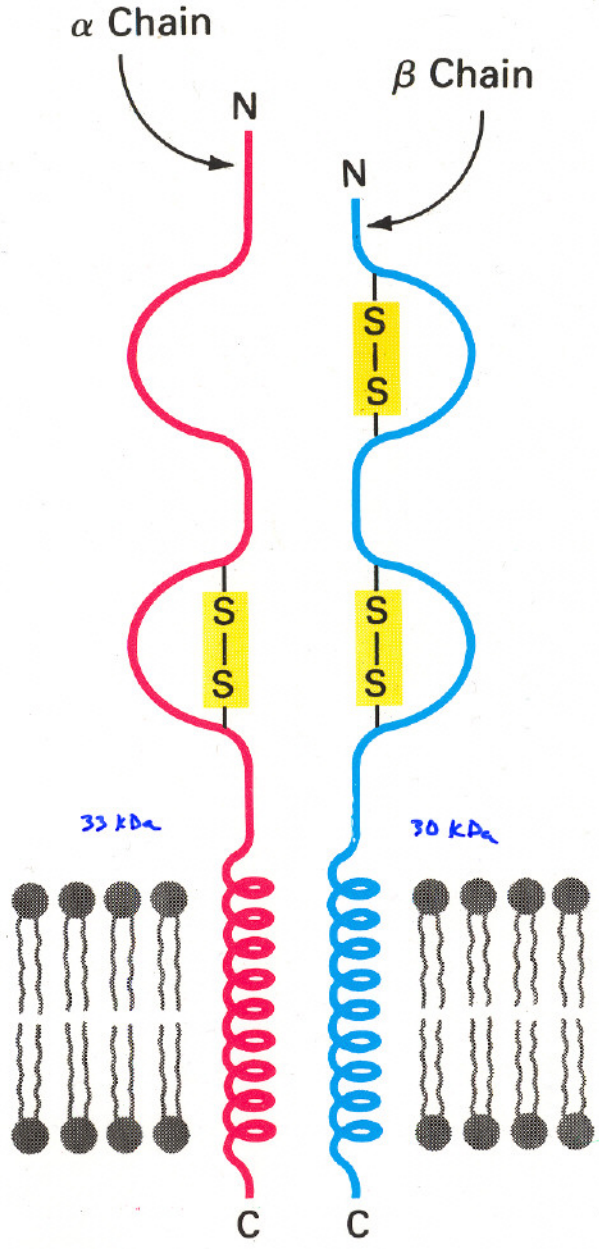


Figure 15.20 Peptide binding by MHC class I and class II molecules. (a) A cross-section of a peptide antigen (green) bound to pockets in the class I molecule (orange). (b) Hydrogen bonds (red) form between the ends of the bound peptide and conserved residues of the class I molecule (orange). (c) Class II molecules bind longer peptides than class I molecules, with the ends of the peptide extending beyond the peptide-binding site. (d) Hydrogen bonds between bound peptide and the class II molecule occur along the length of the binding site, also in contrast to the case with class I complexes.



domain structure of a class I MHC protein



Domain structure of a class II MHC protein

Figures 14-34 and 14-35, page 381

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MHC–complex

- 75 genes / 3500 kB

- highly variable

diversity enables presentation of a wide range of peptides to T-cells

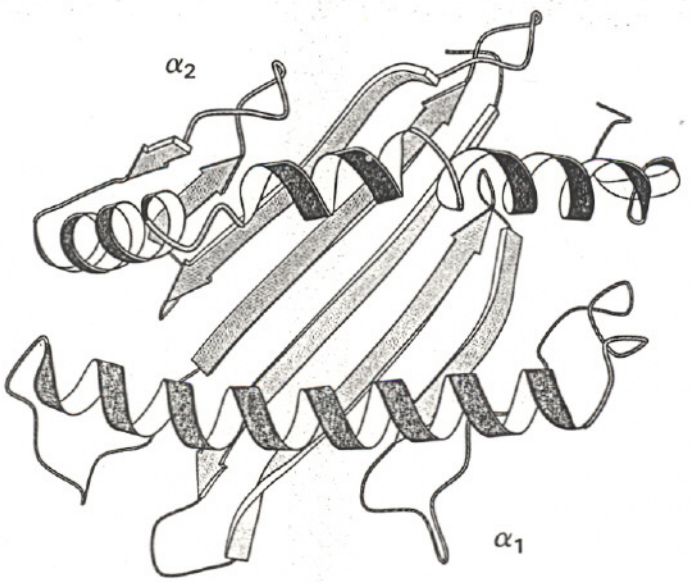
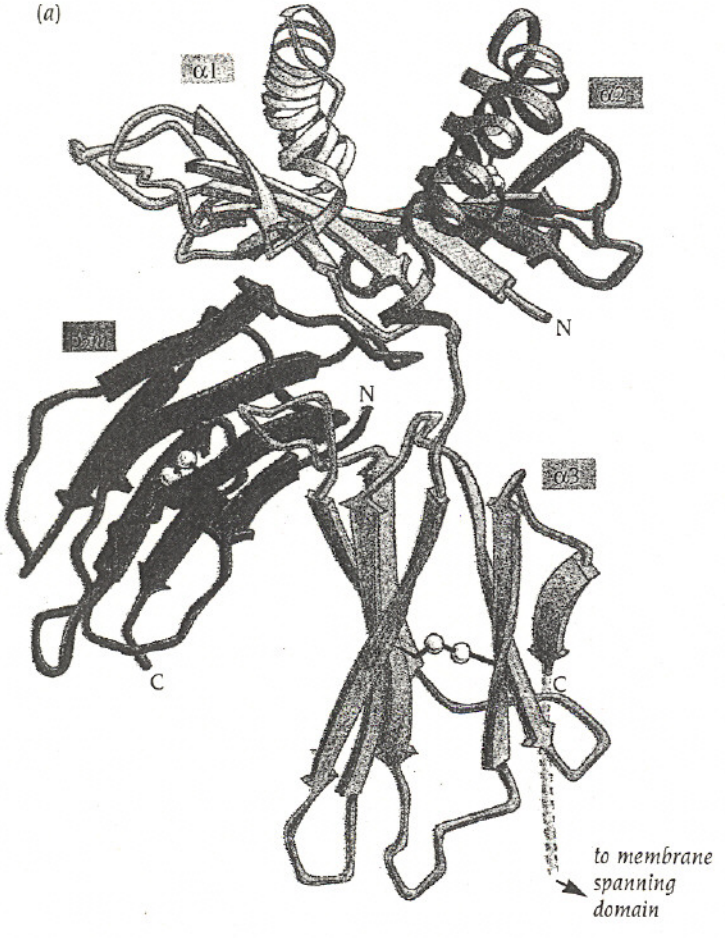


Figure 14-37

Binding groove of a class I MHC protein

Figure 15.18 (a) Schematic representation of the path of the polypeptide chain in the structure of the class I MHC protein HLA-A2. Disulfide bonds are indicated as two connected spheres. The molecule is shown with the membrane proximal immunoglobulin-like domains (α3 and β_2m) at the bottom and the polymorphic α1 and α2 domains at the top. (b) The domain arrangement in class I and class II MHC proteins. The domain structures of the MHC class II molecule are similar to those of the class I molecule shown in (a). [(a) Adapted from P.J. Björkman et al., *Nature* 329: 506–512, 1987.]



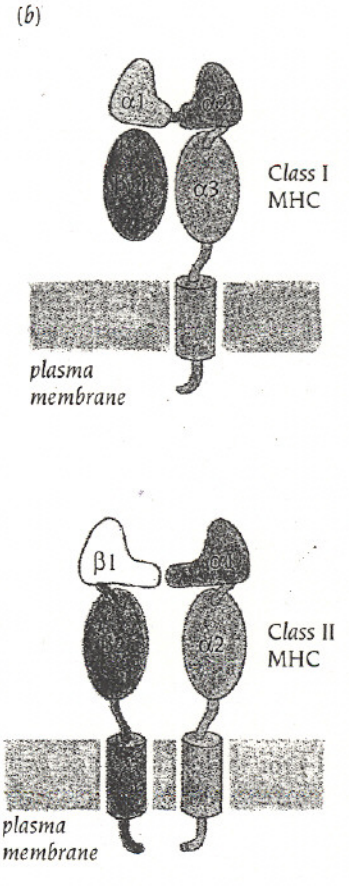
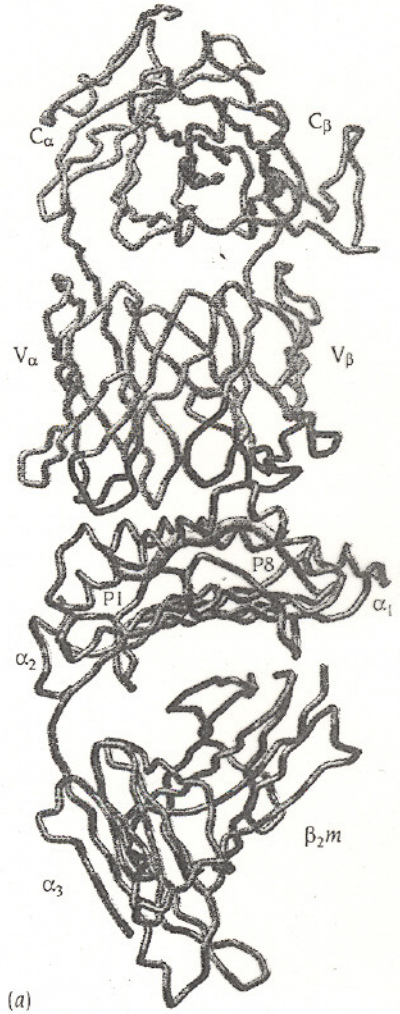


Figure 15.23 Interactions between the class I MHC–peptide complex with the T-cell receptor. (a) The T-cell receptor (top) binds to the MHC–peptide complex with its hypervariable CDR loops effectively burying the eight-residue foreign peptide (yellow, with the N- and C-terminal residues labeled P1 and P8, respectively). The TCR α subunit loops 1–3 are colored light purple (CDR1α), dark purple (CDR2α), and yellow (CDR3α); the β chain loops 1–3 are colored light blue (CDR2β), dark blue (CDR3β), and green (CDR3β). The β subunit hypervariable loop that has no counterpart in immunoglobulins, HV4, is shown in red. (b) A finger-print of how the TCR hypervariable loops contact the MHC–peptide complex, as seen looking down onto the MHC surface as oriented in (a). The TCR sits diagonally across the peptide-binding site, contacting both the MHC molecule (gray and green space-filling model) and its bound peptide (pale green space-filling model). (Courtesy of A.I. Wilson.)



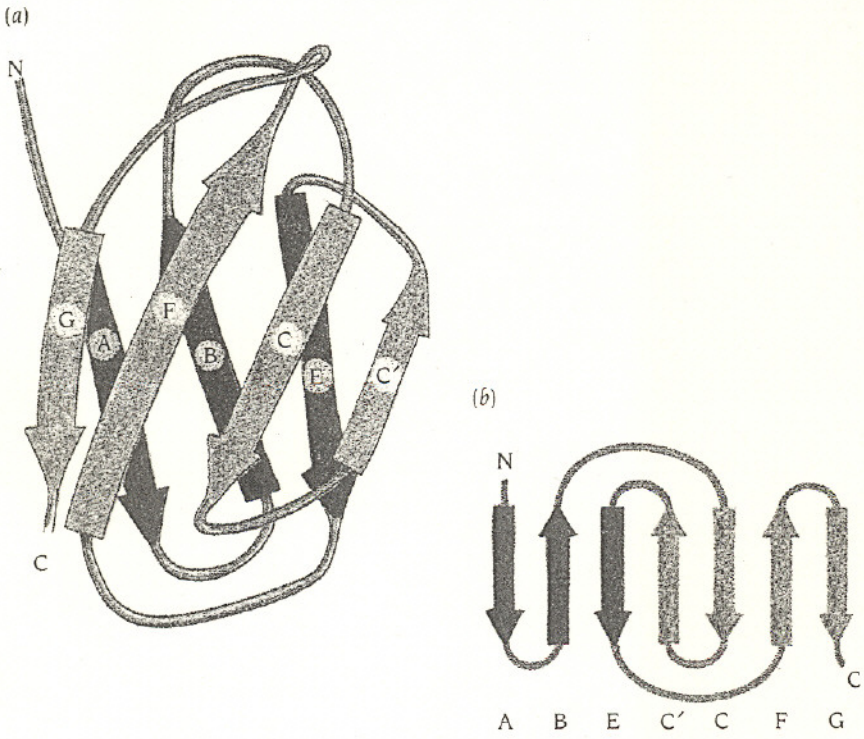


Figure 15.24 Ribbon diagram (a) and topology diagram (b) of the fibronectin type III domain, which is composed of a three-stranded and a four-stranded β sheet packed together as a compressed barrel.

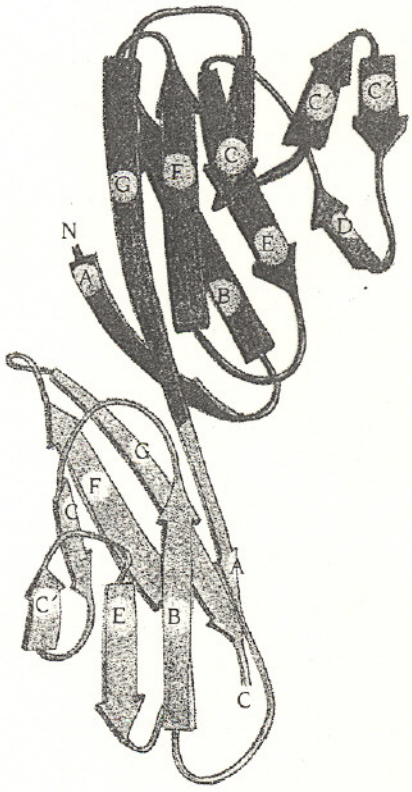


Figure 15.25 Ribbon digram for the first two domains of CD4. The G strand of domain 1 is contiguous with the A strand of domain 2. The C″ ridge has been implicated in binding to the HIV surface protein, gp120.

PROBLEMS

CHAPTER 10

(1) Textbook : # 6, 8, 19

(2) Companion : # 6, 7, 8 (p. 168)

CHAPTER 33

(1) Textbook : # 5, 10, 12

(2) Companion : # 3, 4, 12 (pp. 593-594)