Lecture VII

Cytokines

Development of humoral immune response

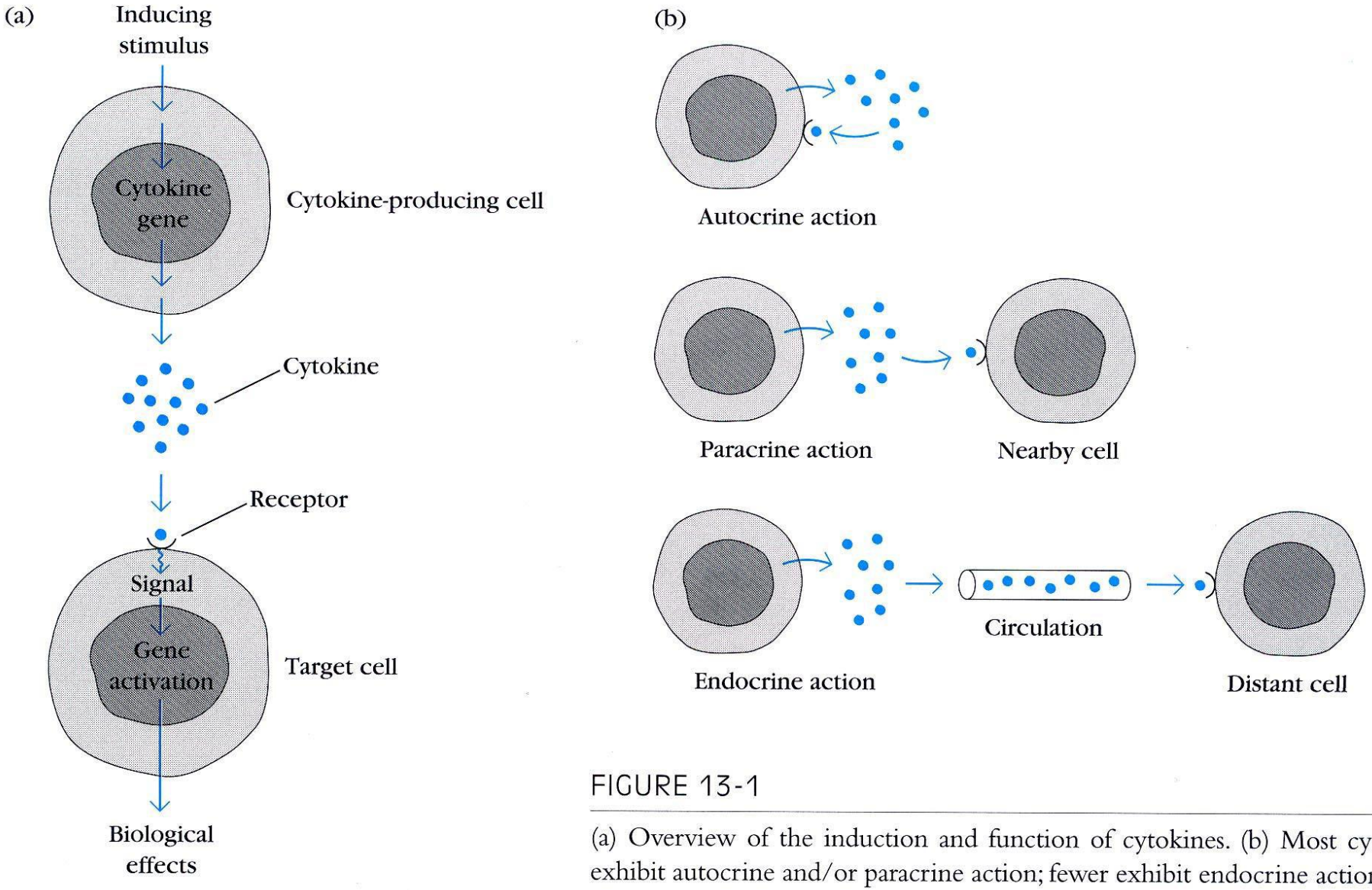


FIGURE 13-1

(a) Overview of the induction and function of cytokines. (b) Most cytokines exhibit autocrine and/or paracrine action; fewer exhibit endocrine action.

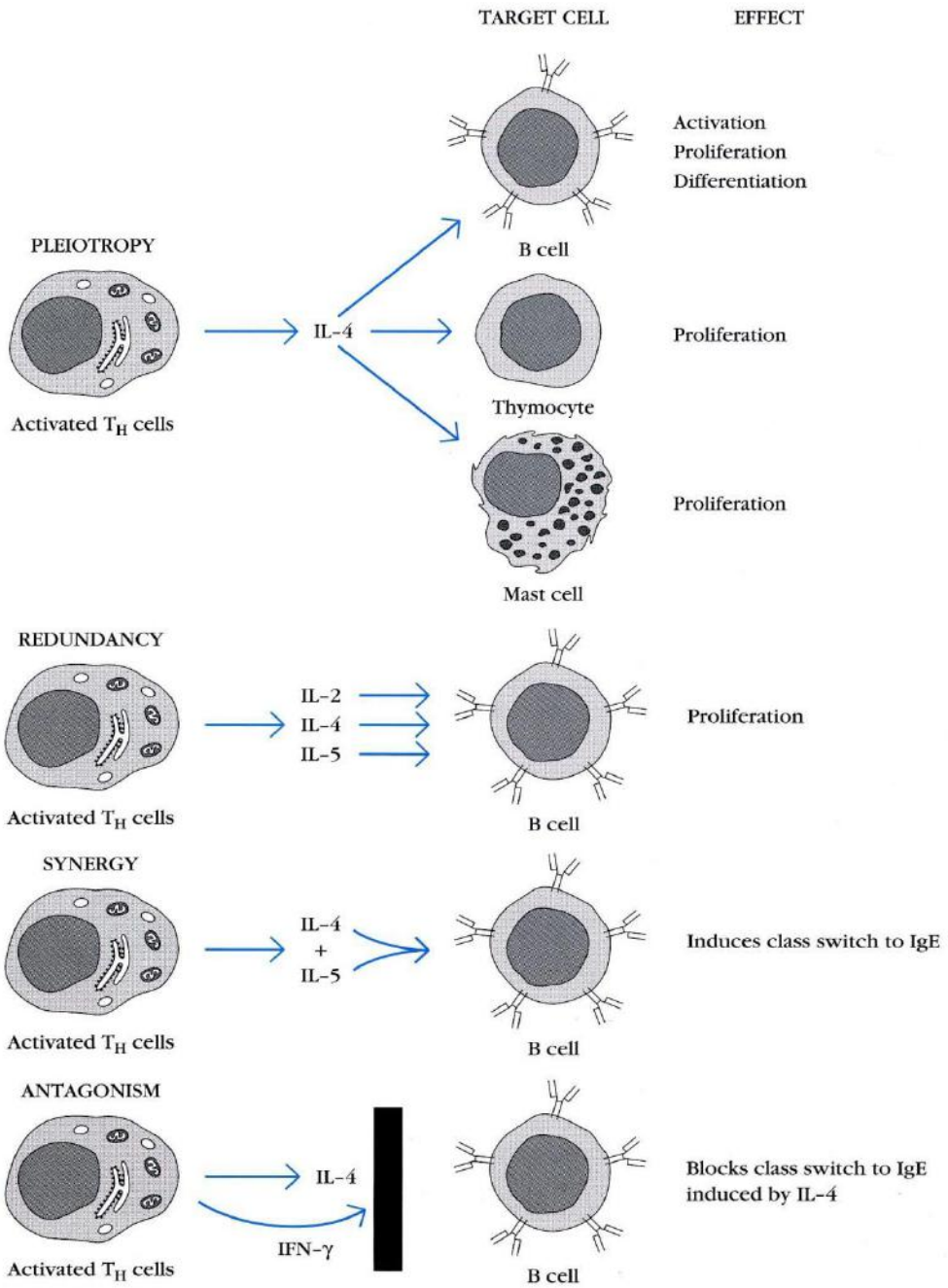


FIGURE 13-2

Examples of the cytokine attributes of pleiotropy, redundancy, synergy (synergism), and antagonism.

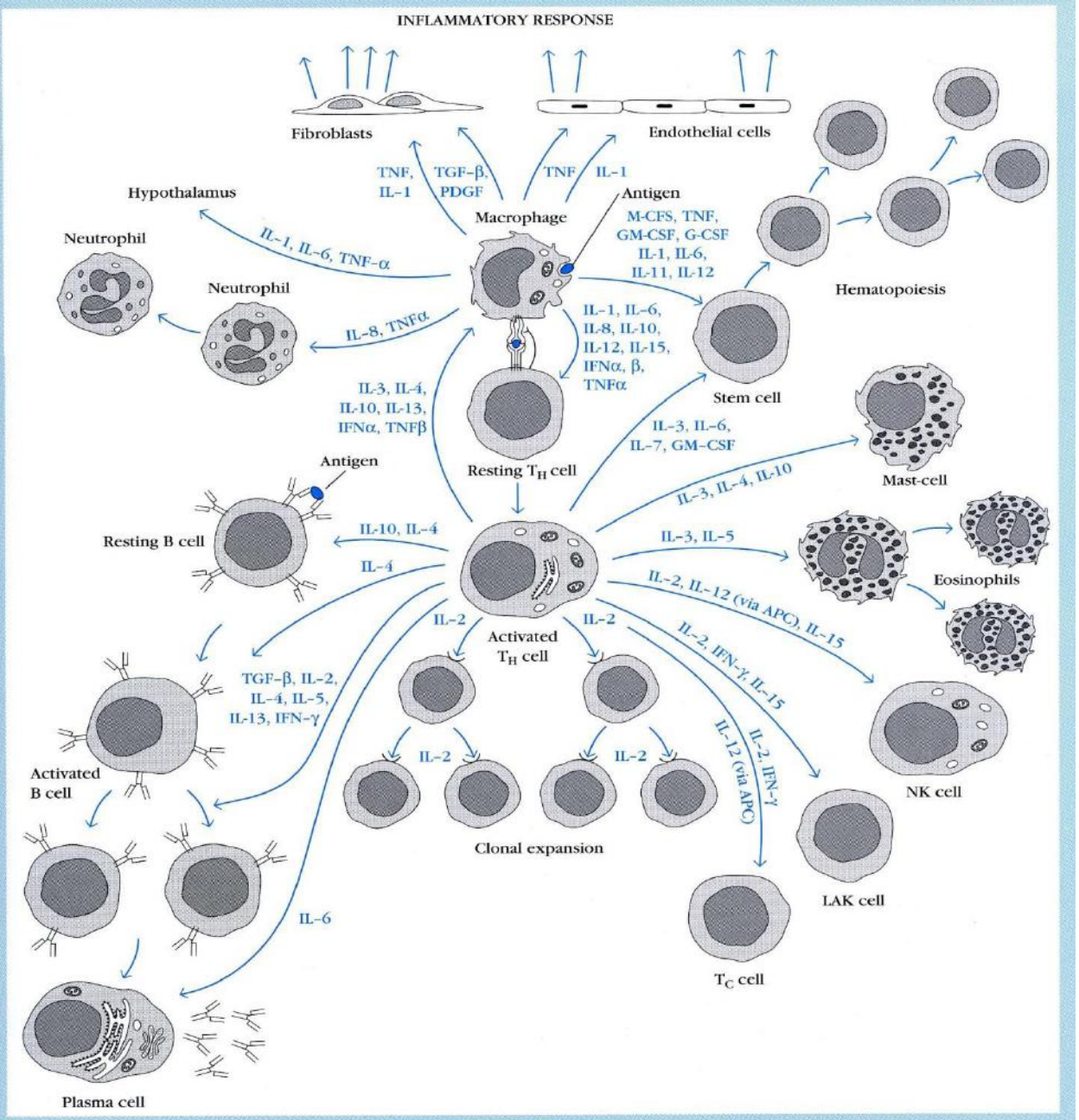
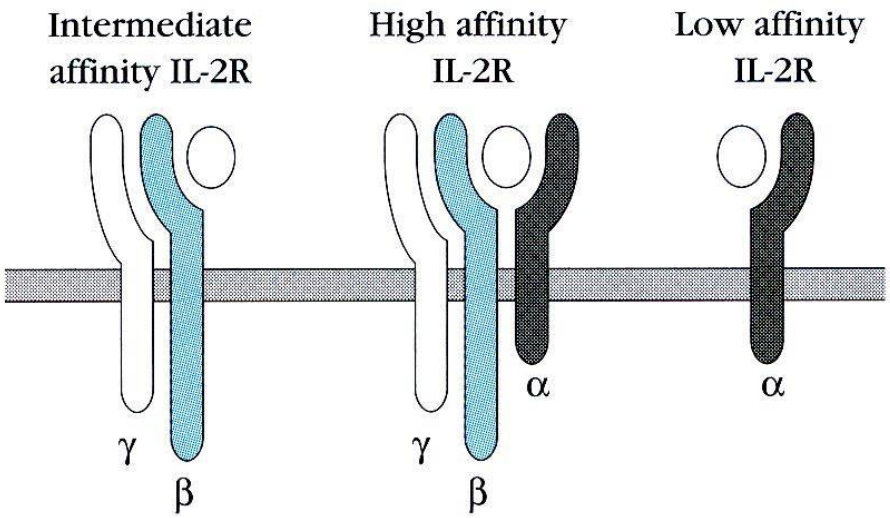


FIGURE 13-4

Interaction of antigen (blue) with macrophages and the subsequent activation of resting T_H cells leads to release of numerous cytokines, generating a complex network of interacting cells in the immune response.



Subunit composition:	IL-2Rβ IL-2Rγ	IL-2Rα IL-2Rβ IL-2Rγ	IL-2Rα
Affinity constant (K_d):	$10^{-9}M$	$10^{-11}M$	$10^{-8}M$
Cells expressed by:	NK cells Resting T cells (low numbers)	Activated $CD4^+$ and $CD8^+$ T cells Activated B cells (low numbers)	

FIGURE 13-8

Comparison of the three forms of the IL-2 receptor. Signal transduction is mediated by the β and γ chains, but all three chains are required for high-affinity binding of IL-2.

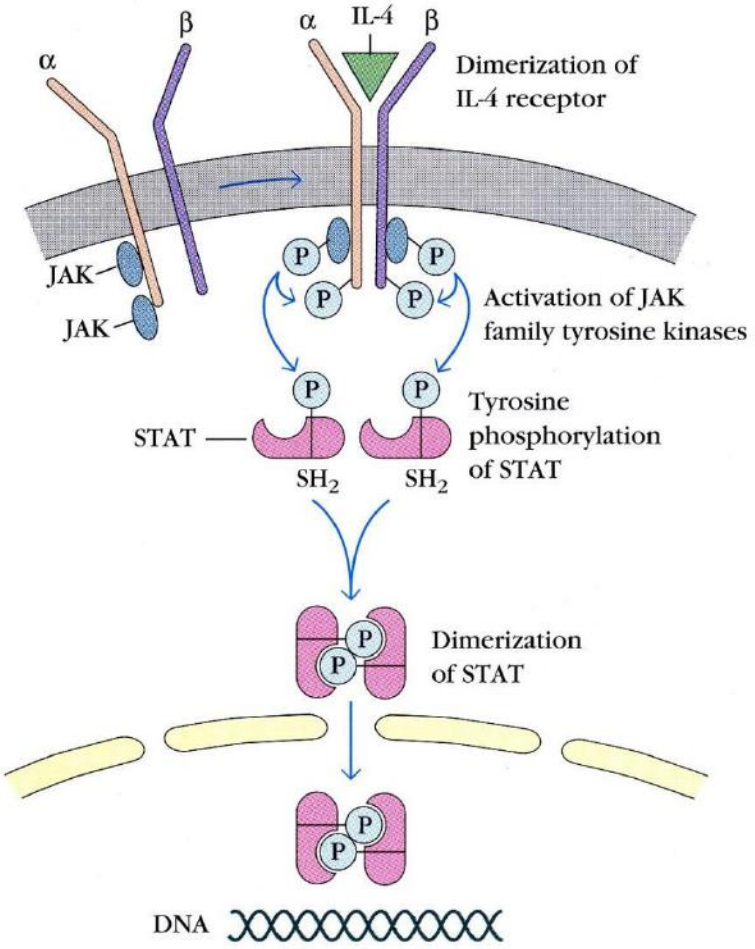


FIGURE 13-9

Model of signal transduction mediated by most class I and class II cytokine receptors. Cytokine binding induces dimerization of the receptor subunits. Association of JAK tyrosine kinases with the dimeric receptor activates the kinases, which then phosphorylate various tyrosine residues, including one or more in STAT transcription factors. After the phosphorylated STATs dimerize, they translocate to the nucleus where they activate transcription of specific genes.

CYTOKINE SECRETION AND PRINCIPAL FUNCTIONS OF MOUSE T_H1 AND T_H2 SUBSETS

CYTOKINE/FUNCTION	T_H1	T_H2
CYTOKINE SECRETION		
IL-2	+	–
IFN-γ	++	–
TNF-β	++	–
GM-CSF	++	+
IL-3	++	++
IL-4	–	++
IL-5	–	++
IL-10	–	++
IL-13	–	++
FUNCTIONS		
Help for total antibody production	+	++
Help for IgE production	–	++
Help for IgG2a production	++	+
Eosinophil and mast-cell production	–	++
Macrophage activation	++	–
Delayed-type hypersensitivity	++	–
T_C-cell activation	++	–

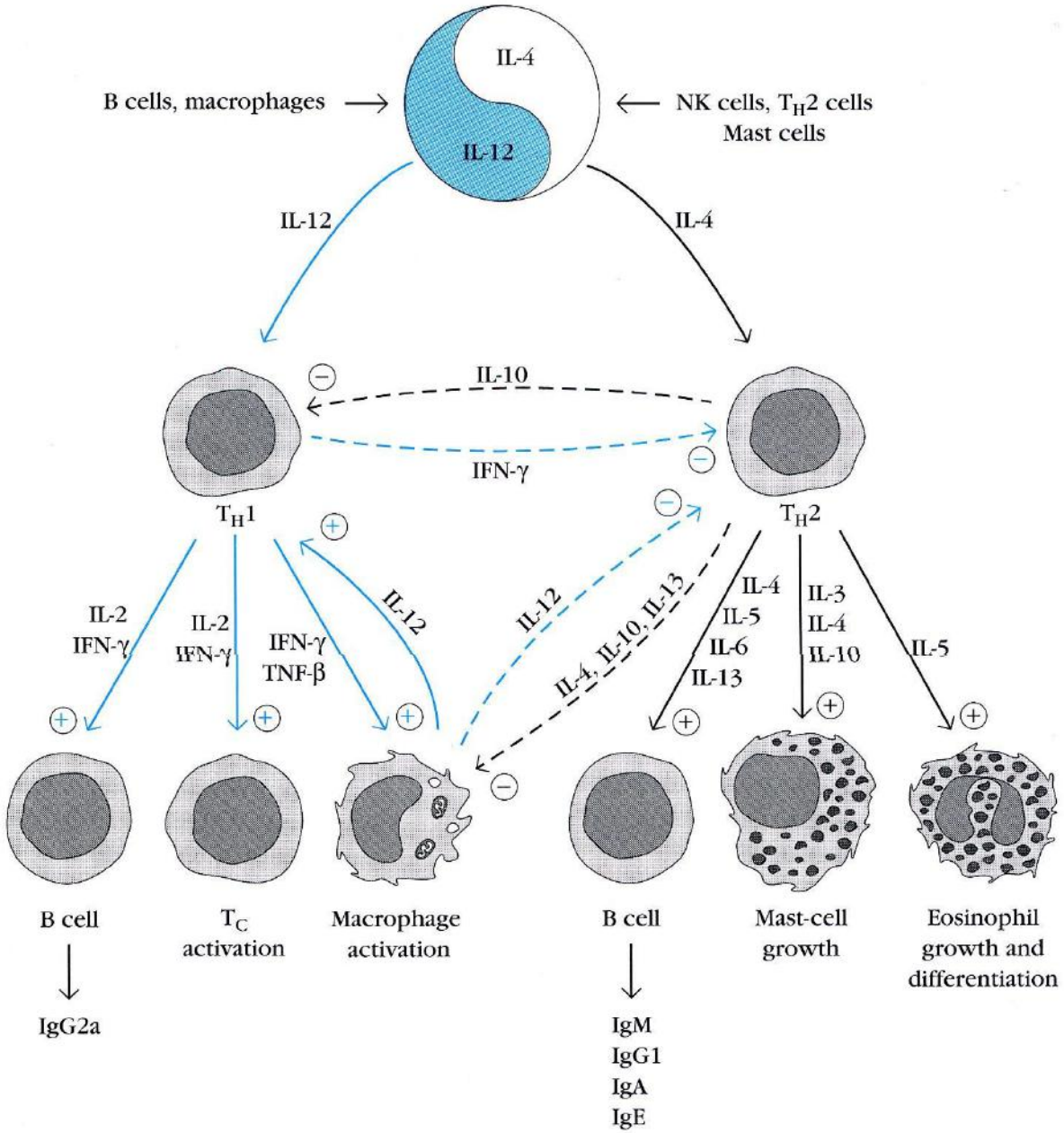
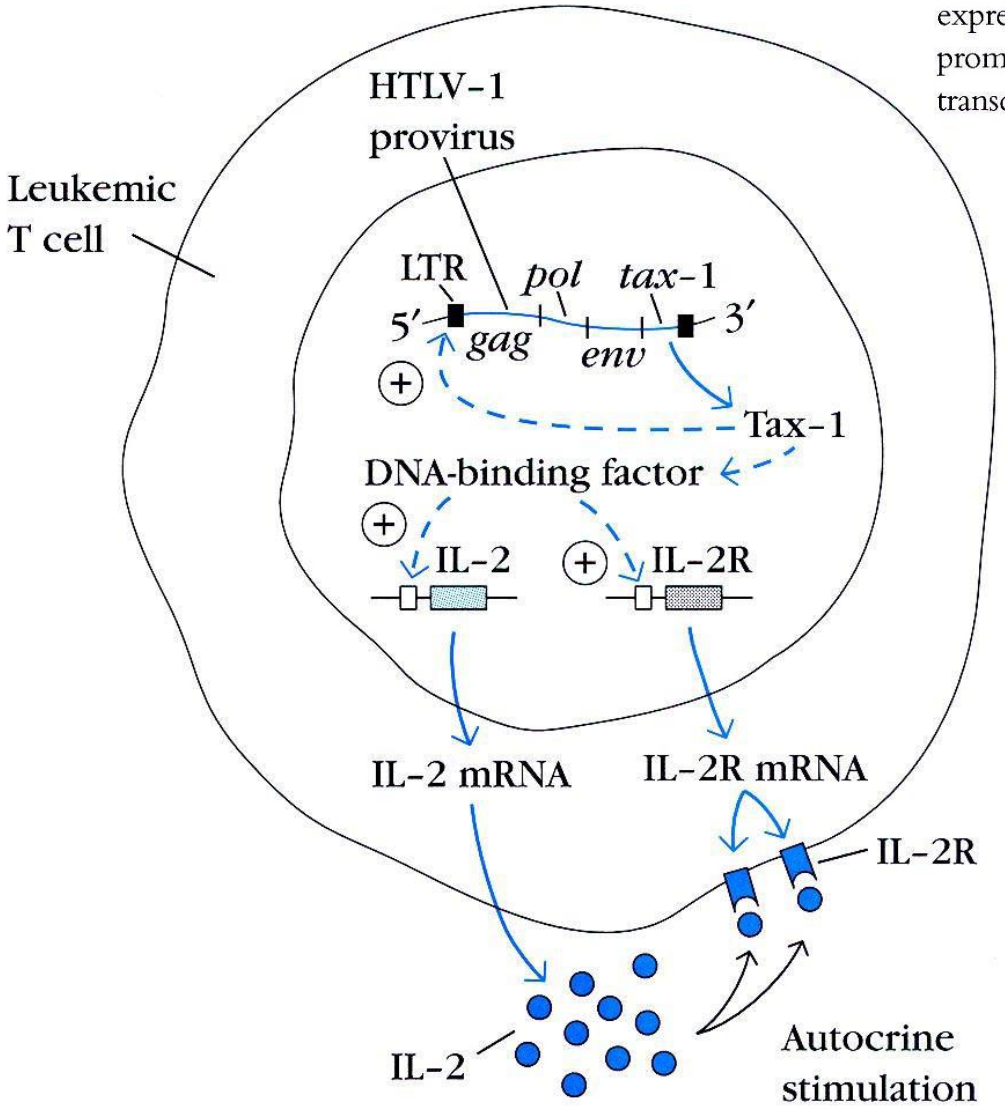


FIGURE 13-11

Cross-regulation by cytokines secreted from T_H1 and T_H2 subsets. Solid arrows indicate stimulatory effects; dashed arrows indicate inhibitory effects. IL-12 and IL-4 preferentially stimulate formation of the T_H1 and T_H2 subsets, respectively.

FIGURE 13-13

In adult T-cell leukemia, infection of T cells with HTLV-1 leads to constitutive expression of IL-2 and the IL-2 receptor (IL-2R). The resulting autostimulation causes T-cell proliferation in the absence of antigen. The virus-encoded protein Tax-1 promotes transcription of the provirus genome by binding to the 5′ LTR. It also stimulates expression of an unknown DNA-binding factor(s) that binds to the promoters (open boxes) of the IL-2 and IL-2R genes, stimulating transcription of these genes.



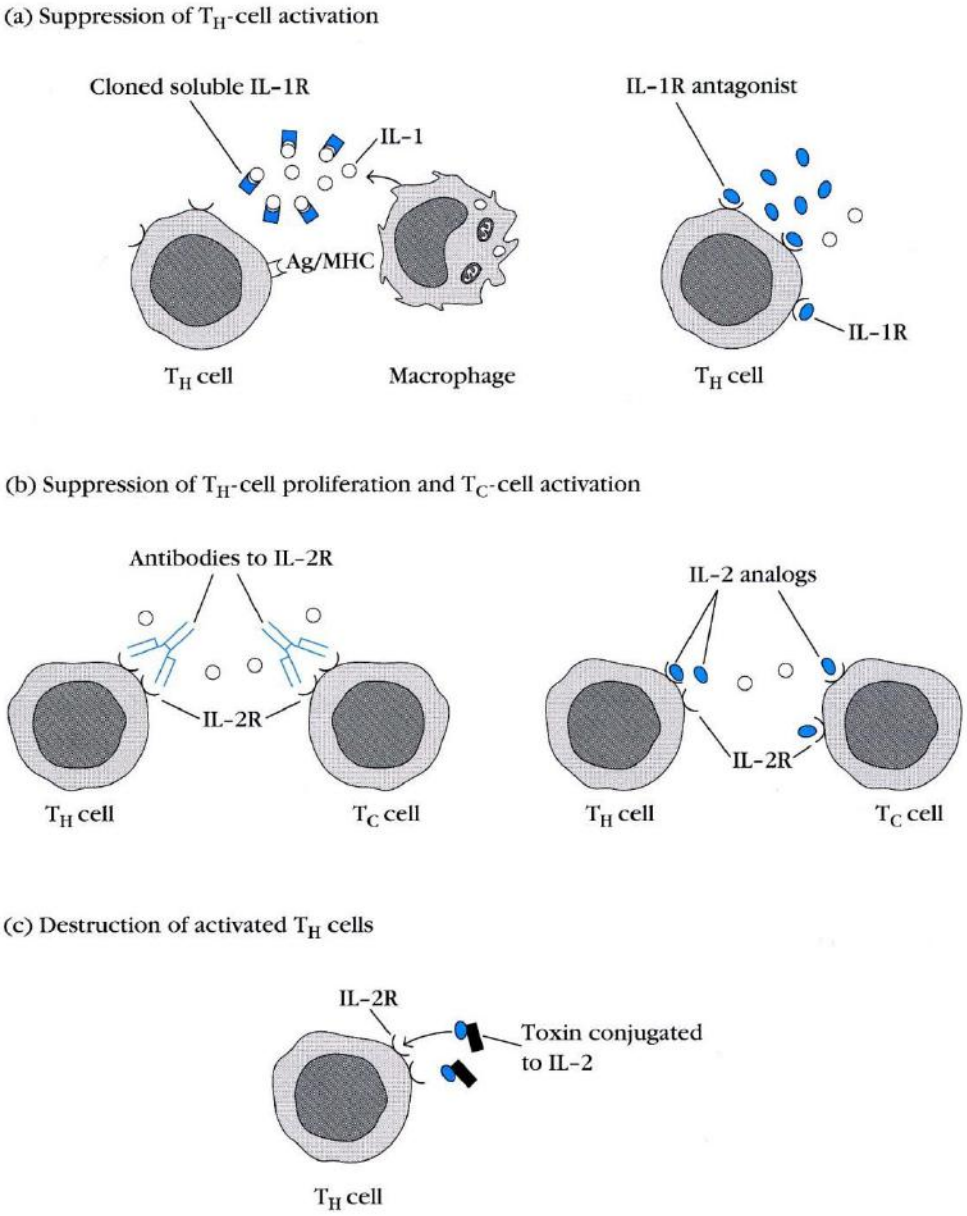


FIGURE 13-14

Experimental cytokine-related therapeutic agents offer the prospect of selectively modulating the immune response. (a,b) The agents (blue) bind either to the cytokine (open circles) or to the cytokine receptor on the cell surface, thereby preventing interaction of the cytokine with its receptor. (c) Conjugation of a toxin with a cytokine results in destruction of cells expressing the cytokine receptor.

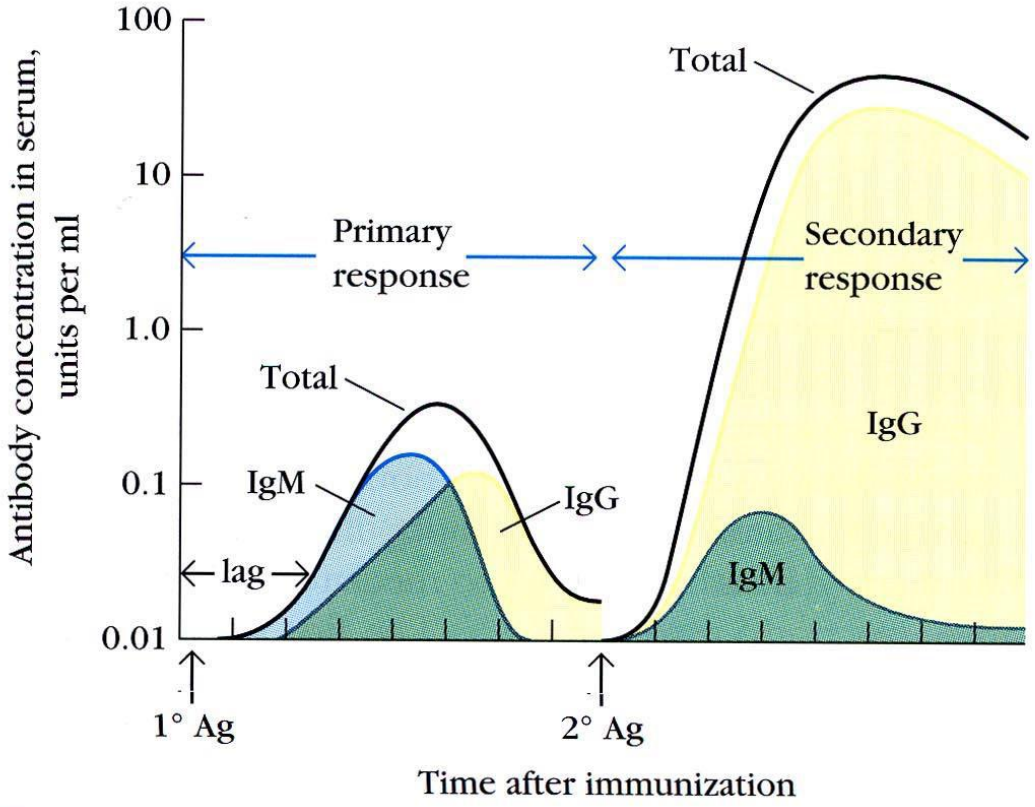


FIGURE 16-19

Concentration and isotype of serum antibody following primary (1°) and secondary (2°) immunization with antigen. The antibody concentrations are plotted on a logarithmic scale. The time units are not specified because the kinetics differ somewhat with type of antigen, administration route, presence or absence of adjuvant, and the species or strain of animal.

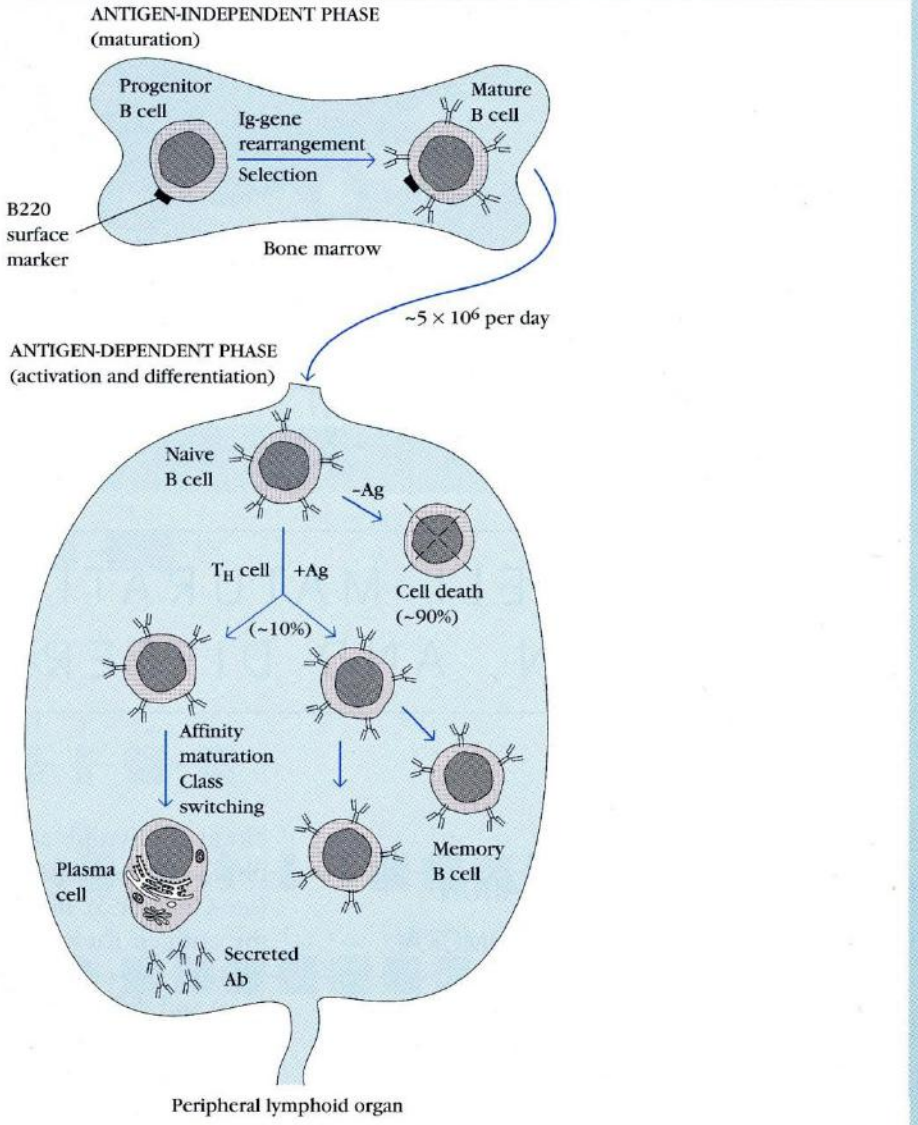


FIGURE 8-1

Overview of B-cell development. During the antigen-independent maturation phase, immunocompetent B cells expressing membrane IgM and IgD are generated in the bone marrow. Only about 10% of the potential B cells reach maturity and exit the bone marrow. In the absence of antigen-induced activation, naive B cells in the periphery die within a few days. In the presence of soluble protein antigen and activated T_H cells, B cells are activated and proliferate within secondary lymphoid organs. Those bearing high-affinity mIg differentiate into plasma cells and memory B cells, which may express different isotypes.

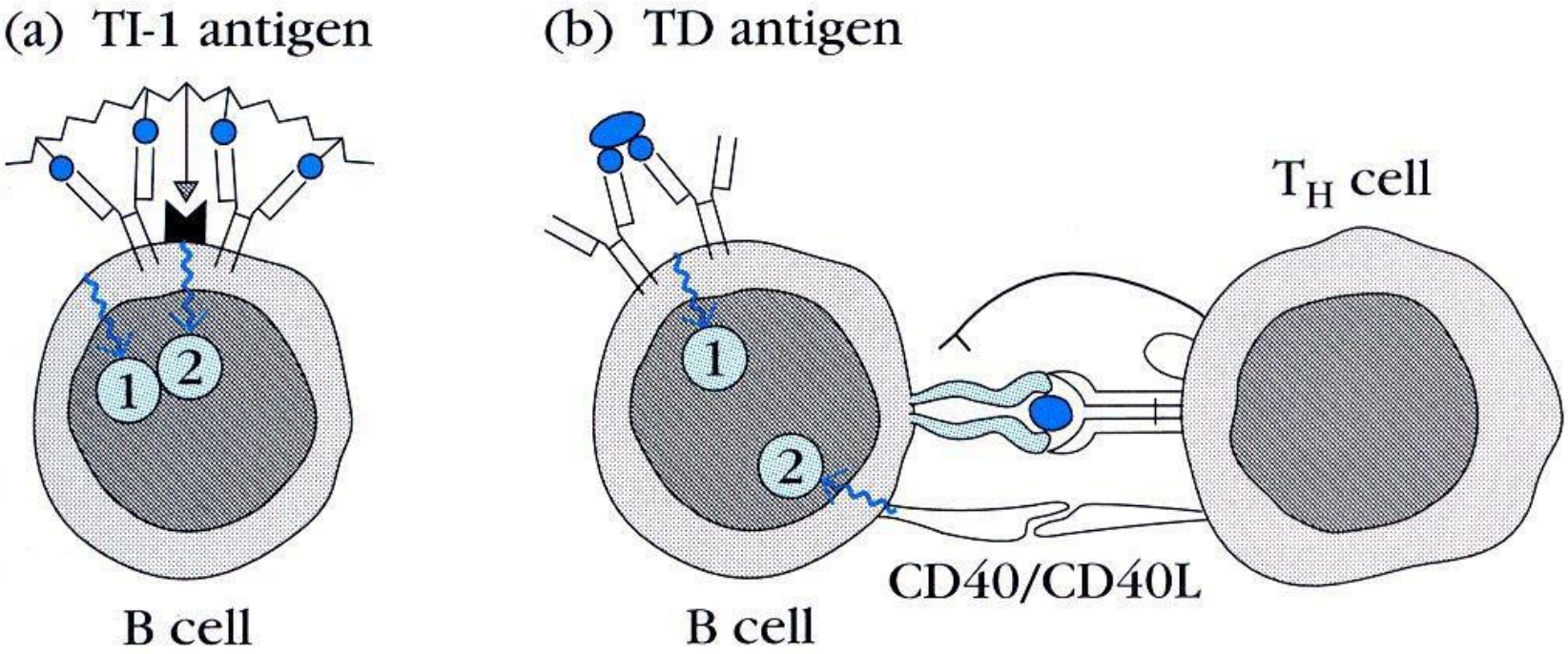


FIGURE 8-6

An effective competence signal for B-cell activation involves two distinct signals induced by membrane events. Binding of a type 1 thymus-independent (TI-1) antigen to a B cell provides both signals. A thymus-dependent (TD) antigen provides signal 1 by cross-linking mIg, but a separate interaction between CD40 on the B cell and CD40L on an activated T_H cell is required to generate signal 2.

(a) 1. Antigen cross-linkage of mIg induces signal (1), which leads to increased expression of class II MHC and co-stimulatory B7 on B cell.
2. T_H cell recognizes antigen-class II MHC on B-cell membrane. This plus co-stimulatory signal activates T_H cell.

(b) 1. Following activation of T_H cell, it begins to express CD40L.
2. Interaction of CD40 and CD40L provides competence signal (2).

(c) 1. B cell begins to express receptors for various cytokines.
2. Binding of cytokines released from T_H cell in a directed fashion provides progression signal (3) for proliferation of B cell.

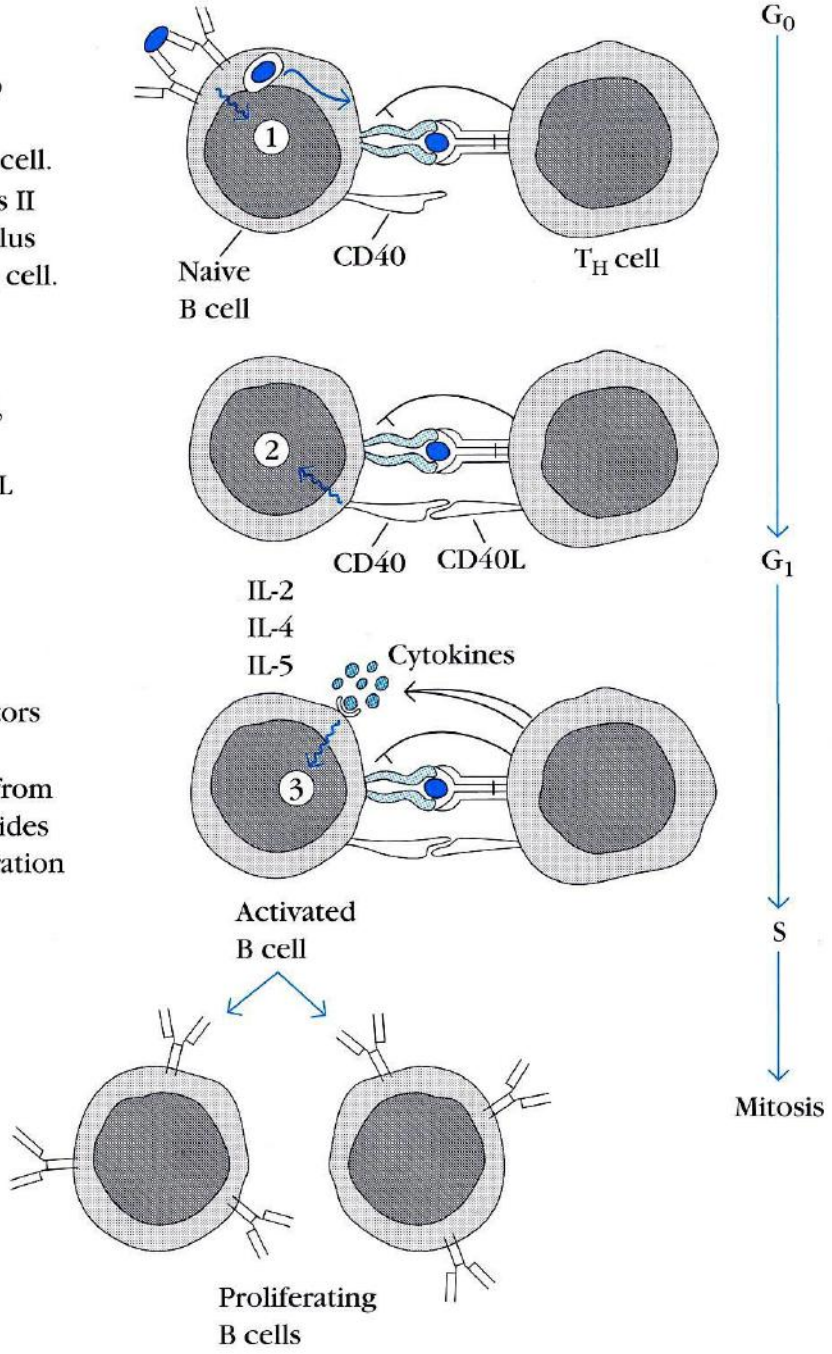


FIGURE 8-10

Sequence of events in B-cell activation by a thymus-dependent antigen. The cell-cycle phase of the B cell is indicated on the right.

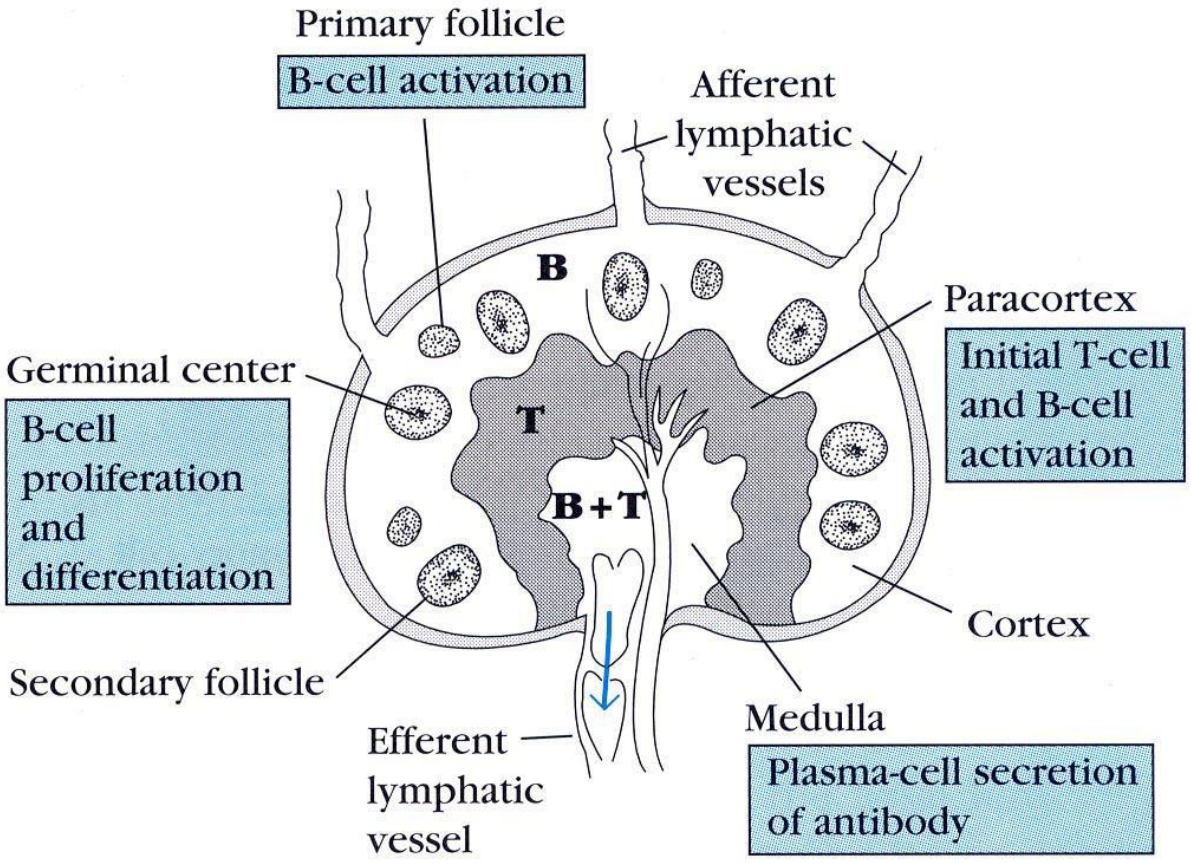


FIGURE 8-15

Schematic diagram of a peripheral lymph node showing anatomic sites at which various steps in B-cell activation, proliferation, and differentiation occur. The cortex is rich in B cells, and the paracortex in T cells; both B and T cells are present in the large numbers in the medulla. A secondary follicle comprises the follicular mantle and germinal center, which contains three distinct zones.

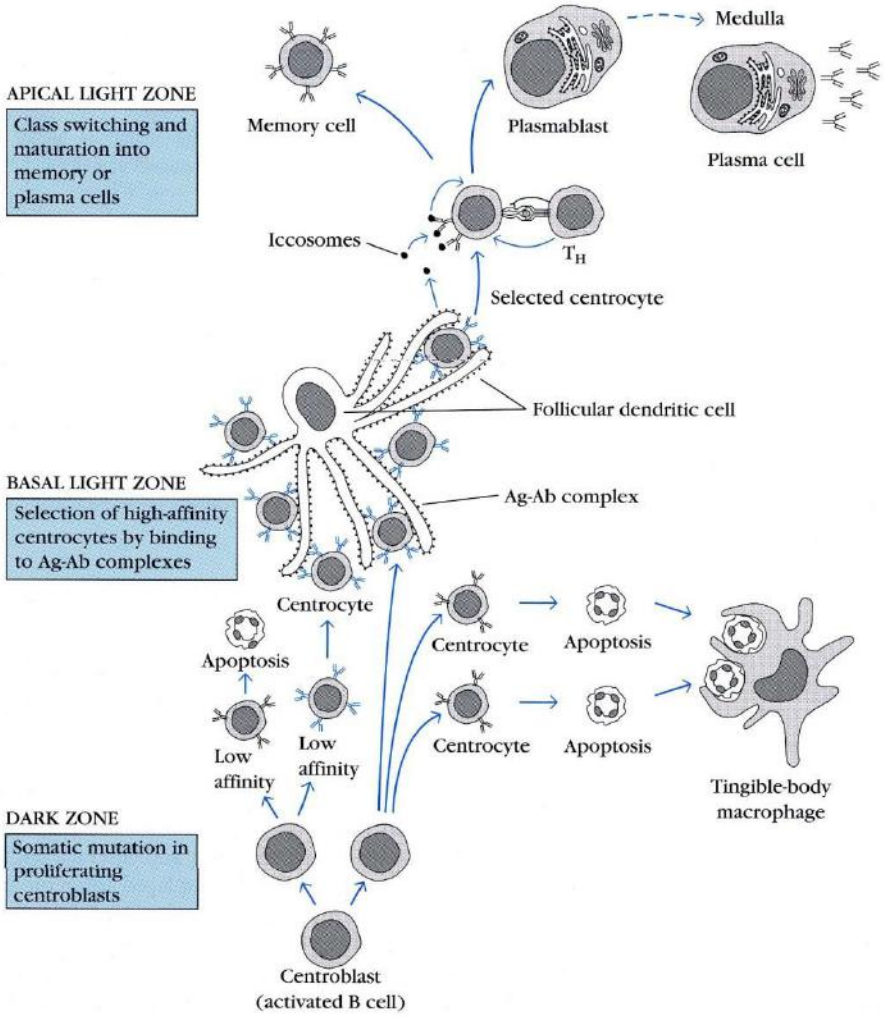


FIGURE 8-16

Overview of cellular events within secondary follicles of peripheral lymph nodes. Follicular dendritic cells bind antigen-antibody complexes along their long processes. Small B cells (centrocytes) bearing high-affinity membrane immunoglobulin (mIg antibodies shown in blue) are thought to interact with antigen presented on the follicular dendritic cells; unselected centrocytes bearing low-affinity mIg die by apoptosis and the debris is phagocytosed by tingible-body macrophages. Selected centrocytes, which may undergo class switching, then mature into memory B cells or plasmablasts; the latter migrate to the medulla where they develop into plasma cells.

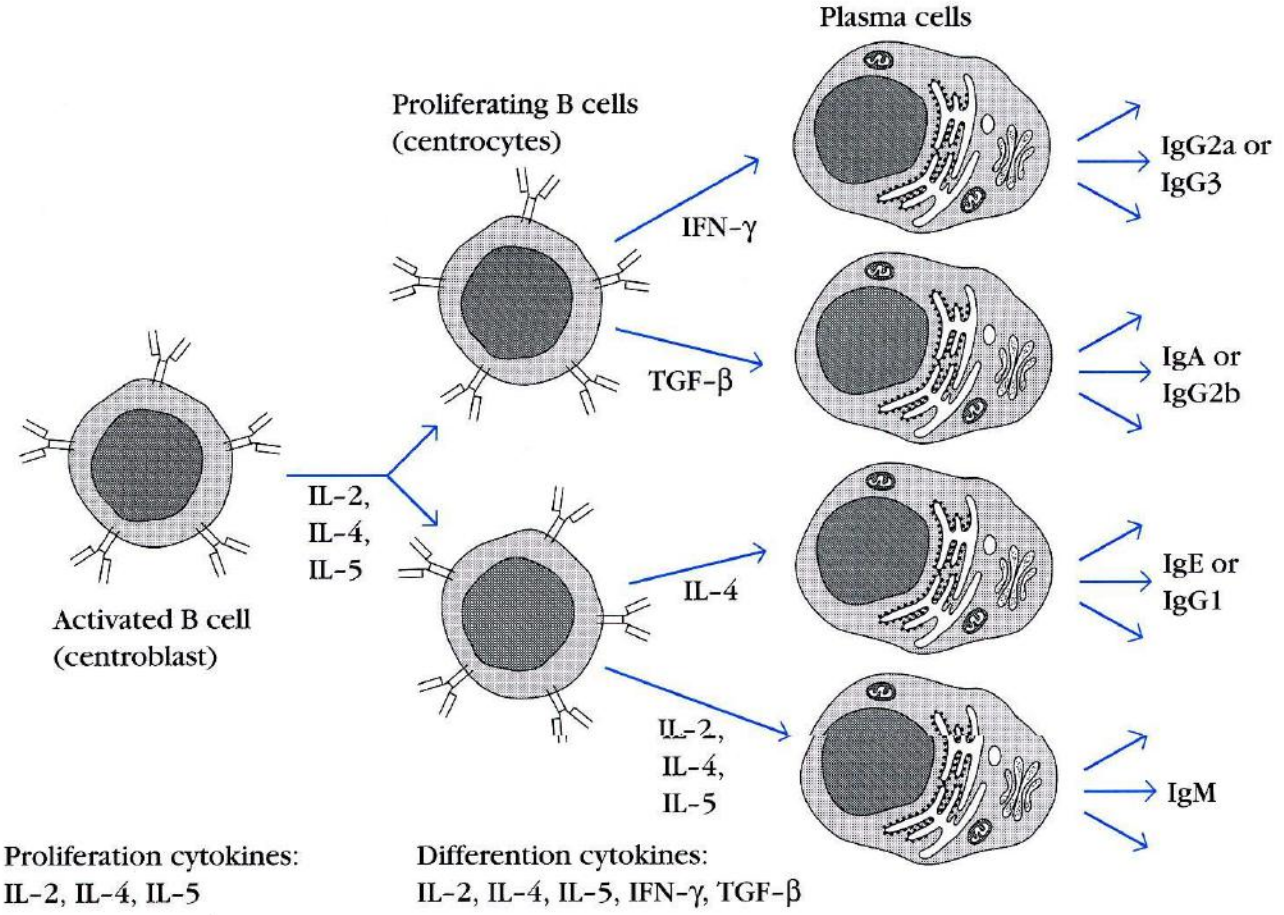


FIGURE 8-19

Numerous cytokines participate in B-cell proliferation and class switching during differentiation into plasma cells. Binding of the proliferation cytokines, which are released by activated T_H cells, provide the progression signal needed for proliferation of activated B cells. The indicated cytokine effects have been demonstrated; however, similar or identical effects may be mediated by other cytokines. Class switching in the response to thymus-dependent antigens also requires the CD40/CD40L interaction, which is not indicated here.

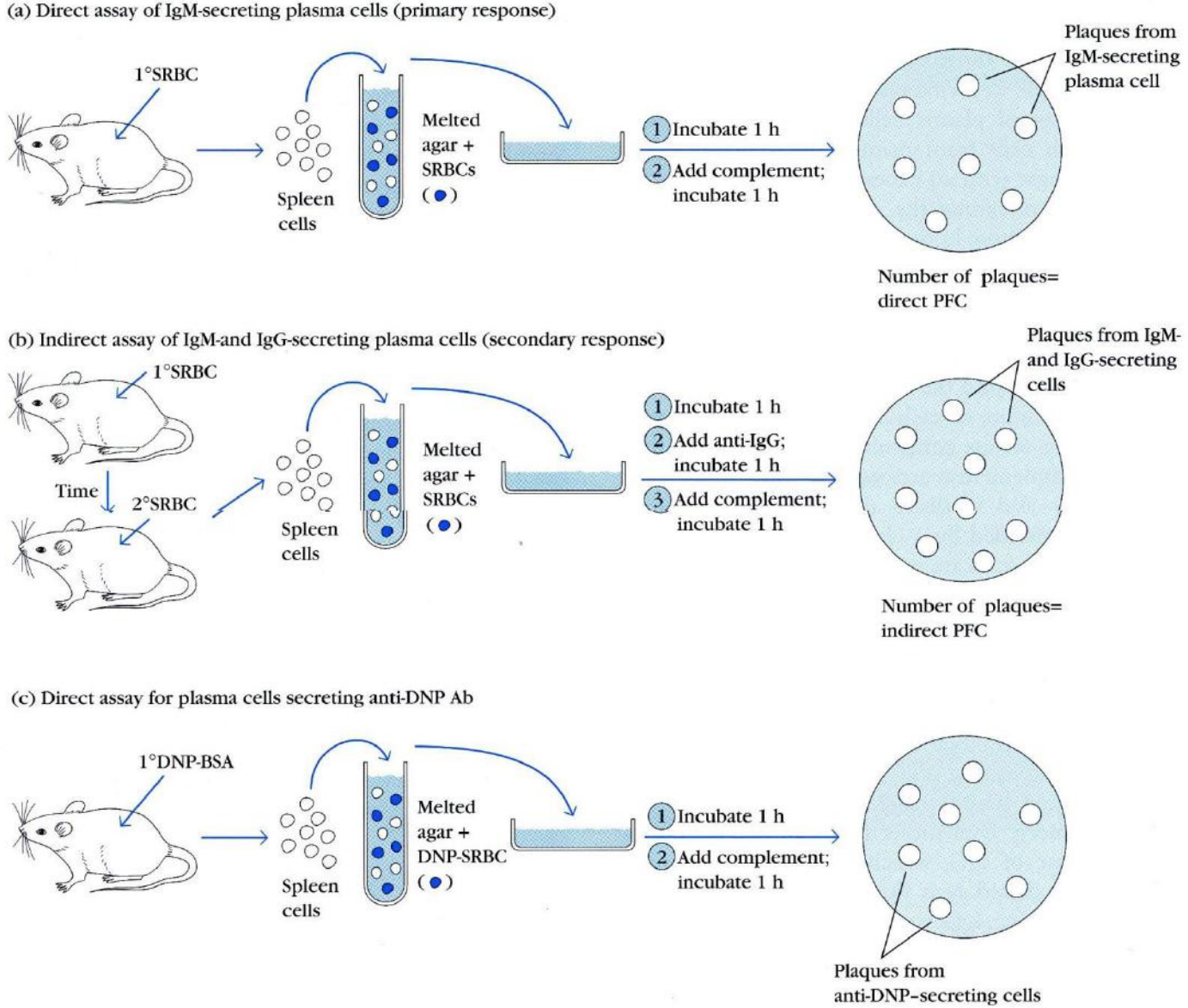


FIGURE 16-20

Hemolytic plaque assays. (a) A direct assay detects IgM-secreting plasma cells, which are predominant in a primary response. (b) In an indirect assay, which detects both IgM- and IgG-secreting plasma cells, antibodies against mouse IgG are added so that complement-mediated lysis of IgG-SRBC complexes will occur. By subtracting the direct PFC from the indirect PFC, the number of IgG-secreting plasma cells can be determined. In a secondary response, the indirect PFC is high and the direct PFC is low. (c) The response to immunization with antigens other than SRBCs can be determined with the hemolytic plaque assay if the immunizing protein or hapten is coupled to SRBCs.

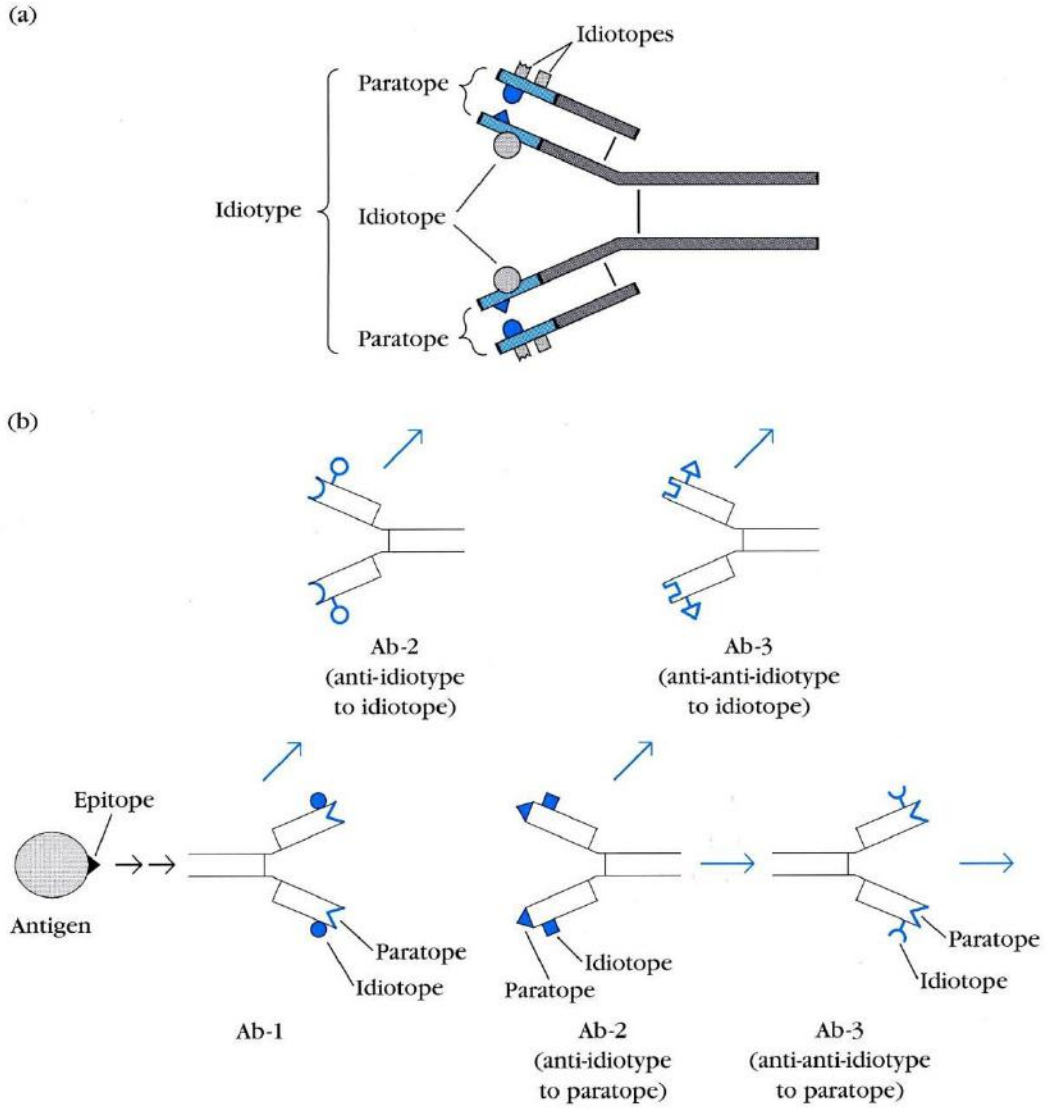


FIGURE 16-23

Network theory proposed by Niels Jerne. (a) Each antibody molecule expresses unique variable-region epitopes called idiotopes; the sum of the idiotopes is its idiotype. Idiotopes may coincide with the antigen-binding site, or paratope. (b) According to the network theory, the immune response to an antigen results in the formation of anti-idiotype antibodies specific for the individual idiotopes of the primary antibody (Ab-1). These anti-idiotype antibodies (Ab-2) in turn induce the formation of anti-anti-idiotype antibodies (Ab-3). A network of interacting antibodies is thus formed that serves to regulate the immune response. Note that the anti-idiotype antibody to the paratope of Ab-1 is an internal image of the original epitope on the antigen.