Immunology

Extra material or not

Organs

1. **Central lymphoid organs** (where immunocompetent cells are developed)
   - **a.** Thymus
   - **b.** Bone marrow
2. **Peripheral lymphoid organs** (where immunocompetency is expressed)
   - **a.** Spleen
   - **b.** Lymph nodes
   - **c.** Tonsils
   - **d.** Intestinal Peyer's patches
   - **e.** Mucosa

Cells. Antigen-presenting cells (APC), thymus-derived (T) cells, and **bone marrow-derived (B) cells** interact in the organs to produce two types of immunity.

1. **Humoral immunity** is mediated by proteins called **antibodies**, which neutralize microorganisms and toxins, and remove antigens in the body fluids by **amplifying phagocytosis or lysis.**
2. Cellular **(cell-mediated) immunity (CMI)** is mediated by **T cytotoxic cells, natural killer (NK) cells,** and **macrophages** and is responsible for **eradicating microorganisms residing within body cells,** as well as the **killing of aberrant host cells.**

. **Acquired immunity (specific antibody and CMI)**
   - **a. Actively acquired** by:
     - **(1)** Infection
     - **(2)** Vaccination
   - **b. Passively acquired** by:
     - **(1)** Placental transfer of antibody
     - **(2)** Injection of specific antibody

CONCERNS IN MEDICINE include:

A. The immune system's role in protection against infectious diseases and cancer

B. Immune-mediated complications of organ transplantation

C. The immune system's role in allergic disorders

D. The immune system's role in autoimmune disorders

E. The development of specific, sensitive assays for the diagnosis of disease

A. Antigen is a foreign substance that induces antibody or CMI after binding to the specific antigenic receptor on T and B cell clones.

B. Epitope (antigenic determinant, ligand). An epitope is the short sequence of amino acids or sugars in an antigen molecule that combines with a hypervariable reactive site on the antibody molecule. The sequence is usually repeated several times, and the number of repeats is referred to as the **valence.**

C. Hapten. A hapten is the portion of the antigen molecule that contains the epitope. This area reacts specifically with an antibody but is incapable of inducing antibody synthesis without a carrier molecule.

D. Superantigen. Certain retroviral proteins and bacterial toxins (e.g., staphylococcal enterotoxins, toxic shock syndrome toxin 1) can link multiple T cells—via particular T-cell receptor (TCR) Vβ regions—to the major histocompatibility complex (MHC) of antigen-presenting cells (APCs). Because this linking occurs at regions independent of the specific peptide-binding sites, many T cells and APCs are activated, secreting extraordinary amounts of cytokines (e.g., IL-2, IL-1).

E. Thymus-independent antigens activate B cells without T helper cell (Th) involvement. Most thymus-independent antigens possess multiple branched polysaccharide repeating units (e.g., lipopolysaccharides from Gram-negative bacteria) and activate B cells polyclonally, without regard to B cell specificity (B cell mitogens).

FACTORS DETERMINING ANTIGENICITY. Antigens are usually protein or polysaccharide; lipids are poorly antigenic. Factors that determine antigenicity include:

A. Degree of "foreignness" and host background

B. Size, shape, chemical composition, and exposure (amount, route, and frequency of exposure)

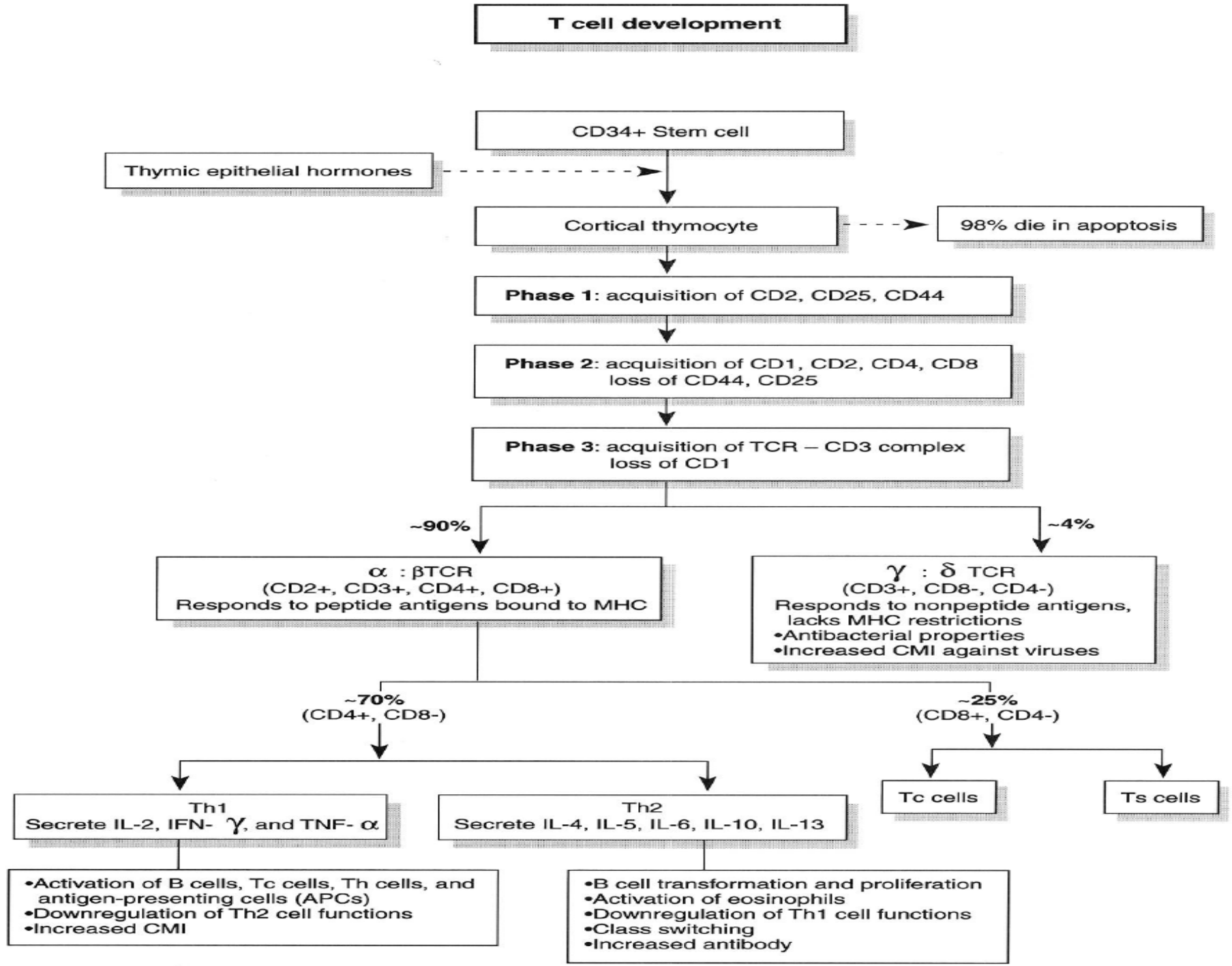
Human tissue antigens

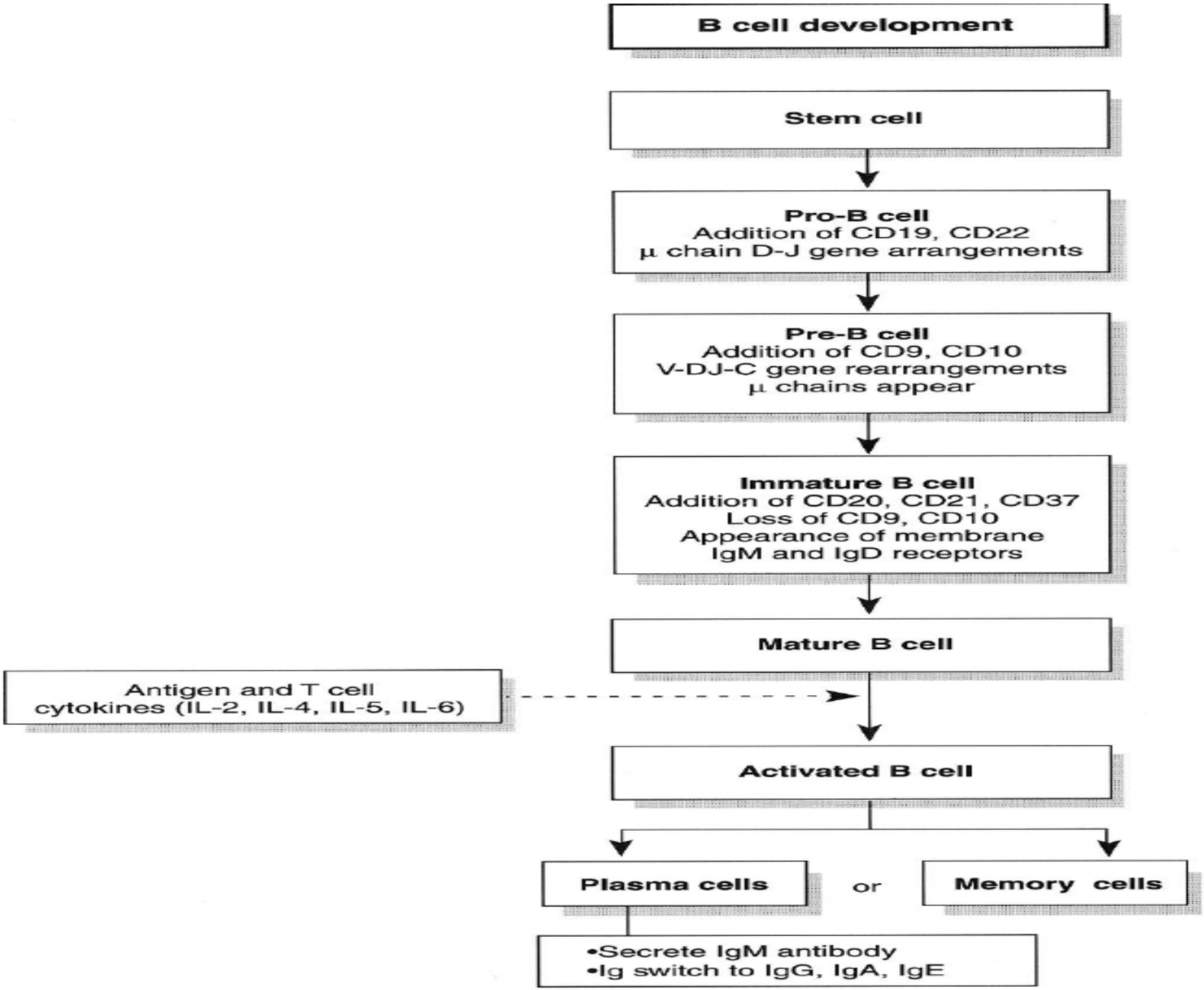
1. Blood-group antigens

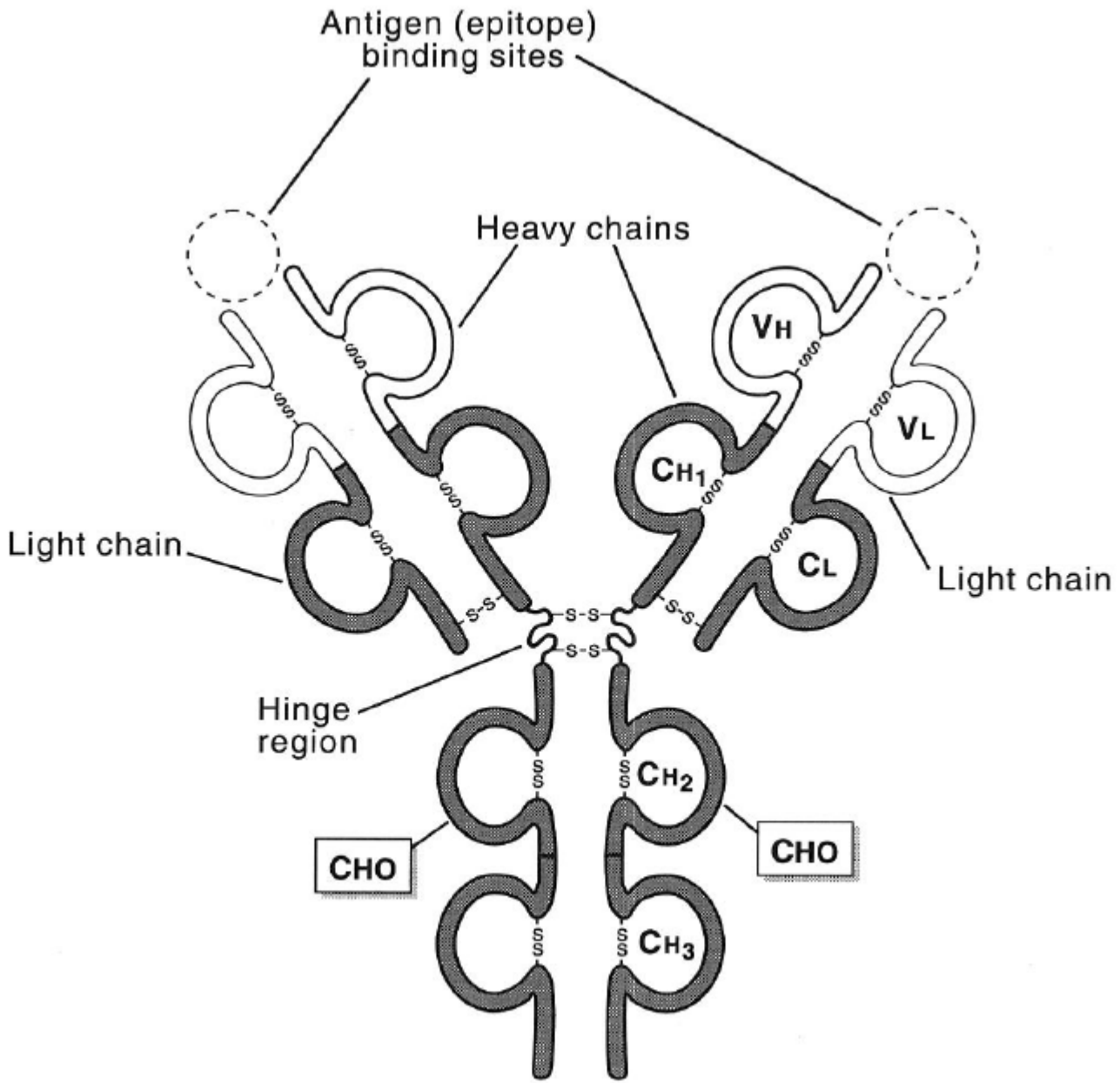
2. Organ-specific antigens

3. Individual-specific leukocytic antigens [e.g., human leukocyte antigens (HLA)]

Definition. Antibodies are mucoproteins that are found in the γ-globulin fraction of serum on electrophoresis. These mucoproteins are called **immunoglobulins (Ig).**


T cell development
CD34+ Stem cell
Thymic epithelial hormones
Cortical thymocyte
98% die in apoptosis
Phase 1: acquisition of CD2, CD25, CD44
Phase 2: acquisition of CD1, CD2, CD4, CD8
loss of CD44, CD25
Phase 3: acquisition of TCR – CD3 complex
loss of CD1
~90%
~4%
α : βTCR
(CD2+, CD3+, CD4+, CD8+)
Responds to peptide antigens bound to MHC
γ : δ TCR
(CD3+, CD8-, CD4-)
Responds to nonpeptide antigens,
lacks MHC restrictions
•Antibacterial properties
•Increased CMI against viruses
~70%
(CD4+, CD8-)
~25%
(CD8+, CD4-)
Th1
Secrete IL-2, IFN- γ, and TNF- α
Th2
Secrete IL-4, IL-5, IL-6, IL-10, IL-13
Tc cells
Ts cells
•Activation of B cells, Tc cells, Th cells, and
antigen-presenting cells (APCs)
•Downregulation of Th2 cell functions
•Increased CMI
•B cell transformation and proliferation
•Activation of eosinophils
•Downregulation of Th1 cell functions
•Class switching
•Increased antibody


B cell development
Stem cell
Pro-B cell
Addition of CD19, CD22
μ chain D-J gene arrangements
Pre-B cell
Addition of CD9, CD10
V-DJ-C gene rearrangements
μ chains appear
Immature B cell
Addition of CD20, CD21, CD37
Loss of CD9, CD10
Appearance of membrane
IgM and IgD receptors
Mature B cell
Antigen and T cell
cytokines (IL-2, IL-4, IL-5, IL-6)
Activated B cell
Plasma cells
or
Memory cells
•Secrete IgM antibody
•Ig switch to IgG, IgA, IgE


Antigen (epitope)
binding sites
Heavy chains
VH
VL
CH1
CL
Light chain
Light chain
S-S
S-S
S-S
S-S
Hinge
region
CH2
CH3
CHO
CHO

a. IgG adheres to cells that possess a receptor for the Fc fragment from IgG (Fcγ).
b. IgG fixes complement (i.e., a series of enzymes resulting in cell lysis).
c. IgG mediates placental passage of maternal antibody to the fetus.

Enzymatic cleavage

a. Papain splits IgG into three fragments.

(1) Two of these fragments **(Fab; fragment, antigen binding)** are similar, with each containing only one of the reactive sites for the epitope. Because Fab is monovalent, it can bind to but cannot enter into lattice formation and precipitate or agglutinate antigen.

(2) A third fragment **(Fc; crystallizable)** activates complement, controls catabolism of IgG, fixes IgG to tissues or cells via an Fc receptor, and mediates placental transfer.

b. Pepsin splits behind the disulphide bond joining the two H chains, permitting the two Fab fragments to remain joined. Consequently, this fragment is termed **F(ab′)2.**

(1) Because F(ab′)2 is bivalent, it is capable of lattice formation and aggregation of antigens.

(2) F(ab′)2 is removed more rapidly from the circulation than the intact IgG.

(3) The Fc fragment is extensively degraded.

Enzyme-linked immunosorbent assay (ELISA)

1. **Antibody detection** is useful in detecting antibodies in a patient's serum (e.g., HIV).
   a. Dilutions of the test antibody solution are added to antigen adsorbed onto plastic wells. The complex is washed, and an enzyme-conjugated, anti-isotype antibody is added.
   b. After washing, the enzyme substrate is added.
   c. The resulting color is measured using a spectrophotometer. The titer is recorded as the highest dilution of antibody giving a color above the background.

2. **Antigen detection** is useful for measuring nanogram (ng) amounts of hormones, drugs, and serum proteins.
   a. Dilutions of antigen are added to antibody that is adsorbed onto plastic wells. The resulting complex is washed, and an enzyme-conjugated antibody specific for a different epitope on the test antigen is added.
   b. After washing, the enzyme substrate is added, and the colored reaction is measured using a spectrophotometer. The titer is recorded as the highest dilution of antigen giving a color above background.

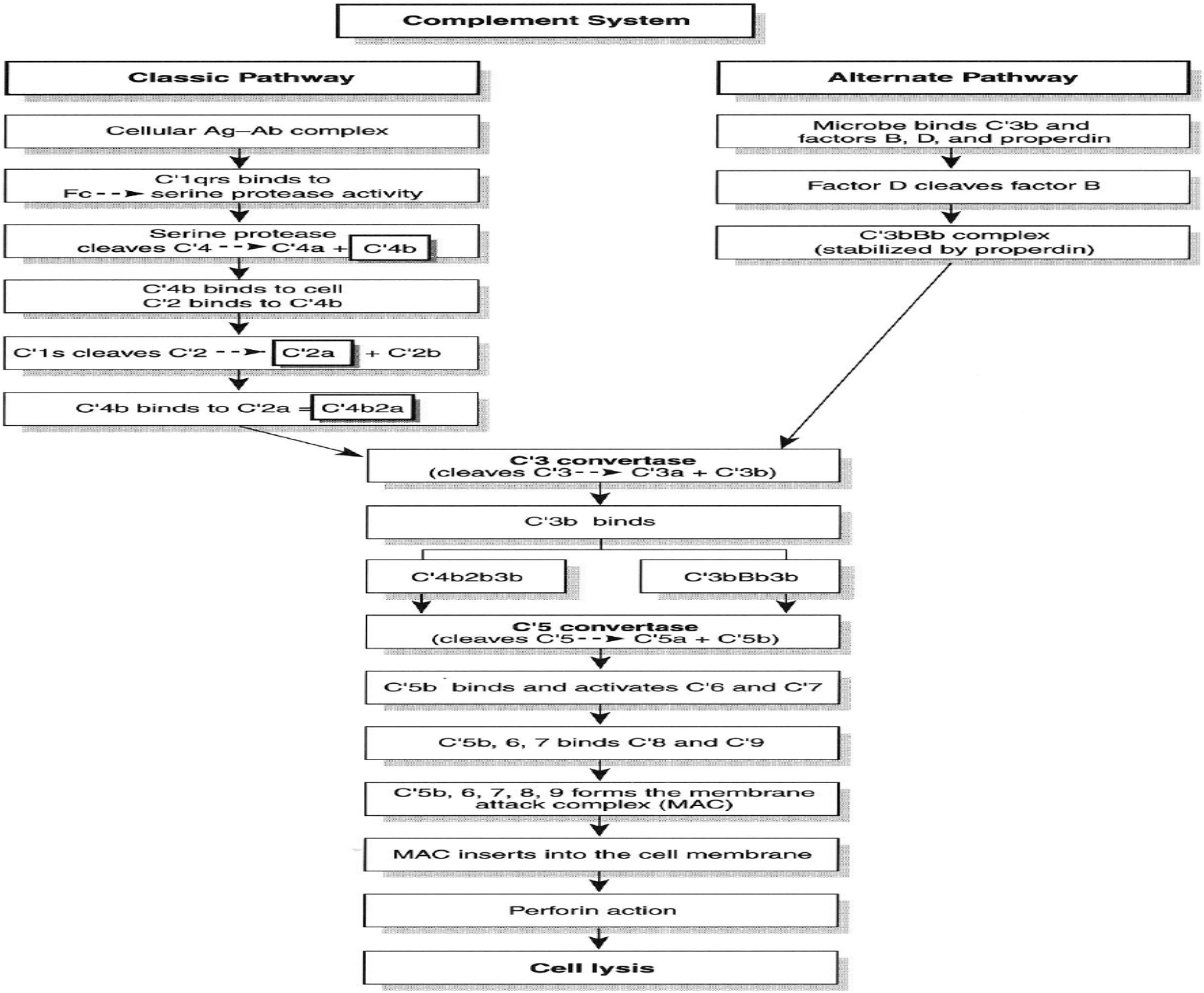
COMPLEMENT FIXATION

A. Complement system. Complement (C′) fixation results in **cell lysis** and requires **nine major factors (C′1–C′9),** which have enzymatic functions. Complement is fixed via **two pathways** (Figure 4-4).

1. Classic pathway. Binding of the proenzyme C′1 to an Ag–Ab complex triggers a sequential reaction that results in cell lysis.

- **a.** IgM or a doublet of IgG bound to a cell surface antigen activates C′1qrs, which cleaves C′4 and C′2.
- **b.** Fragments C′4b and C′2b bind to the cell surface as C′4b2b, becoming a C′3 convertase that cleaves C′3 into two fragments, C′3a and C′3b.
- **c.** C′3b complexes with C′4b2b to become a C′5 convertase, which cleaves C′5 to C′5a and C′5b.
- **d.** C′5b combines with C′6 and C′7 and inserts into the cell membrane.
- **e.** C′8 and C′9 combine with the C′5b, 6, 7 complex to form the **membrane attack complex (MAC),** resulting in cell lysis.

2. **Alternate pathway.** This pathway is activated by cell walls of certain bacteria, yeasts, and aggregated IgA. It does not require antibody or C′1, C′4, or C′2.
   - **a.** The cell walls bind to C′3b, which exists in normal serum. This complex binds with three other serum factors (B, D, and properdin), leading to a C′3 convertase. C′3bBb generates additional C′3b.
   - **b.** A C′3bBbC′3b complex forms, which becomes a C′5 convertase leading to the reactions that result in the MAC.


Complement System
Classic Pathway
Cellular Ag–Ab complex
C'1qrs binds to
Fc - - ➤ serine protease activity
Serine protease
cleaves C'4 - - ➤ C'4a + C'4b
C'4b binds to cell
C'2 binds to C'4b
C'1s cleaves C'2 - - ➤ C'2a + C'2b
C'4b binds to C'2a = C'4b2a
Alternate Pathway
Microbe binds C'3b and
factors B, D, and properdin
Factor D cleaves factor B
C'3bBb complex
(stabilized by properdin)
C'3 convertase
(cleaves C'3 - - ➤ C'3a + C'3b)
C'3b binds
C'4b2b3b
C'3bBb3b
C'5 convertase
(cleaves C'5 - - ➤ C'5a + C'5b)
C'5b binds and activates C'6 and C'7
C'5b, 6, 7 binds C'8 and C'9
C'5b, 6, 7, 8, 9 forms the membrane
attack complex (MAC)
MAC inserts into the cell membrane
Perforin action
Cell lysis

Characteristics of IgG and IgM antibodies

Clinical significance

Clinical of red cell antibodies in blood bank depend on whether they can cause in vivo hemolysis, which in turn will cause transfusion reactions or hemolytic disease of the newborn.

IgG will frequently cause in vivo hemolysis due to antibody coating the red blood cells.

IgM, with a few important exceptions, usually does NOT cause in vivo hemolysis. The most important of these exceptions are ABO antibodies.

Size of the antibodies

IgG is relatively small since it is comprised of only one immunoglobulin subunit. (monomer)

IgM is relatively large since it is comprised of 5 immunoglobulin subunits. (pentamer)

Serum concentration

IgG is found in the largest concentration of all immunoglobulins in the plasma.

IgM is found in relatively small amounts

IgG > IgA > IgM

Complement activation

IgG = will do it if conditions are optimal

IgM = very good complement activator

Placental transfer

IgG is small enough to easily cross placenta and is the only immunoglobulin capable of doing so.

IgM and the other classes do not cross placenta

Optimum temperature of reactivity

a. IgG = 37^{o}C

b. IgM = 4 ^{o}C (may react at any temperature below 30C)

Number of antigen-binding sites

IgG has 2 binding sites

IgM has 10 binding sites