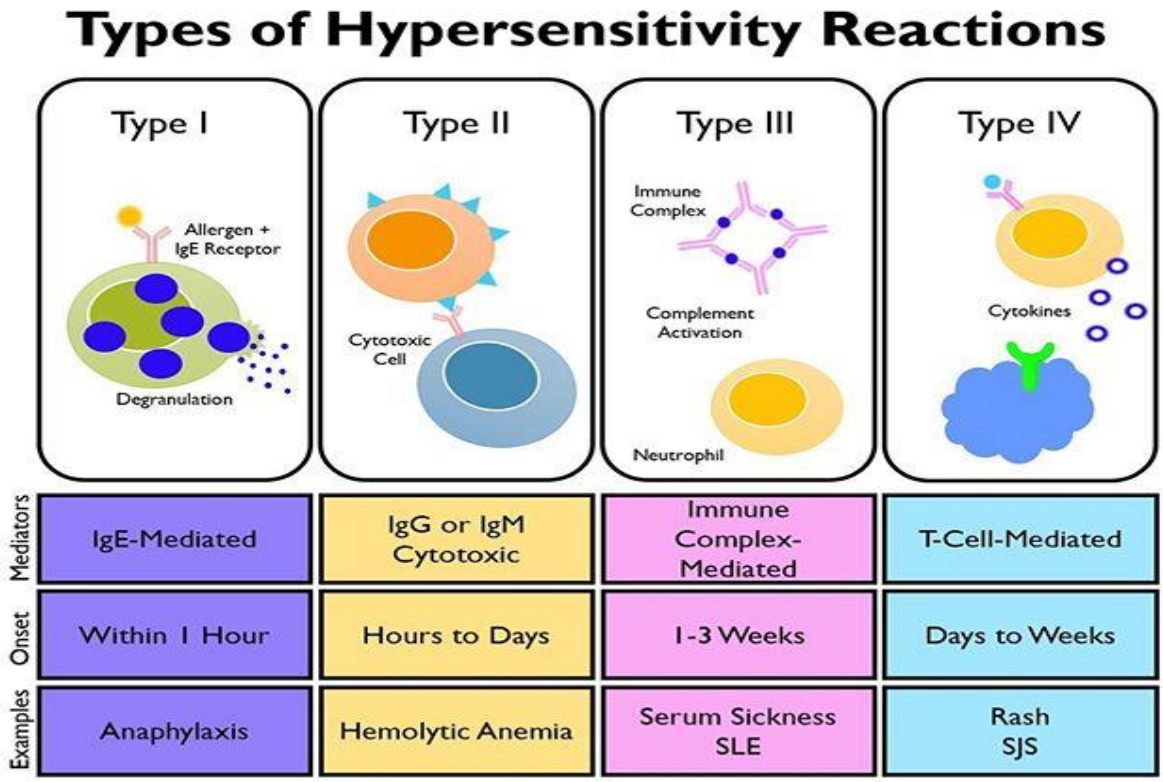
Hypersensitivity Reactions

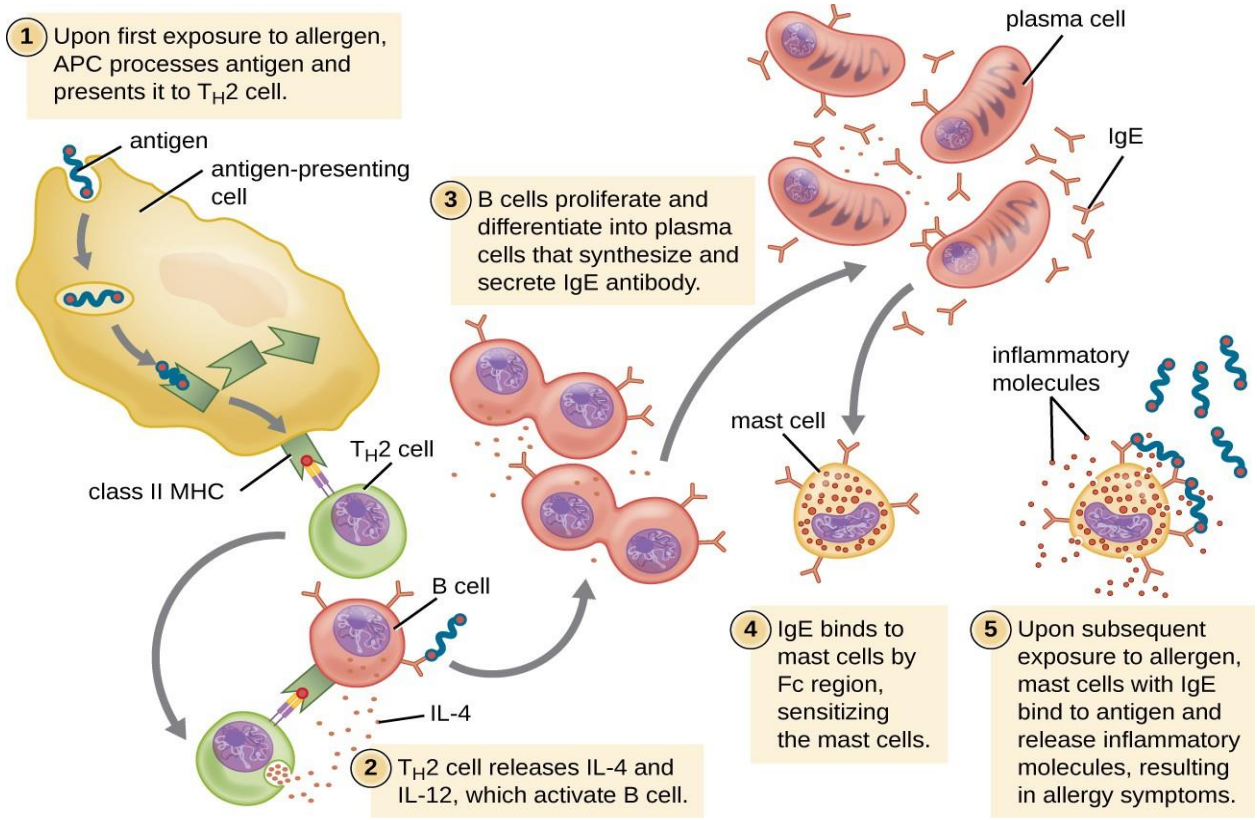
Excessive or inappropriate immune responses sometimes lead to host tissue damage resulting from prolonged or repeated antigen exposure. These reactions, called hypersensitivity reactions, cause tissue injury by the release of chemical substances that attract and activate cells and molecules resulting in inflammation. These reactions are classified into four hypersensitivity types depending on the mechanism(s) that underlie the tissue damage in table below; the first three types involve antigen antibody reactions, whereas the fourth is antibody-independent, involving cell-mediated immune responses only.

1. **Type I** (also called immediate hypersensitivity) hypersensitivity reactions are rapid, occurring within minutes of exposure to an antigen, and always involve lgE-mediated degranulation of basophils or mast cells.
2. **Type II hypersensitivity** reactions are initiated by the binding of antibody to a cell membrane or to the extracellular matrix.
3. **Type Ill hypersensitivity** reactions involve the interaction of antibodies with soluble molecules to make soluble antigen-antibody complexes that become deposited in tissues.
4. **Type IV hypersensitivity** reactions are those in which cells of the immune system directly attack host cells in the absence of antibody. These reactions include contact dermatitis (CD, also called contact sensitivity, CS); delayed-type hypersensitivity (DTH); and, occasionally, cytotoxic T-lymphocyte (CTL) responses.



TYPE I HYPERSENSITIVITY

Commonly called allergic or immediate hypersensitivity reactions, type I responses occur within minutes to hours of antigen exposure. Some individuals develop lgE antibodies in response to relatively harmless environmental antigens or allergens. lgE molecules readily bind to Fc receptors (FcR£ or CD23) on the surfaces of mast cells and basophils (Fig. below). Cross-linking of surface-bound lgE molecules generates intracellular signals via CD23, leading to mast cell or basophil degranulation and the release of vasoactive amines (e.g., histamine) and other inflammatory mediators. Histamine and other inflammatory mediators cause vascular endothelial cell junctions to loosen (vasodilation) and increase vascular permeability, resulting in fluid accumulation in the tissues (edema). Histamine also induces smooth muscle contraction in arterial and arteriole walls (vasoconstriction) to accelerate fluid distribution from the central trunk of the body into peripheral tissues.



A. Localized reactions

Because mast cells accumulate in respiratory passages, intestinal walls, and the skin, type I reactions are often most pronounced in these tissues. Sites affected are typically those where the initiating antigen is most often encountered. Antigens that enter the body by inhalation localize primarily to the nasopharyngeal and bronchial tissues, where smooth muscle contraction and vasodilation increase mucous production and the constriction of respiratory passages.1n combination, these responses can produce the severe and potentially fatal disorder known as asthma. Allergens that contact other tissues may produce lgE-mediated inflammatory responses, causing rashes, redness, and edema-the classic "wheal and flare" appearance. Food or ingested allergens primarily affect the gastrointestinal tract.

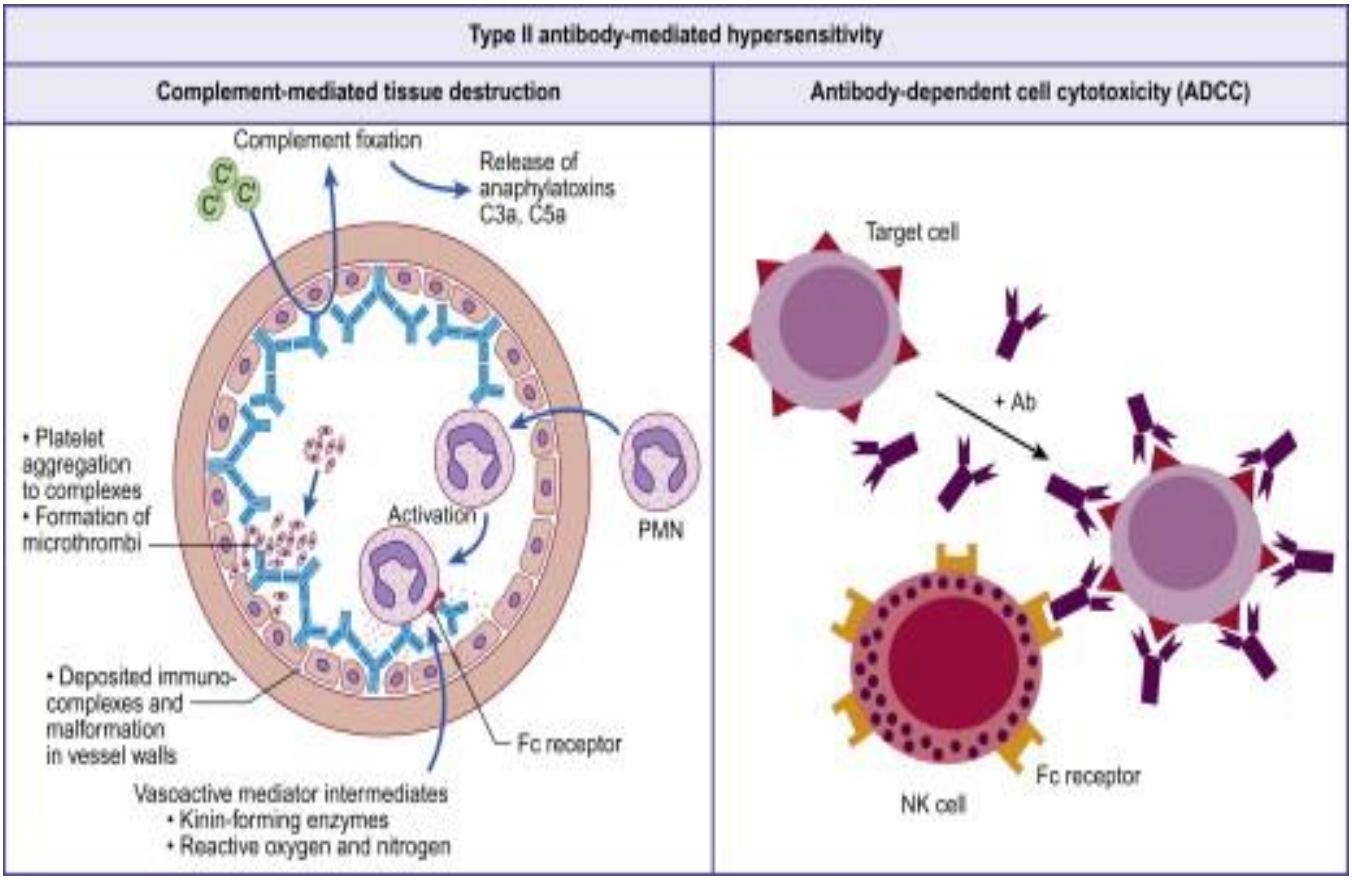
B. Systemic reactions

In some cases, such as injected allergens (e.g., venom or toxins), antigen may be disseminated by the bloodstream, resulting in systemic inflammation. The experiments found that initial injection of dogs with a small amount of toxin had

little effect. However, when a second injection of the same amount of the toxin was administered several weeks later, the dogs suffered immediate shock and even death. Termed anaphylaxis ("against protection"), this clinical shock syndrome is characterized by vascular smooth muscle constriction (vasoconstriction) combined with gap formation between adjacent capillary endothelial cells (vasodilation) that results in severe fluid loss and leads to shock. This kind of response can also occur in humans when an allergen, to which the individual is highly sensitive, enters the body.

TYPE II HYPERSENSITIVITY

Type II hypersensitivity reactions are initiated by the interaction of antibody (lgM or lgG, not lgE) with cell membranes or with the extracellular matrix. Complement may also be involved. The antigens that are recognized maybe intrinsic to the cell membrane or extracellular matrix, or they may be exogenous molecules, such as a drug metabolite adsorbed onto the cell membrane or extracellular matrix. (Fig. below).



A. Interaction of antibody with cells

Cell-surface or extracellular matrix epitope binding by antibodies (usually lgM or lgG) results in a conformational change in the Fe portion of the antibody molecule. The conformational change in the Fe portion of the antibody molecule is recognized by cellular FcRs and by complement; and several immune-mediated destructive mechanisms may then come into play, targeted on the site(s) of antibody binding.

1. Antibody-dependent cell-mediated cytotoxicity (ADCC): This is complement independent but requires the cooperation of leukocytes. FcR-bearing cells (e.g., monocytes, neutrophils, eosinophils, and natural killer [NK] cells) bind to cells that have lgG or lgM antibodies bound to surface epitopes on a cell.

2. Complement: Complement activated by lgM and lgG antibodies generates active components of the classical pathway, namely, C3b and C4b. These components are then deposited on the surfaces of antibody-coated cells or extracellular matrix to function as opsonins. Phagocytes recognize bound antibody through their FcRs and bound complement components through their complement receptors. In this manner, both complement and antibody function as opsonins to increase phagocytosis and the destruction of microorganisms.

3. Blood group antibodies: These exempl ify type II hypersensitivity reactions. Hemolytic anemias may result from the binding of lgM antibodies to carbohydrate structures on erythrocytes (notably anti-A or anti-B antibodies) resulting in their phagocytosis and in the presence of complement, their rapid lysis (hemolysis). Antibodies (lgG) to certain protein molecules on erythrocytes (e.g., Rh factor[s]) do not activate complement; erythrocytes are destroyed by phagocytosis.

B. Interaction of antibody with the extracellular matrix

Antibodies that bind to extracellular matrix proteins (e.g., basement membrane) may activate the classical pathway of complement, generating anaphylotoxins (e.g., C5a, C4a, C3a, in descending order of potency, not in order of appearance) that recruit neutrophils and monocytes. FcR engagement

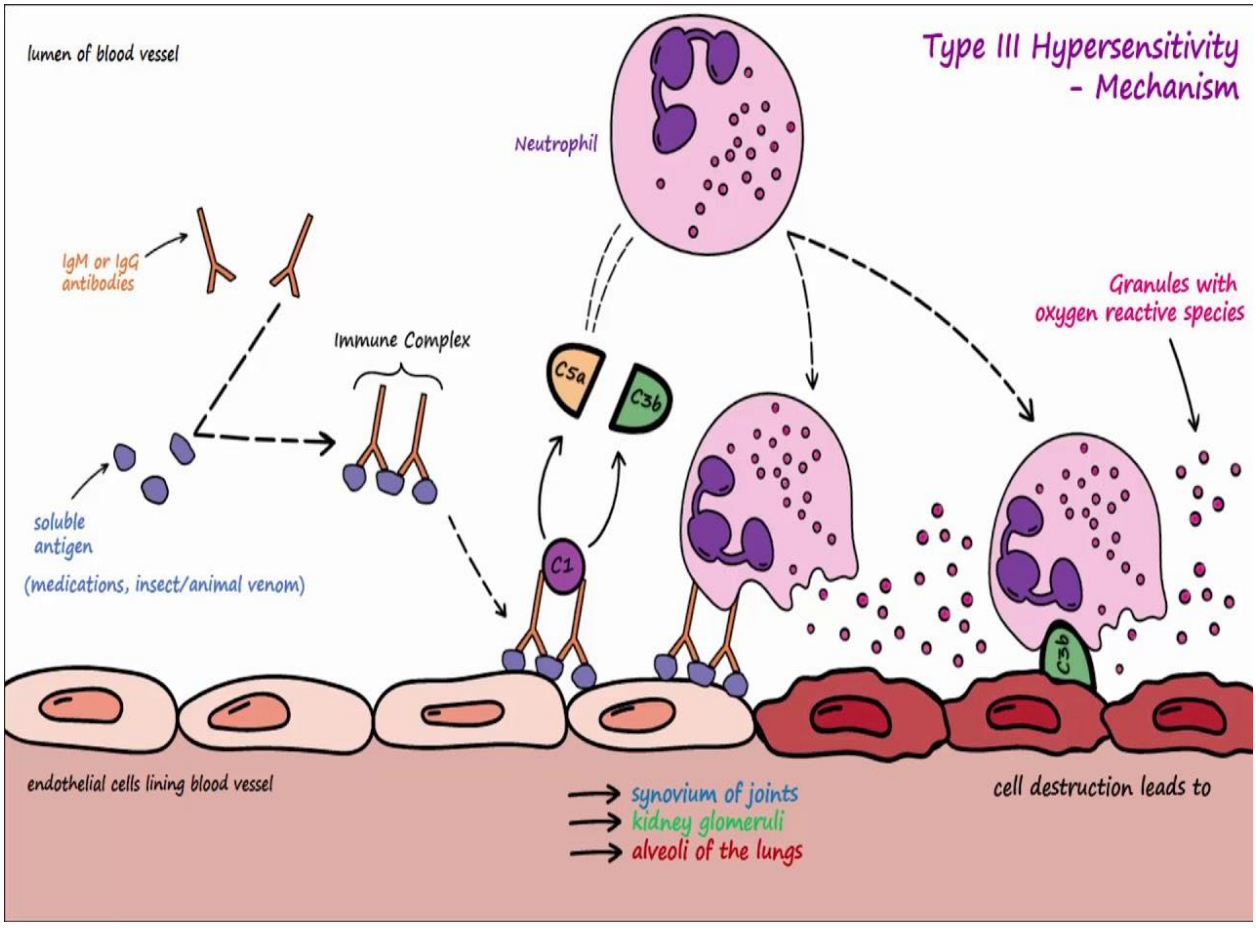
with the bound antibody results in the release of reactive oxygen intermediates, resulting in inflammation and tissue injury.

C. Antibody-mediated disruption of cellular function

Sometimes antibodies bind to cell surface receptors without activating complement or binding to FcRs. This binding blocks the receptor's ability to interact with its natural ligand. The antibody-receptor interaction may be stimulatory (e.g., Graves disease) or inhibitory (e.g., myasthenia gravis) to the receptor's signaling pathway(s).

TYPE Ill HYPERSENSITIVITY

Circulating antigen-antibody complexes may lead to inflammation at their sites of deposition, often resulting in blood vessel inflammation (vasculitis). Immune complexes may cause injury resulting from the interaction with exogenous (e.g., microbes, viruses, or chemically modified self-proteins) or endogenous antigens (e.g., serum proteins). Type Ill reactions may occur locally or systemically.



A. Localized reactions

Localized type Ill hypersensitivities, also known as Arthus reactions, result from acute immune complex vascul itis causing tissue necrosis. These reactions are el icited 4 to 6 hours after the intradermal introduction of a small amount of antigen. Antibody diffuses from the vasculature to form large immune precipitates that activate complement to induce a painful localized edematous inflammatory lesion (Fig. above). Lesions range from necrotizing vasculitis with polymorphonuclear cell infiltration to the formation of a sterile abscess.

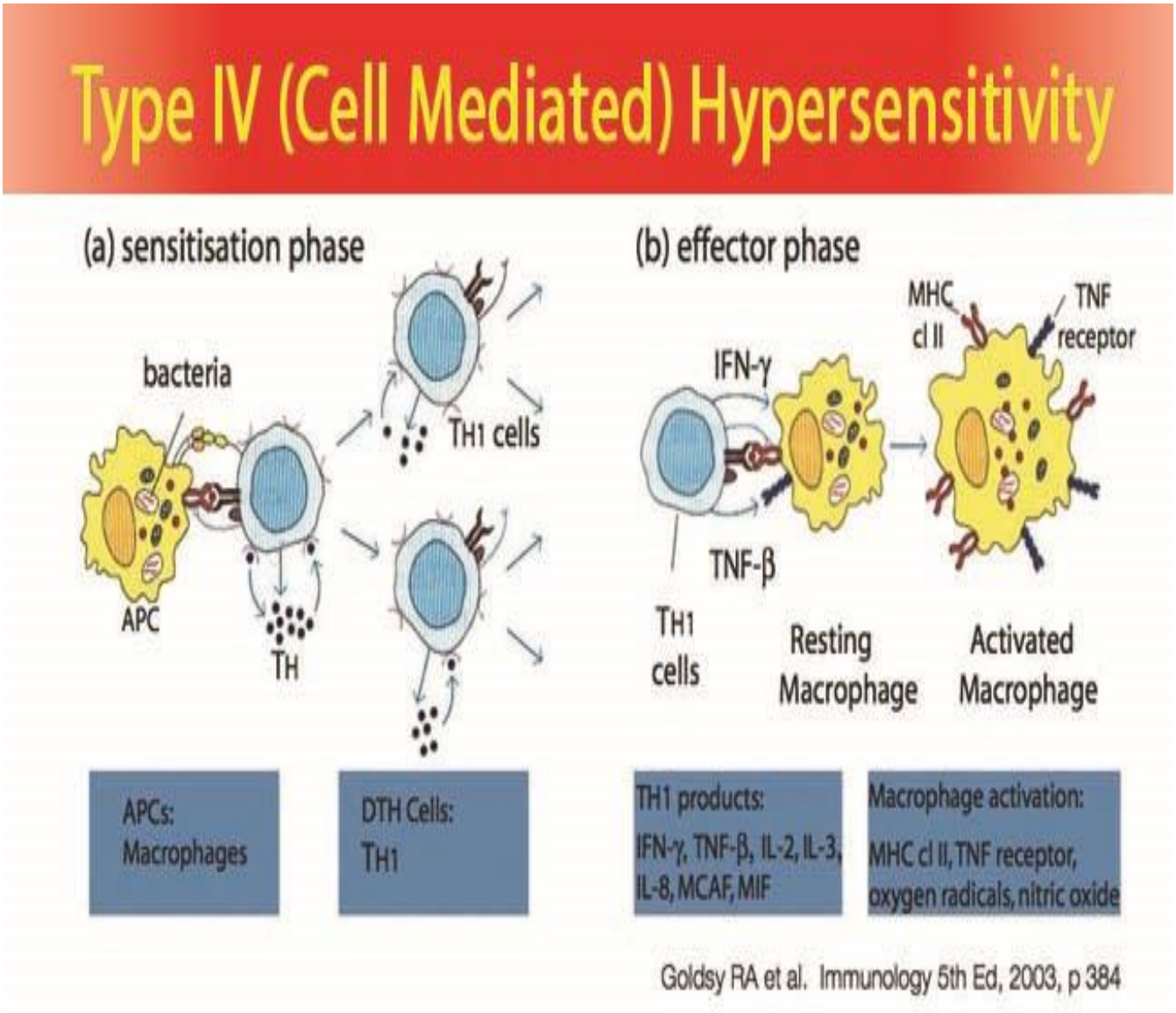
B. Systemic reactions

Systemic immune complex disease, in some cases termed serum sickness, occurs with the wide dissemination of antigen-antibody complexes throughout the body. Very large immune complexes are rapidly cleared from the body by phagocytic cells and are relatively harmless. Smaller, circulating immune complexes have less chance to be seen by phagocytes and remain in the circulation longer. These complexes have the greatest pathologic consequences.

1. **Exogenous antigens**: Administered either in large amounts or for a prolonged period, these may induce antibody responses. Soluble antigen-antibody complexes immobilized along the endothelium activate complement to cause vascular injury (e.g. Serum sickness).
2. **Endogenous antigens**: These may also cause immune-complex disease. Unlike exogenous antigens, continually produced endogenous antigens are responsible for chronic antigen exposure, chronic immunization, and prolonged immune-complex disease (e.g. systemic lupus erythematosus SLE).

TYPE IV HYPERSENSITIVITY

Type IV hypersensitivity reactions result from the interaction of T cell-initiated inflammation and do not involve antibody. Inflammatory responses result from the manner in which T cells encounter and respond to antigen. CD4+ T cells may be sensitized and respond to topically applied antigen (contact dermatitis, CD, also called contact sensitivity) and by antigen-injected antigen (delayed [-type] hypersensitivity, DTH), also T cell-mediated cytotoxicity (CTL) by C8+ T lymphocytes cells (Fig. below).


Type IV (Cell Mediated) Hypersensitivity
(a) sensitisation phase
bacteria
APC
TH
TH1 cells
(b) effector phase
MHC cl II
TNF receptor
IFN-γ
TNF-β
TH1 cells
Resting Macrophage
Activated Macrophage
APCs: Macrophages
DTH Cells: TH1
TH1 products: IFN-γ, TNF-β, IL-2, IL-3, IL-8, MCAF, MIF
Macrophage activation: MHC cl II, TNF receptor, oxygen radicals, nitric oxide
Goldsy RA et al. Immunology 5th Ed, 2003, p 384