

## Nonspecific Defenses & Immune System

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### Immunity

- ability to provide resistance to ds
- two systems
  - nonspecific ~ innate
  - adaptive ~ specific
  - always work together

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### Nonspecific System

- always prepared
- responds w/in minutes
- protects body from all foreign substances
- provides two lines of defenses
  - 1) external body membranes
  - 2) action by chemical signals
- see Table 22.2

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### Nonspecific Lines of Defense

- external body membranes (1st line)
  - prevent entry of microorganisms
    - intact skin
    - mucosae
- action by chemical signals (2nd line)
  - inhibition of foreign substances
    - antimicrobial proteins & phagocytes
      - when external defenses are penetrated
  - hallmark
    - inflammation

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### Adaptive System

- provides third line of defense
- fights against particular foreign substances
- reinforces & enhances the nonspecific system
- requires more time

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### Pathogen

- harmful or disease-causing microorganism
- usually destroyed by nonspecific defenses alone
  - ward off infection

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### Surface Barriers

- skin & mucous membranes
  - & their secretions
- provide 1st line of defense
- serve as a physical barrier to most microorganisms
- effective if epidermis is unbroken
  - nicks & cuts
- if epidermis is broken
  - need internal innate defenses

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### Surface Barriers

- keratin
  - resistant
    - most weak acids & bases
    - bacterial enzymes & toxins
- intact mucosae
  - provides barrier by lining all body cavities that open to exterior
    - digestive
    - respiratory
    - urinary
    - reproductive

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### Surface Barriers

- epithelial membranes
  - produce variety of protective chemicals
- 1) acidity of skin secretions
  - ph 3-5
  - inhibit bacterial growth
  - includes sebum & vagina
    - toxic or acidic secretions
- 2) stomach mucosa
  - concentrated HCl solution
  - protein-digesting enzymes

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### Surface Barriers

- epithelial membranes
- 3) saliva & lacrimal fluid
  - cleanses oral cavity and teeth
  - washes external eye surfaces
    - contain lysozyme
      - enzyme kills bacteria
- 4) sticky mucus
  - traps microorganisms
    - enter digestive & respiratory passageways

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### Surface Barriers

- respiratory mucosae
- structural modifications
  - counteract pot'l invaders
    - 1) mucus coated hairs in nose
      - trap inhaled particles
    - 2) upper respiratory tract ciliated mucosa
      - sweep dust & bacteria to mouth
      - prevent entrance into lower respiratory tract

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### Internal Innate Defenses

- variety of chemical & cellular means
- recognize unique CHO
  - on surface of harmful substances
- include
  - phagocytes
  - natural killer cells
  - inflammatory response
  - antimicrobial proteins
  - fever

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### Phagocytes

- macrophages
- neutrophils
- eosinophils
- mast cells
  - share capabilities

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### Macrophages

- chief phagocytes
- derived from WBCs
  - monocytes
    - leave bloodstream
    - enter tissues
    - enlarge
    - develop into macrophages

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### Macrophages

- free
  - wander around looking for cellular debris or foreign invaders
  - example
    - alveolar macrophages (lungs)
    - dendritic cells (epidermis)
- fixed
  - permanent residents of organs
  - example
    - microglia (brain)
    - Kupfer cells (liver)

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### Phagocytes

- neutrophils
  - most abundant type of WBC
  - become phagocytic
    - when encounter infectious material in tissues
- eosinophils
  - another WBC
  - weakly phagocytic
    - fights parasitic worms

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### Phagocytes

- mast cells
  - not phagocyte
  - shares ability
  - role in allergies
    - ingest a wide variety of bacteria

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### Inflammatory Response

- triggered whenever body tissues are injured
  - physical trauma
  - intense heat
  - irritating chemicals
  - infections
    - viral
    - fungal
    - bacterial

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### Inflammatory Response

- functions
  - 1) prevent the spread to nearby tissue
  - 2) dispose of cellular debris & pathogens
  - 3) prepare for repair process

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### Inflammatory Response

- four cardinal signs
  - acute or short-term inflammation
  - 1) redness
  - 2) heat
  - 3) swelling
  - 4) pain
    - temporarily hinder joint movement
  - 5) impairment of function

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### Steps in Inflammatory Process

- "chemical alarm"
  - influx of inflammatory chemicals into ECF
    - from injured cells, phagocytes, lymphocytes, mast cells, blood proteins
  - results in:
    - vasodilation
    - increased capillary permeability
    - chemotaxis
      - pus formation

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### Steps in Inflammatory Process

- 1) "chemical alarm"
- 2) dilation of blood vessels
  - injured site
- 3) local hyperemia
  - increased blood flow to injured site
    - results in 4)
- 4) heat & redness (cardinal signs)

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### Steps in Inflammatory Process

- 1) "chemical alarm"
- 2) increased capillary permeability
- 3) leakage of fluid
- 4) exudate formation
  - fluid containing proteins (CF, AB)
    - results in 5)
- 5) pain & swelling (cardinal signs)
  - local edema (swelling)
    - pressure on adjacent nerve endings causes pain (see text for adf1 causes)

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### Inflammation Events (fig 22.2)

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### Edema

- surge of protein-rich fluids into tissue spaces
- functions
  - 1) dilute harmful substances present
  - 2) bring large amounts oxygen and nutrients needed for repair
  - 3) allow entry of clotting proteins
    - form gel-like fibrin mesh that isolates the injured site

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### Homeostatic Imbalance

- pus
  - creamy, yellow mixture
    - dead or dying neutrophils
    - broken down tissue cells
    - living and dead pathogens
- abscess
  - sac of pus walled off by collagen fibers
  - forms when inflammatory process does not remove all the debris

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### Complement System

- AKA complement
- group of at least 20 plasma proteins
  - normally circulate in blood in an inactive state
- a nonspecific defense mechanism
- also "complements" or enhances nonspecific & specific defenses

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### Complement System

- actions
  - 1) lyse microorganisms
  - 2) enhance phagocytosis
  - 3) intensify inflammatory & immune response

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### Interferon

- family of related proteins
- slightly different physiological effects
- produced by variety of body cells
  - host cell 1
    - infected by virus
    - makes interferon
    - killed by virus
  - host cell 2
    - entered by interferon made by host cell 1
    - interferon induces changes
      - provides protection

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### Interferon

- stimulates synthesis of a protein
  - known as PKR
  - acts as antiviral
    - interferes w/ viral replication
      - blocks against protein synthesis
    - activates macrophages
    - mobilizes natural killer cells
  - protection is not virus-specific
    - protects against a variety of other viruses

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### Interferon Mechanism

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### Fever

- abnormally high body temperature
- systemic response to invading microorganisms
- initiated by pyrogens
  - chemicals
    - secreted by leukocytes & macrophages
      - exposed to bacteria & foreign substances in body

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### Fever

- normal temp
  - regulated by cluster of neurons in hypothalamus
- high fever
  - dangerous
  - inactivates (denatures) enzymes

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### Fever

- mild or moderate fever
  - adaptive response
  - benefits body
  - liver & spleen sequester nutrients
    - iron & zinc
      - needed by bacteria for multiplication
  - increased metabolic rate
    - speeds up the repair process

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### Adaptive (Specific) Defenses

- built-in specific defense system
- "stalks" and eliminates w/ ~precision
  - any type of pathogen
- recognizes specific foreign substances
  - immobilize, neutralize or destroy them
- provides protection
  - infectious agents & abnormal body cells

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### Adaptive (Specific) Defenses

- amplifies inflammatory response
- responsible for most complement activation
- primed by initial exposure to a specific foreign substance
- time consuming
- failure or malfunction — ds
  - cancer, AIDS

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### Important Aspects of Adaptive Defenses

- ⚡ 1) antigen-specific
  - recognizes and is directed against particular antigens
    - pathogens or substances that initiate the immune response
- ⚡ 2) systemic
  - immunity is not restricted to initial infection site
- ⚡ 3) has "memory"
  - after initial exposure, it recognizes and fights stronger

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### Humoral Immunity

- ⚡ AKA antibody-mediated immunity
- ⚡ provided by AB's present in body fluids
  - blood, lymph

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### Humoral Immunity

- ⚡ AB's produced by lymphocytes
  - circulate freely in blood or lymph
  - bind primarily to bacteria & their toxins & free viruses
  - inactivate pathogen temporarily
    - marks it for destruction
      - phagocytes or complement

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### Cellular Immunity

- ⚡ AKA cell-mediated immunity
- ⚡ lymphocytes themselves defend the body
- ⚡ lymphocytes target infected cells

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### Cellular Immunity

- ⚡ lymphocytes
  - 1) directly
    - lyse the foreign cell OR
  - 2) indirectly
    - releasing chemical mediators
      - enhance the inflammatory response OR
      - activate other lymphocytes or macrophages

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### Antigens (Ags)

- ⚡ substances that can mobilize the immune system
  - provoke an immune response
- ⚡ target all immune responses
- ⚡ usually large, complex molecules
  - natural, man-made
- ⚡ not normally present in the body
  - intruders

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### Cells of Adaptive Immune System

- ⚡ three cells
  - 1) B lymphocytes\*
  - 2) T lymphocytes\*
  - 3) antigen-presenting cells (APCs)
- ⚡ \*two distinct populations of lymphocytes

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### Cells of Adaptive Immune System

- ⚡ B lymphocytes
  - B cells
    - oversee humoral immunity
- ⚡ T lymphocytes
  - T cells
    - non-AB producing lymphocytes
    - function in cell-mediated immunity
- ⚡ antigen-presenting cells (APCs)
  - play auxiliary roles
  - do not respond to specific antigens

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### Immunocompetent

- ⚡ ability of the body's immune cells to recognize (bind) specific antigens
- ⚡ reflects the presence of plasma membrane bound proteins

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### Lymphocytes

- originate in red bone marrow
  - hematopoietic stem cells
- identical immature lymphocytes
  - when released from bone marrow
- whether a lymphocyte matures into T or B lymphocyte
  - depends on where in the body it becomes immunocompetent
    - thymus (T cells)
    - bone marrow (B cells)

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### T Cell Selection

- occurs in thymus
  - under direction of thymic hormones
- 2-3 day process
- cells divide rapidly
- only T cells w/ best ability to ID foreign antigens survive
  - selection process

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### T Cell Selection

- process that requires both negative & positive selection
- negative selection
  - vast majority bind strongly to body's antigens and attack themselves
    - self-antigens
    - weeded out via negative selection
      - thymic medulla

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### T Cell Selection

- positive selection
  - only T cells w/ intermediate affinity for self peptides continue to develop
    - interact weakly w/ self antigens
    - do not produce a strong activation signal
      - positive selection
        - thymic cortex
        - selection or ID of T cells that best recognize one's own tissue cells when bound to an antigen

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### Fetal Life Lymphocyte Education

- Includes the ability to:
  - accomplish immunocompetence and
  - develop self-tolerance or relative unresponsiveness to self-antigens

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### T Cell Selection (fig 22.7)

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### B Cell Selection

- occurs in the bone marrow
- little is known
- some self-reactive B cells are inactivated
  - via process called anergy
- other B cells are killed outright

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### Immunocompetence

- immunocompetent B or T cells display a unique type of receptor
  - recognize & bind to a specific antigen
- antigen receptors of T and B cells are different structurally
  - but both can respond to same antigens
- committed lymphocyte reacts to only one distinct antigen
  - all cell's antigens are the same

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### Immunocompetence

- our "genes"
  - determine what specific foreign substances our immune system will be able to recognize & resist
- an antigen
  - determines only which of the existing T or B cells will proliferate & mount an attack against it

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### Lymphoid Organs

- primary
  - where the lymphocytes become immunocompetent
    - thymus
    - bone marrow
- secondary
  - all other lymphoid organs
    - tonsils
    - spleen
    - Peyer's patch

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### Immunocompetence

- Naive (immature) cells
  - after becoming immunocompetent
  - exported to lymph nodes, spleen & other secondary lymphoid organs
    - encounter antigens
- maturity is complete
  - when lymphocytes bind w/ recognized antigens
  - complete differentiation into fully functional antigen activated cells

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### Lymphocyte Maturation (fig 22.8)

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### Antigen-Presenting Cells (APC)

- engulf foreign particles
- present fragments of antigens on their own surfaces
  - recognized by T cells
    - act as antigen presenters
      - examples
        - dendritic cells
        - Langerhans cells
        - activated B lymphocytes

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### Antigen-Presenting Cells (APC)

- antigen presenters
  - located in convenient sites
    - encounter & process antigens
- activated T cells release chemicals
  - increase mobilization & maturation of APCs & produce macrophages (phagocytes)
    - secrete bactericidal chemicals

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### APCs & Lymphocytes

- found throughout each lymphoid organ
- specific cells tend to be more numerous in certain areas
  - lymph nodes
    - paracortical areas
      - mostly T cells
    - germinal centers
      - dendritic & B cells
    - medullary sinuses
      - macrophages
        - remain fixed in organ
        - await the arrival of the antigen

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### APCs & Lymphocytes

- tonsils
  - lymphocytes & APCs
    - trap microorganisms
      - invade oral & nasal cavities
- spleen
  - primarily lymphocytes
    - act as a filter
      - trap bloodborne antigens

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### APCs & Lymphocytes

- lymphocytes
  - especially T cells
  - ~65-85% of bloodborne lymphocytes
  - circulate continuously throughout the body
- active migration of DCs (APC)
  - lymph nodes & other secondary organs
    - ensure that immune cells encounter invading antigens

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### APCs

- DCs
  - body's "outposts or frontiers"
  - act as mobile sentinels
  - present in connective tissue throughout body
  - efficient antigen catchers
    - internalize antigens by phagocytosis
    - enter nearby lymphatics
    - lymphoid organ
    - present antigen to T & B cells

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### Adaptive Immune System

- utilizes lymphocytes, APCs, & specific molecules
  - to ID & destroy all substances
- dependent on ability of cells to
  - recognize antigens
  - bind to them
  - communicate w/ one another
  - specific response to antigen

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### Clonal Selection & Differentiation of B Cells

- activation of B cells
  - stimulation to complete differentiation
    - occurs when antigen binds to its surface receptor
      - via series of activating events that trigger clonal selection
        - stimulate B cell to grow
        - multiply rapidly
        - form array of identical cells w/ same antigen-specific receptors
- prior to activation
  - B cell is immunocompetent but naive

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### Clone

- resulting family of identical cells
- all descended from same ancestor cell
- most become plasma cells
- antigen
  - selects by "choosing" a lymphocyte w/ complementary receptors

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### Plasma Cell

- AB-secreting effector cell of humoral response
  - immunity is conferred by AB's present in blood plasma or body fluids
- secretes AB's at rate of ~2000 molecules/sec
- function at this pace for 4-5 days, then die

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### Plasma Cell

- B parent cells
  - secrete limited amts of AB's
- secreted AB's
  - have same antigen-binding properties as receptor molecules on surface of parent B cell
  - circulate in blood or lymph
    - bind to free antigens
    - mark them for destruction

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### Memory Cells

- clone cells that do not differentiate into plasma cells
  - primed to respond to subsequent exposures
- mount an almost immediate humoral response
  - if they encounter the same antigen again

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### Immunological Memory

- humoral immune response
  - produces AB's
  - AB's produced each time an antigen enters the body
  - primary immune response
  - secondary immune response

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### Immunological Memory

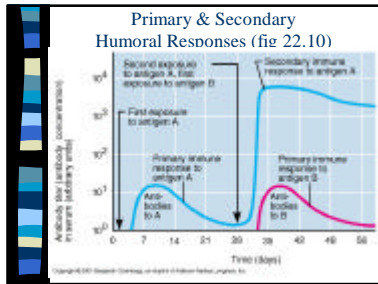
- primary immune response
  - occurs the first time an antigen enters the body
  - takes ~ one week to produce AB's
- secondary immune response
  - occurs every time the same antigen enters the body *after* the first exposure
  - produces AB's in only a few days
  - produces many more AB's than primary response

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### Clonal Selection of B Cells (fig 22.9)

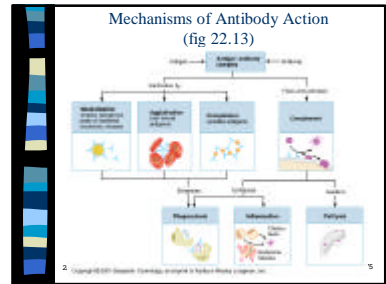
The diagram illustrates the clonal selection of B cells. It shows an antigen being presented by an Antigen Presenting Cell (APC) to a B cell. The B cell's surface receptors bind to the antigen, leading to its activation. This activated B cell then undergoes clonal selection, where it proliferates and differentiates into two types of cells: plasma cells and memory cells. Plasma cells are shown secreting antibodies (AB's) at a high rate. Memory cells are shown as a long-lived population that can quickly respond to a subsequent exposure to the same antigen.

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### Antibodies

- AKA immunoglobulins (Igs)
- soluble proteins
- secreted by activated B cells or plasma cells
  - in response to an antigen
- capable of binding specifically w/ antigen
- formed in response to large number of different antigens



### Monoclonal Antibodies

- produced by descendants of a single cell
- pure AB preparations
- specific for a single antigenic determinant
- sensitive
- rapid

### Monoclonal Antibodies

- used diagnose
  - pregnancy
  - certain STDs
  - certain cancers
  - hepatitis
  - rabies

### Immunity Homeostatic Imbalances

- depression or failure of immune system
- immunodeficiencies
- hypersensitivities
- autoimmune diseases

### Immunodeficiencies

- production or function of immune cells, phagocytes, or complement is abnormal
- most devastating
  - AIDS
    - acquired immune deficiency syndrome
    - cripples the immune system
    - interferes w/ activity of helper T cells

### AIDS

- caused by virus transmitted in body secretions
  - blood, semen, vaginal secretions
  - also present in saliva and tears
  - called human immunodeficiency virus
    - HIV
      - destroys helper T cells
      - depresses cell-mediated immunity

### AIDS

- virus enters body
  - blood transfusions
  - blood-contaminated needles
  - during sexual contact
    - torn mucosa
    - open lesions (STDs)

### Autoimmune Diseases

- ⚡ immune system loses its ability to distinguish self from foreign antigens
- ⚡ immune system turns against itself
- ⚡ body produces AB's (autoantibodies) and sensitized cytotoxic T cells
  - destroy its own tissues
    - autoimmunity
      - disease results
        - ▶ autoimmune ds

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### Common Autoimmune Ds'

- ⚡ Multiple sclerosis
  - destroys white matter of brain & spinal cord
- ⚡ Myasthenia gravis
  - impairs nerve & skeletal muscle communication
- ⚡ Graves' ds
  - causes thyroid gland to produce excessive thyroxine

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### Common Autoimmune Ds'

- ⚡ Type I (Juvenile) Diabetes mellitus
  - destroys pancreatic beta cells
    - deficit of insulin
    - inability to use CHO
- ⚡ Systemic lupus erythematosus (SLE)
  - systemic ds
  - primarily affects kidneys, heart, lungs, skin

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### Common Autoimmune Ds'

- ⚡ Glomerulonephritis
  - severe impairment of renal function
- ⚡ Rheumatoid arthritis
  - systemically destroys joints

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### Hypersensitivities

- ⚡ AKA allergies
- ⚡ result of immune responses in which the immune system causes tissue damage
  - as it fights off a perceived threat
    - pollen
- ⚡ allergen
  - term used to describe these types of antigens

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### Cellular Immunity

- ⚡ clonal selection & differentiation stimulus
  - same as in B cells
    - binding of antigen
- ⚡ mechanism of recognition is different

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### Specific T Cell Roles

- ⚡ Helper T cells
  - regulatory cells
    - central role in immune response
  - major function
    - chemically or directly stimulate proliferation
      - other T cells
      - B cells bound to antigen
        - ▶ release cytokines
  - must be first primed by an APC

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### Specific T Cell Roles

- ⚡ Cytotoxic T cells
  - aka killer T cells
  - only T cells that can directly attack & kill other cells
    - binds to target cells
    - releases a cytotoxic chemical (perforin)
    - chemical is inserted into target cell membrane
      - causes lysis of target cell
  - target mainly virus-infected & cancer cells
  - also activated by APC

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### Cytotoxic T Cell Action (fig 22.17a)

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### Specific T Cell Roles

- Suppressor T cells
  - regulatory cells
    - like helper T cells
  - suppress activity of both T and B cells
    - stop immune response
      - post antigen inactivation or destruction
    - prevent autoimmune rxns

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### Specific T Cell Roles

- memory T cells
  - descendent of T cell
  - generated during initial immune response
    - primary response
      - can exist for years
  - respond quickly to subsequent infections with same antigen

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### Active vs Passive Immunity

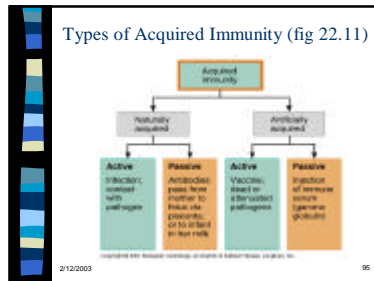
- active
  - acquired during an infection or via vaccination
  - ABs are made by one's plasma cells
  - provides immunological memory
  - protection is long-lived

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### Active vs Passive Immunity

- passive
  - conferred when a donor's ABs are injected into bloodstream or when a mother's ABs cross placenta
  - ABs are obtained from another donor
    - B cells are not "challenged" by antigens
    - no immunological memory
  - protection short-lived

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### Vaccinations

- contain dead or attenuated (living, but weakened) pathogens
- beneficial
  - relieve most symptoms
  - weakened pathogens provide functional antigenic determinants

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