14-1 Anatomical barriers and defense mechanisms constitute nonspecific defense, and lymphocytes provide specific defense
Overview of the Lymphoid System

• Pathogens
  – Microscopic organisms that cause disease:
    • Viruses
    • Bacteria
    • Fungi
    • Parasites
  – Each attacks in a specific way
• The Lymphoid System
  – Protects us against disease
  – Lymphoid system cells respond to:
    • Environmental pathogens
    • Toxins
    • Abnormal body cells, such as cancers
Overview of the Lymphoid System

• Specific Defenses

  – Lymphocytes:

    • Part of the immune response
    • Identify, attack, and develop immunity:
      – to a specific pathogen
Overview of the Lymphoid System

• The Immune System
  – Immunity:
    • The ability to resist infection and disease
  – All body cells and tissues involved in production of immunity:
    • Not just lymphoid system
Overview of the Lymphoid System

• Nonspecific Defenses
  – Block or attack any potential infectious organism
  – Cannot distinguish one attack from another
14-2 Lymphatic vessels, lymphocytes, lymphoid tissues, and lymphoid organs function in body defenses
Components of the Lymphoid System

- **Lymphatic vessels (lymphatics)**
  - Carries lymph from peripheral tissues to the venous system
- **Fluid (Lymph)**
  - A fluid similar to plasma but does not have plasma proteins
- **Lymphocytes, phagocytes, and other immune system cells**
- **Lymphoid tissues and lymphoid organs**
Functions of the Lymphoid System

- To produce, maintain, and distribute lymphocytes
- Return fluid and solutes to the blood
- Distribute hormones, nutrients, and waste products from their tissues of origin to the general circulation
Lymphatic Vessels

• Are vessels that carry lymph
  – Lymphoid system begins with the smallest vessels:
    • Lymphatic capillaries (terminal lymphatics):
      – differ from blood capillaries in four ways:
        » start as pockets rather than tubes
        » have larger diameters
        » have thinner walls
        » are flat or irregular in section
Lymphatic Vessels

Figure 14-2a
Lymphatic Vessels

Figure 14-2b

(b) LM × 43

Lymphatic valve

Lymphatic vessel
Lymphatic Vessels

• Major Lymph-Collecting Vessels
  – The base of the thoracic duct:
    • Expands into cisterna chyli
  – Cisterna chyli receives lymph from:
    • Right and left lumbar trunks
    • Intestinal trunk
Lymphatic Vessels

• The Inferior Segment of Thoracic Duct
  – Collects lymph from:
    • Left bronchiomediastinal trunk
    • Left subclavian trunk
    • Left jugular trunk
  – Empties into left subclavian vein
Lymphatic Vessels

• The Right Lymphatic Duct
  – Collects lymph from:
    • Right jugular trunk
    • Right subclavian trunk
    • Right bronchiomediatinal trunk
  – Empties into right subclavian vein
The Lymphatic Ducts and the Venous System

Figure 14-3
Lymphocytes

• Three Classes of Circulating Lymphocytes
  – T cells:
    • Thymus dependent
  – B cells:
    • Bone marrow derived
  – NK cells:
    • Natural killer cells
Lymphocytes

• T Cells
  – Make up 80% of circulating lymphocytes

• Three Main Types of T Cells
  – Cytotoxic T cells
  – Helper T cells
  – Suppressor T cells
Lymphocytes

• B Cells
  – Make up 10% to 15% of circulating lymphocytes
  – Differentiate (change) into plasma cells
  – Plasma cells:
    • Produce and secrete antibodies (immunoglobulin proteins)
  – Antibody-mediated immunity:
    • A chain of events that destroys the target compound or organism
Lymphocytes

• Natural Killer (NK) Cells
  – Also called large granular lymphocytes
  – Make up 5% to 10% of circulating lymphocytes
  – Responsible for immunological surveillance
  – Attack foreign cells, virus-infected cells, and cancer cells
Figure 14-4
The Origins of Lymphocytes

• T Cells and B Cells
  – Migrate throughout the body:
    • To defend peripheral tissues
  – Retain their ability to divide:
    • Is essential to immune system function
The Origins of Lymphocytes

• Differentiation
  – B cells differentiate:
    • With exposure to hormone called cytokine (interleukin-7)
  – T cells differentiate:
    • With exposure to several thymic hormones
Lymphoid Nodules

- Areolar tissue with densely packed lymphocytes
- Germinal center contains dividing lymphocytes
The Tonsils

Figure 14-5

- Palate
- Pharyngeal tonsil
- Lingual tonsil
- Palatine tonsil
Lymphoid Nodules

• Distribution of Lymphoid Nodules
  – Lymph nodes
  – Spleen
  – Respiratory tract (tonsils)
  – Along digestive and urinary tracts
Lymphoid Organs

• Lymph nodes
• Thymus
• Spleen
• Are separated from surrounding tissues by a fibrous connective tissue capsule
Lymphoid Organs

• Lymph Nodes
  – Trabeculae:
    • Bundles of collagen fibers
    • Extend from capsule into interior of lymph node
  – Hilum:
    • A shallow indentation where blood vessels and nerves reach the lymph node
Lymphoid Organs

• Lymph Nodes
  – **Afferent lymphatic vessels:**
    • Carry lymph:
      – from peripheral tissues to lymph node
  – **Efferent lymphatic vessels:**
    • Leave lymph node at hilum
    • Carry lymph to venous circulation
The Structure of a Lymph Node

Figure 14-6
Lymphoid Organs

• The Thymus
  – Located in mediastinum
  – Atrophies after puberty:
    • Diminishing effectiveness of immune system

• Divisions of the Thymus
  – Thymus is divided into two thymic lobes
  – Septa divide lobes into smaller lobules
The Thymus

- Thyroid gland
- Trachea
- Right lobe
- Left lobe
- Right lung
- Left lung
- Heart

Figure 14-7a
The Thymus

Figure 14-7b
The Thymus

Figure 14-7c

(c)
Lymphoid Organs

• Three Functions of the Spleen
  – Removal of abnormal blood cells and other blood components by phagocytosis
  – Storage of iron recycled from red blood cells
  – Initiation of immune responses by B cells and T cells:
    • In response to antigens in circulating blood
Lymphoid Organs

• Structure of the Spleen
  – Inside fibrous capsule:
    • **Red pulp**: contains many red blood cells
    • **White pulp**: resembles lymphoid nodules
The Spleen

Figure 14-8a
The Spleen

Figure 14-8b

(b)
The Spleen

Figure 14-8c

Veins
Capsule
Arteries

Red pulp

White pulp

LM × 38
Roles of the Lymphoid System in Body Defenses

• Body defenses provide resistance to fight infection, illness, and disease
• Two categories of defenses
  – Nonspecific defenses
  – Specific defenses
• Nonspecific and specific defenses operate together to provide resistance to infection and disease
14-3 Each nonspecific defense responds in a characteristic way regardless of the potential threat
Nonspecific Defenses

• Seven major categories of nonspecific defenses
  – Physical barriers
  – Phagocytes
  – Immunological surveillance
  – Interferons
  – Complement
  – Inflammatory response
  – Fever
Nonspecific Defenses

• **Physical Barriers**
  – Keep hazardous materials outside the body

• **Phagocytes**
  – Attack and remove dangerous microorganisms

• **Immunological Surveillance**
  – Constantly monitors normal tissues:
    • With natural killer cells (NK cells)
Nonspecific Defenses

• **Interferons**
  – Chemical messengers that trigger production of antiviral proteins in normal cells
  – Antiviral proteins:
    • Do not kill viruses
    • Block replication in cell

• **Complement (C) Proteins**
  – Form the complement system
  – Complement action of antibodies
Nonspecific Defenses

• **Inflammation**
  – Triggers a complex inflammatory response

• **Fever**
  – A high body temperature:
    • Increases body metabolism
    • Accelerates defenses
    • Inhibits some viruses and bacteria
### Figure 14-9

#### PHYSICAL BARRIERS
Prevent approach of and deny access to pathogens

- Duct of eccrine sweat gland
- Hair
- Secretions
- Epithelium

#### PHAGOCYTES
Remove debris and pathogens

- Fixed macrophage
- Neutrophil
- Free macrophage
- Eosinophil
- Monocyte

#### IMMUNOLOGICAL SURVEILLANCE
Destroys abnormal cells

- Natural killer cell
- Lysed abnormal cell

#### INTERFERONS
Increase resistance of cells to viral infection; slow the spread of disease

- Interferons released by activated lymphocytes, macrophages, or virus-infected cells
# Nonspecific Defenses

## Complement System
Attacks and breaks down cell walls; attracts phagocytes; stimulates inflammation

![Complement System Diagram](image)

**Mast cell**

1. Blood flow increased
2. Phagocytes activated
3. Capillary permeability increased
4. Complement activated
5. Clotting reaction walls off region
6. Regional temperature increased
7. Specific defenses activated

## Inflammatory Response
Multiple effects

**Mast cell**

## Fever
Mobilizes defenses; accelerates repairs; inhibits pathogens

Body temperature rises above 37.2°C in response to pyrogens

---

*Figure 14-9*
Figure 14-10

Tissue damage leads to:

- Area becomes red, swollen, warm, and painful
- Dilation of blood vessels, increased blood flow, increased vessel permeability
- Clot formation (temporary repair)
- Pathogen removal, clot erosion, scar tissue formation

Chemical change in interstitial fluid leads to:

- Mast cells release histamine and heparin
- Attraction of phagocytes, especially neutrophils

Release of cytokines leads to:

- Removal of debris by neutrophils and macrophages; stimulation of fibrocytes
- Activation of specific defenses

Tissue repair
14-4 Immunity (specific defenses) responds to specific threats and is either cell mediated or antibody mediated
Types of Immunity

• Active Immunity
  – Naturally acquired:
    • Through environmental exposure to pathogens
  – Induced:
    • Through vaccines containing pathogens
Types of Immunity

• Passive Immunity
  – Naturally acquired:
    • Antibodies acquired from the mother
  – Induced:
    • By an injection of antibodies
Types of Immunity

**SPECIFIC RESISTANCE (IMMUNITY)**
- Responds to threats on an individualized basis

**INNATE IMMUNITY**
- Genetically determined—no prior exposure or antibody production involved

**ACQUIRED IMMUNITY**
- Produced by prior exposure or antibody production

**ACTIVE IMMUNITY**
- Naturally acquired active immunity: Develops after exposure to antigens in environment
- Induced active immunity: Develops after administration of antigen to prevent disease

**PASSIVE IMMUNITY**
- Naturally acquired passive immunity: Conferred by transfer of maternal antibodies across placenta or in breast milk
- Induced passive immunity: Conferred by administration of antibodies to combat infection

Figure 14-11
Properties of Immunity

• **Specificity**
  – Each T or B cell responds only to a specific antigen and ignores all others

• **Versatility**
  – The body produces many types of lymphocytes:
    • Each fights a different type of antigen
    • Active lymphocyte **clones** itself to fight specific antigen

• **Memory**
  – Some active lymphocytes (memory cells):
    • Stay in circulation
    • Provide immunity against new exposure

• **Tolerance**
  – Immune system ignores “normal” (self) antigens
An Overview of the Immune Response

Figure 14-12

Antigens
- Bacteria
- Viruses

Specific Defenses (Immune response)

Direct physical and chemical attack

Cell-Mediated Immunity
- Phagocytes activated
- T cells activated

Communication and feedback

Antibody-Mediated Immunity
- B cells activated

Attack by circulating antibodies
14-5 T cells play a role in the initiation and control of the immune response
Antigen Presentation

• Antigen Recognition
  – T cells only recognize antigens that are bound to glycoproteins in plasma membranes
Antigen Presentation

• MHC Proteins
  – The membrane glycoproteins that bind to antigens
  – Genetically coded in chromosome 6:
    • The major histocompatibility complex (MHC)
    • Differs among individuals
Antigen Presentation

• Two Classes of MHC Proteins
  – **Class I:**
    • Found in membranes of all nucleated cells
  – **Class II:**
    • Found in membranes of **antigen-presenting cells** (APCs)
    • Found in lymphocytes
Antigen Presentation

• Class I MHC Proteins
  – Pick up small peptides in cell and carry them to the surface:
    • T cells ignore normal peptides
    • Abnormal peptides or viral proteins activate T cells to destroy cell
Antigen Presentation

• Class II MHC Proteins
  – Antigenic fragments:
    • From **antigenic processing** of pathogens
    • Bind to Class II proteins
    • Inserted in plasma membrane to stimulate T cells
Antigen Presentation

• Antigen-Presenting Cells (APCs)
  – Responsible for activating T cells against foreign cells and proteins

• Phagocytic APCs
  – Free and fixed macrophages:
    • In connective tissues
  – Kupffer cells:
    • Of the liver
  – Microglia:
    • In the CNS
T Cell Activation

• Cytotoxic T Cells
  – Also called killer T cells
  – Seek out and immediately destroy target cells
T Cell Activation

• Actions of Cytotoxic T Cells
  1. Release perforin:
     • To destroy antigenic plasma membrane
  2. Secrete poisonous *lymphotoxin*:
     • To destroy target cell
  3. Activate genes in target cell:
     • That cause cell to die
• Helper T Cells
  – Activated CD4 T cells divide into:
    • Active helper T cells ($T_H$ cells):
      – secrete cytokines
    • Memory $T_H$ cells:
      – remain in reserve
• **Memory T\(_C\) Cells**
  
  – Produced with cytotoxic T cells
  
  – Stay in circulation
  
  – Immediately form cytotoxic T cells if same antigen appears again
• Suppressor T Cells
  – Secrete suppression factors
  – Inhibit responses of T and B cells
  – Act *after* initial immune response
  – Limit immune reaction to single stimulus
T Cell Activation

Figure 14-13

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14-6 B Cells respond to antigens by producing specific antibodies
B Cells and Immunity

• B Cells
  – Responsible for antibody-mediated immunity
  – Attack antigens by producing specific antibodies
  – Millions of populations, each with different antibody molecules
The Sensitization and Activation of B Cells

**Figure 14-14**

**STEP 1: Sensitization**
- Antigens
- Class II MHC
- Antibodies

**Inactive B cell**
- Antigens bound to antibody molecules
- Antigen binding
- Sensitized B cell

**STEP 2: Activation**
- Class II MHC
- T cell receptor
- Antigen

**B cell**
- Stimulation by cytokines
- Helper T cell
- Sensitized B cell
- Activated B cells
- Memory B cells (inactive)

**STEP 3: Division and Differentiation**
- Antibody production
- Plasma cells
Antibody Structure

• Two parallel pairs of polypeptide chains
  – One pair of heavy chains
  – One pair of light chains

• Each chain contains
  – Constant segments
  – Variable segments
Antibody Structure

Figure 14-12

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<table>
<thead>
<tr>
<th>CLASS</th>
<th>FUNCTION</th>
<th>REMARKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>Responsible for defense against many viruses, bacteria, and bacterial toxins</td>
<td>Largest class (80%) of antibodies, with several subtypes; also cross the placenta and provide passive immunity to fetus; anti-Rh antibodies produced by Rh-negative mothers are IgG antibodies that can cross the placenta and attack fetal Rh-positive red blood cells, producing hemolytic disease of the newborn. ⇨ p. 394</td>
</tr>
<tr>
<td>IgM</td>
<td>Anti-A and anti-B forms responsible for cross-reactions between incompatible blood types; other forms attack bacteria insensitive to IgG</td>
<td>First antibody type secreted following initial exposure to antigen; levels decline as IgG production accelerates</td>
</tr>
<tr>
<td>IgA</td>
<td>Attacks pathogens before they enter the body tissues</td>
<td>Found in glandular secretions (tears, mucus, and saliva)</td>
</tr>
<tr>
<td>IgE</td>
<td>Accelerates inflammation on exposure to antigen</td>
<td>Bound to surfaces of mast cells and basophils and stimulates release of histamine and other inflammatory chemicals; also important in allergic response</td>
</tr>
<tr>
<td>IgD</td>
<td>Binds antigens in the extracellular fluid to B cells</td>
<td>Binding can play a role in activation of B cells</td>
</tr>
</tbody>
</table>
Antibody Function

• Seven Functions of Antigen–Antibody Complexes
  – Neutralization of antigen-binding sites
  – Precipitation and agglutination: formation of immune complex
  – Activation of complement
  – Attraction of phagocytes
  – Opsonization: increasing phagocyte efficiency
  – Stimulation of inflammation
Primary and Secondary Responses to Antigen Exposure

• First exposure
  – Produces initial primary response
• Next exposure
  – Triggers secondary response
  – More extensive and prolonged
  – Memory cells already primed
Primary and Secondary Responses to Antigen Exposure

- **The Primary Response**
  - Takes time to develop
  - Antigens activate B cells
  - Plasma cells differentiate
  - *Antibody titer* (level) slowly rises
Primary and Secondary Responses to Antigen Exposure

• The Primary Response
  – Peak response:
    • Can take 2 weeks to develop
    • Declines rapidly
  – IgM:
    • Is produced faster than IgG
    • Is less effective
Primary and Secondary Responses to Antigen Exposure

• The Secondary Response
  – Activates memory B cells:
    • At lower antigen concentrations than original B cells
    • Secretes antibodies in massive quantities
Primary and Secondary Responses

Figure 14-16

- **First Exposure**
- **Second Exposure**
- Secondary response

Antibody concentration in blood over time (weeks).
Hormones of the Immune System

• Six Groups of Hormonal Cytokines
  – Interleukins
  – Interferons
  – Tumor necrosis factors (TNFs)
  – Chemicals that regulate phagocytic activities
  – Colony-stimulating factors (CSFs)
  – Miscellaneous cytokines
<table>
<thead>
<tr>
<th>COMPOUND</th>
<th>FUNCTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTERLEUKINS</td>
<td></td>
</tr>
<tr>
<td>IL-1</td>
<td>Stimulates T cells to produce IL-2, promotes inflammation, causes fever; stimulates the secreting cell in a positive feedback loop that recruits more immune cells</td>
</tr>
<tr>
<td>IL-2, -12</td>
<td>Stimulate T cells and NK cells; stimulate the secreting cell in a positive feedback loop that recruits more immune cells</td>
</tr>
<tr>
<td>IL-3</td>
<td>Stimulates production of mast cells and other blood cells</td>
</tr>
<tr>
<td>IL-4, -5, -6, -7, -10, -11</td>
<td>Promote differentiation and growth of B cells, and stimulate plasma cell formation and antibody production</td>
</tr>
<tr>
<td>IL-8</td>
<td>Stimulates blood vessel formation</td>
</tr>
<tr>
<td>IL-13</td>
<td>Suppresses production of several cytokines (IL-1, IL-8, TNF)</td>
</tr>
<tr>
<td>INTERFERONS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Activate other cells to prevent viral entry and replication, stimulate NK cells and macrophages</td>
</tr>
</tbody>
</table>
### TABLE 14-2  Examples of Cytokines of the Immune Response

<table>
<thead>
<tr>
<th>COMPOUND</th>
<th>FUNCTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TUMOR NECROSIS FACTORS (TNFs)</strong></td>
<td>Kill tumor cells, slow tumor growth; stimulate activities of T cells and eosinophils, inhibit parasites and viruses</td>
</tr>
<tr>
<td><strong>PHAGOCYTIC REGULATORS</strong></td>
<td></td>
</tr>
<tr>
<td>Monocyte-chemotactic factor (MCF)</td>
<td>Attracts monocytes, transforms them into macrophages</td>
</tr>
<tr>
<td>Migration-inhibitory factor (MIF)</td>
<td>Prevents macrophage migration from the area</td>
</tr>
<tr>
<td><strong>COLONY-STIMULATING FACTORS (CSFs)</strong></td>
<td></td>
</tr>
<tr>
<td>M-CSF</td>
<td>Stimulate RBC and WBC production</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>Stimulates production of monocytes</td>
</tr>
<tr>
<td>Multi-CSF</td>
<td>Stimulates production of granulocytes, monocytes, and RBCs</td>
</tr>
</tbody>
</table>
14-7 Abnormal immune responses result in immune disorders
Autoimmune Disorders

• A malfunction of system that recognizes and ignores “normal” antigens
• Activated B cells make autoantibodies against body cells
• Thyroiditis
• Rheumatoid arthritis
• Insulin-dependent diabetes mellitus (IDDM)
Immunodeficiency Diseases

- Problems with embryological development of lymphoid tissues
  - Can result in **severe combined immunodeficiency disease** (SCID)
- Viral infections such as HIV
  - Can result in AIDS
- **Immunosuppressive drugs** or radiation treatments
  - Can lead to complete immunological failure
Allergies

• Inappropriate or excessive immune responses to antigens
  – Allergens:
    • Antigens that trigger allergic reactions
Allergies

• Four Categories of Allergic Reactions
  – Type I:
    • Immediate hypersensitivity
  – Type II:
    • Cytotoxic reactions
  – Type III:
    • Immune complex disorders
  – Type IV:
    • Delayed hypersensitivity
Allergies

- **Type I Allergy**
  - Also called *immediate hypersensitivity*
  - A rapid and severe response to the presence of an antigen
  - Most commonly recognized type of allergy
  - Includes allergic rhinitis (environmental allergies)
Allergies

• Type I Allergy
  – Sensitization leads to:
    • Production of large quantities of IgE antibodies distributed throughout the body
  – Second exposure leads to:
    • Massive inflammation of affected tissues
• Type I Allergy
  – Severity of reaction depends on:
    • Individual sensitivity
    • Locations involved
  – **Allergens** (antigens that trigger reaction) in bloodstream may cause anaphylaxis
Allergies

• Anaphylaxis
  – Can be fatal
  – Affects cells throughout the body
  – Changes capillary permeability:
    • Produces swelling (hives) on skin
  – Smooth muscles of respiratory system contract:
    • Make breathing difficult
  – Peripheral vasodilatation:
    • Can cause circulatory collapse (anaphylactic shock)
14-8 The immune response diminishes with advancing age
Immune System and Aging

• Four Effects of Aging on the Immune Response
  – Thymic hormone production is greatly reduced
  – T cells become less responsive to antigens
  – Fewer T cells reduces responsiveness of B cells
  – Immune surveillance against tumor cells declines
14-9 For all body systems, the lymphoid system provides defenses against infection and returns tissue fluid to the circulation
The Lymphoid System in Perspective

Functional Relationships Between the Lymphoid System and Other Systems
The Integumentary System

- The Integumentary System provides physical barriers to pathogen entry; macrophages in dermis resist infection and present antigens to trigger immune response; mast cells trigger inflammation, mobilize cells of lymphoid system

- The Lymphoid System provides IgA antibodies for secretion onto integumentary surfaces
The Skeletal System’s bone marrow produces and stores lymphocytes and other cells involved in the immune response.

The Lymphoid System assists in repair of bone after injuries; macrophages fuse to become osteoclasts.
The Nervous System’s microglia present antigens that stimulate specific defenses; glial cells secrete cytokines; innervation stimulates antigen-presenting cells.

The Lymphoid System’s cytokines affect hypothalamic production of CRH and TRH.
The Endocrine System’s glucocorticoids have anti-inflammatory effects; thymosins stimulate development and maturation of lymphocytes; many hormones affect immune function

The Lymphoid System’s thymus secretes thymosins; cytokines affect cells throughout the body
The Cardiovascular System distributes WBCs; carries antibodies that attack pathogens; clotting response helps restrict spread of pathogens; hemocytoblasts give rise to stem cells that produce WBCs.

The Lymphoid System fights infections of cardiovascular organs; returns tissue fluid to bloodstream.
The Muscular System protects superficial lymph nodes and lymphatic vessels in the abdominopelvic cavity; muscle contractions help propel lymph along lymphatic vessels.

The Lymphoid System assists in repair after injuries.
The Respiratory System’s alveolar phagocytes present antigens and trigger specific defenses; provides oxygen and eliminates carbon dioxide for the lymphoid system.

The Lymphoid System’s tonsils protect against infection at entrance to respiratory tract.
The Digestive System provides nutrients required by lymphatic tissues; digestive acids and enzymes provide nonspecific defense against pathogens.

The Lymphoid System’s tonsils and intestinal lymphoid nodules defend against infection and toxins absorbed from the digestive tract; lymphatics carry absorbed lipids to venous system.
The Urinary System eliminates metabolic wastes generated by cellular activity; acid pH of urine provides nonspecific defense against urinary tract infection.

The Lymphoid System provides specific defenses against urinary tract infections.
The Reproductive System’s secretions contain lysozymes and bactericides that provide nonspecific defense against reproductive tract infections.

The Lymphoid System provides IgA antibodies for secretion by epithelial glands.