Capillary exchange
Fluid movement in capillaries

Not all fluid is reclaimed at the venous end of the capillaries; that is the job of the lymphatic system.
Lymphatic vessels

_Lymphatic capillaries_ permeate our tissues
Amazingly permeable
Contain _minivalves_ that allow for only one-way flow
All lymph flows toward heart
Major collecting ducts (dump into subclavian veins):

*right lymphatic duct*
*thoracic duct*
The lymphatic system is connected to the venous system through the heart. It includes lymph ducts, lymph trunks, lymph nodes, lymphatic collecting vessels, lymph capillaries, tissue fluid (which becomes lymph), blood capillaries, and loose connective tissue around capillaries.
Lymphatic capillaries
**Lymphatic vessels**

*Lymphatic capillaries* permeate our tissues

Amazingly permeable.

Contains minivalves that allow for only one-way flow.

All lymph flows toward the heart.

Major collecting ducts (dump into subclavian veins):

- right lymphatic duct
- thoracic duct

*Because the lymphatic capillaries are so permeable, diseases and viruses could easily use them as freeways to move through the body easily!*
Lymph nodes

Lymph is filtered through *lymph nodes* on its way back to the heart

Found in large clusters in *inguinal, axillary, and cervical regions* of the body

*Macrophages* are found in lymph nodes

Helps produce *lymphocytes* (a type of white blood cell) that also function in the immune response
Distribution of lymph nodes
The immune system distinguishes “self” from “non-self”

When we think of the immune system, we often only think that it protects us from pathogens (bacteria, viruses, fungi, parasites)

But, the immune system also removes dead or damaged cells (“housekeeping”)

Works to recognize and destroy abnormally functioning cells (i.e. protect us from cancer)
What is a pathogen?

In developed countries (like the U.S.) we really only have to worry about viruses and bacteria. Worldwide, parasites can be a major concern. Malaria is transmitted by mosquitoes (~100 million infected worldwide). Others enter via the digestive tract, or are inhaled.
One method to cure them all? --sort of.

Some methods of keeping us well are not “immune responses” at all, but simply physical or chemical barriers.

Our skin, mucus, and stomach acid are examples of these barriers (lysozyme, etc)

However, if a pathogen does get into the body, the same set of steps is followed to remove it:

- Detection and identification of the substance
- Communication between immune system cells
- Recruitment and coordination
- Destruction or suppression of the invader
We have evolved both acquired and innate immunity.

By definition, barriers are innate (we are born with these), but this "branch" of immunity also includes:

- **Phagocytosis**: neutrophils and macrophages respond to PAMPs (pathogen-associated molecular patterns) such as chemotaxins to engulf the invader (this is receptor-mediated); antibodies may need to "mark" the invader first.
We have evolved both **acquired** and **innate** immunity

By definition, barriers are innate (we are born with these), but this “branch” of immunity also includes:

**Natural Killer Cells (NK Cells)** respond to viral infections quickly

- They attack cells infected by virus and induce them to self-destruct (*apoptosis*), ceasing replication of the virus
- Release cytokines, including interferons (which interfere with viral replication)
- Interferons can target host cells or activate macrophages
We have evolved both **acquired** and **innate** immunity

By definition, barriers are innate (we are born with these), but this “branch” of immunity also includes:

Cytokines are released by activated macrophages and initiate the inflammation response:

- Immune cells are attracted to the site of damage
- A physical barrier is put in place to prevent the spread of infection
- Promotes tissue repair
We have evolved both **acquired** and **innate** immunity.

Many other types of cytokines are released as well:

- **Acute-Phase Proteins** are proteins that are released immediately following injury.
- **Histamine** is a powerful vasodilator, and opens pores in capillaries to encourage inflammation.
- **Interleukins** play several roles in the body, mostly mediating the immune response by acting as a liaison between tissues.
- **Bradykinin** vasodilates and stimulates pain receptors.
- **Complement** is a large collective of proteins (about 25 different ones) that work to form a **membrane attack complex**.
Our immune system has the capability of responding to specific antigens

Innate immune responses are evolutionarily very old; all classes of animals and plants have some sort of innate immunity, as do most prokaryotic organisms.

*Acquired immunity* comprises *antigen-specific responses* and is mediated primarily by lymphocytes (at least in jawed vertebrates…in other animal classes, other molecules are common).

There is overlap between innate and acquired immunity.
Acquired immunity can be **active** or **passive**

**Active immunity** occurs when we are exposed to a pathogen and make our own antibodies. When you get a cold, you make antibodies to the virus. When you receive a vaccine, you make antibodies in response to a **killed** version of the virus.

**Passive immunity** occurs when we receive antibodies from other animals (maternal-fetal exchange of antibodies, gamma globulins, etc); not long-lasting.
We have millions of types of lymphocytes

Lymphocytes are the mediators of acquired immunity, and are differentiated into clones (based on membrane-bound proteins)

Clone 1
Clone 2
Clone 3
We have millions of types of lymphocytes

Lymphocytes are the mediators of acquired immunity, and are differentiated into clones (based on membrane-bound proteins)

Upon exposure to an antigen, naïve lymphocytes expand via a process called clonal expansion; they then differentiate into effector cells (which only live a few days), and memory cells (which are long-lived, and maintain a “memory” of the antigen in the body)
A naïve lymphocyte encounters an antigen for the first time. These effector cells will die soon after carrying out the immediate response. Memory cells will continue to circulate, and will expand more rapidly if it encounters the same antigen again.
In humoral immunity, B cells secrete antibodies

B cells (a type of lymphocyte) undergo clonal selection and secrete antibodies into our body fluids.

Functional classes (G, A, E, M, & D) and have several functions.

An antibody molecule is composed of two identical light chains and two identical heavy chains, linked by disulfide bonds.
Initial exposure to antigen

Primary immune response

Second exposure to antigen

Secondary immune response

Response is larger

Response is faster

Figure 49-16 Biological Science, 2/e © 2005 Pearson Prentice Hall, Inc.
Once pathogens infect cells, they are invisible to the humoral immune system

Infected cells display fragments of foreign antigens on their surface as part of the major histocompatibility complex (MHC) (has huge genetic variation between individuals)

**T cells (T lymphocytes)** can bind to MHC-antigen complexes on the surface of a target cell

**MHC Class I** molecules are found on nucleated host cells; **cytotoxic T cells** can recognize invaders on these “platforms” and destroy them to prevent them from replicating

**MHC Class II** molecules are found primarily on macrophages, B lymphocytes, etc, and **helper T cells** can recognize these platforms, and secrete cytokines that enhance the immune response
Multipotent stem cell in bone marrow → T-cell precursor → migrates to Thymus gland → Natural killer cells → kill Antibody-coated cells

Thymus gland → Cytotoxic T cells → kill MHC class I target cells

Cytotoxic T cells → Helper T cells → secrete Cytokines that activate other immune cells

Bind to MHC-II antigen-presenting cells
Cytotoxic T cells prevent replication of infected cells

The easiest way to prevent replication of a cell infected with viruses, parasites, or some bacteria is to kill it; this is the job of cytotoxic T cells.

They release **perforin**, a cytotoxic molecule that literally perforates cells; **granzymes** are enzymes that digest protein and enter through the pores created by perforin.

Cells undergo apoptosis as a result.

Cytotoxic T cells also activate **Fas**, a protein on the target cell membrane that speeds up apoptosis.
Helper T cells secrete cytokines that influence other cells

- Interferon-gamma (IFN-γ) activates macrophages
- Interleukins activate antibody production and cytotoxic T cells
- Colony-stimulating factors enhance leukocyte production
- Interleukins support mast cells and eosinophils

Also...

- Bind to B lymphocytes and promote their differentiation into plasma cells or memory cells.

The main target of HIV (the virus that causes AIDS) is helper T cells
Allergens are nonpathogenic antigens

Some antigens are not harmful, but individuals can be hypersensitive to them, which results in an inflammatory response to get rid of it.

Responses can be mediated by antibodies (immediate) or helper T cells & macrophages (delayed).

Allergies have a strong genetic component, and development of allergies can be affected by geographic, cultural, and social conditions.
Autoimmune diseases result when our immune system fails to recognize “self”

During development, some clones develop that can combine with MHC-self-antigen complexes; these must be eliminated by *clonal deletion*

Reasons why *self-tolerance* may suddenly fail are unclear
Sick and tired of physiology

Elevated levels of cortisol are a good indicator of long-term or repetitive stress

Elevated levels of cortisol also are known to suppress the immune system

The exact mechanisms behind this suppression are unclear due to the fact that ‘stress’ is difficult to study in non-human models
Sick and tired of physiology

When we are burdened, we often compensate for a lack of time by giving up sleep

Over the last 25 years, our society has become chronically sleep-deprived; a common perception is that this leads to a higher susceptibility to viral illnesses.

Is there any evidence to suggest this?

Sick and tired of physiology

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Variable effects of sleep deprivation on human immune-system components</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immune response</strong></td>
<td><strong>Quantity/Quality</strong></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cells</strong></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>Number</td>
</tr>
<tr>
<td></td>
<td>Function</td>
</tr>
<tr>
<td>Monocytes</td>
<td>Number</td>
</tr>
<tr>
<td></td>
<td>Function</td>
</tr>
<tr>
<td>Natural killer cells</td>
<td>Number</td>
</tr>
<tr>
<td></td>
<td>Function</td>
</tr>
<tr>
<td>CD4⁺ T cells</td>
<td>Number</td>
</tr>
<tr>
<td></td>
<td>Function</td>
</tr>
<tr>
<td>CD8⁺ T cells</td>
<td>Number</td>
</tr>
<tr>
<td></td>
<td>Function</td>
</tr>
<tr>
<td>B cells</td>
<td>Number</td>
</tr>
<tr>
<td></td>
<td>Function</td>
</tr>
<tr>
<td><strong>Endogenous cytokine levels</strong></td>
<td></td>
</tr>
<tr>
<td>IL-1⁺</td>
<td></td>
</tr>
<tr>
<td>IL-2⁺</td>
<td></td>
</tr>
<tr>
<td>IL-6</td>
<td></td>
</tr>
<tr>
<td>IL-10</td>
<td></td>
</tr>
<tr>
<td>TNF receptor</td>
<td></td>
</tr>
<tr>
<td><strong>Cytokine levels after in vitro stimulation</strong></td>
<td></td>
</tr>
<tr>
<td>PHA-induced</td>
<td></td>
</tr>
<tr>
<td>PWM-induced</td>
<td></td>
</tr>
<tr>
<td>ConA-induced</td>
<td></td>
</tr>
<tr>
<td>LPS-induced</td>
<td></td>
</tr>
</tbody>
</table>

*Confounded by strenuous exercise and decreased caloric intake.⁺By indirect measurement. ↑, increased; ↓, decreased; ←, no change; ConA, concanavalin A; IL, interleukin; LPS, lipopolysaccharide; PHA, phytohaemagglutinin; PWM, pokeweed mitogen; TNF, tumour-necrosis factor.
The circadian rhythms of cortisol and ACTH remain unchanged in response to sleep deprivation.

Figure 3 | Relationship between sleep, circadian rhythm, and the neuroendocrine, autonomic nervous and immune systems. The evidence for the reciprocal relationship between sleep and the immune system — that is, that changes in the immune system cause changes in sleep and, conversely, that sleep has an important role in restoring the immune system — is the subject of this review. Possible mechanisms for these interactions are discussed in BOX 3.