Function of Protein

Introduction

Oxygen bind to prosthetic group

Myoglobin

Protein/ligand interaction

Oxygen transportation

- **Hemoglobin**
- **R&T state**
- **Cooperative bind**
- **Transport of H^+/CO_2**
- **BPG**
- **Sickle-cell anemia**

Immunosystem

- **Transport**
- **Regulatory**
- **Motor**
- **Fibrous Protein**
- **Enzyme**
- **Immunoglobulin**

Enzyme: Substrate - catalytic site (active site)
Protein: binding site -ligand
Receptor /signal
Complementary fit
Induced fit

How can oxygen bind to biomolecules?

No charge
Non polar
Weak hydrophobic interaction

Coordination complex

18-e rule

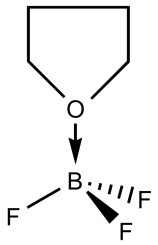
Stabilized after binding to transition metal ion

CO, NO, CN

When a Lewis base donates a pair of electrons to a Lewis acid, a **<u>coordinate covalent bond</u>** is formed and the resulting species is referred to as an ***adduct***.

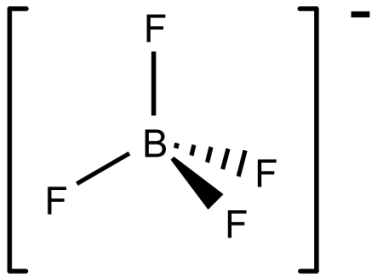
$BF_3 + THF$ -----> BF_3THF

Lewis acid + Lewis base ---> Adduct



In a coordination complex:
• a line is used to show the bonding interaction between an anionic ligand and the acceptor central atom.

$BF_3 + F^-$ -----> $[BF_4]^-$



Definitions

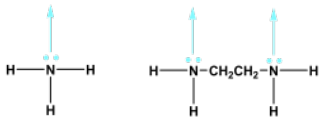
Lewis Acid = acceptor = usually a transition metal cation

Lewis Base = donor = ligand = usually something with a lone electron pair

Coordination number = # of metal-ligand attachments

Denticity = # of attachments a ligand makes

- Metals are able to bind or chelate (greek to claw) to other molecules or ions in solution called ligands
  - Common Ligands are Lewis bases (electron pair donors)
    - Monodentate Bidentate



- Common Metal ions are Lewis acids (electron pair acceptors)
- ♦ Coordinate Covalent bonds are formed L → M
- ♦ Complexes using polydentate ligands are called chelates

Coordination Numbers

TABLE 24.1 Some Common Coordination Numbers of Metal Ions

Cu^{+}	2, 4		
Ag^{+}	2		
Au^{+}	2, 4	Al^{3+}	4, 6
		Sc^{3+}	6
		Cr^{3+}	6
Fe^{2+}	6	Fe^{3+}	6
Co^{2+}	4, 6	Co^{3+}	6
Ni^{2+}	4, 6	Au^{3+}	4
Cu^{2+}	4, 6	Pt^{4+}	6
Zn^{2+}	4		
P			

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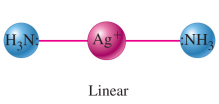

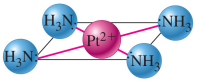

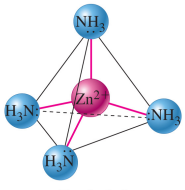

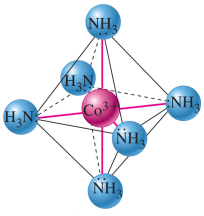

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TABLE 24.2 Some Common Monodentate Ligands

Formula	Name as Ligand	Formula	Name as Ligand	Formula	Name as Ligand
Neutral molecules		Anions		Anions	
H_2O	Aqua	F^-	Fluoro	SO_4^{2-}	Sulfato
NH_3	Ammine	Cl^-	Chloro	$S_2O_3^{2-}$	Thiosulfato
CO	Carbonyl	Br^-	Bromo	NO_2^-	Nitrito-*N*-[a]
NO	Nitrosyl	I^-	Iodo	ONO^-	Nitrito-*O*-[a]
CH_3NH_2	Methylamine	O^{2-}	Oxo	SCN^-	Thiocyanato-*S*-[b]
C_5H_5N	Pyridine	OH^-	Hydroxo	NCS^-	Thiocyanato-*N*-[b]
		CN^-	Cyano		

[a] If the nitrite ion is attached through the N atom (—NO_2), the designation *nitrito-N-* is used; if attached through an O atom (—ONO), *nitrito-O-*.
[b] If the thiocyanate ion is attached through the S atom (—SCN), the name *thiocyanato-S-* is used; if attachment is through the N atom (—NCS), *thiocyanato-N-*.

– *ide* endings change to –*o* – *ate* endings change to –*ato*

Common Ligands

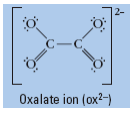
Monodentate Ligands:

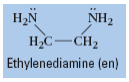
Halides: F^-, Cl^-, Br^-, I^-

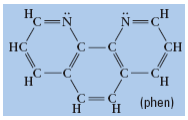
O^{2-}, S^{2-}, OH^-, CN^-

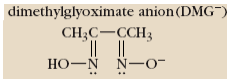
NH_3, H_2O, CO

Bidentate Ligands:

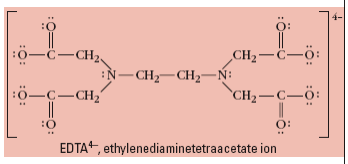








Polydentate Ligands:



heme, salen

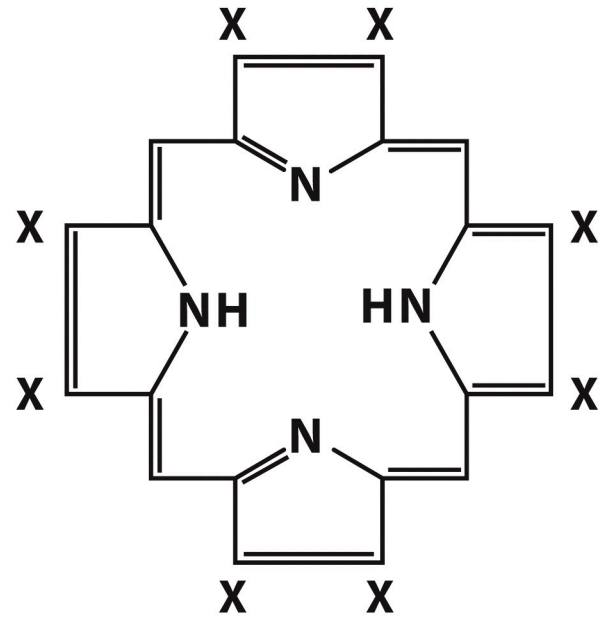
Spectrochemical Series

Large Δ
Strong field ligands

$CN^- > \underline{N}O_2^- >$ en > py ≈ NH_3 > $EDTA^{4-}$ > $SC\underline{N}^- > H_2O >$

$ON\underline{O}^- > ox^{2-} > OH^- > F^- > \underline{S}CN^- > Cl^- > Br^- > I^-$

Small Δ
Weak field ligands



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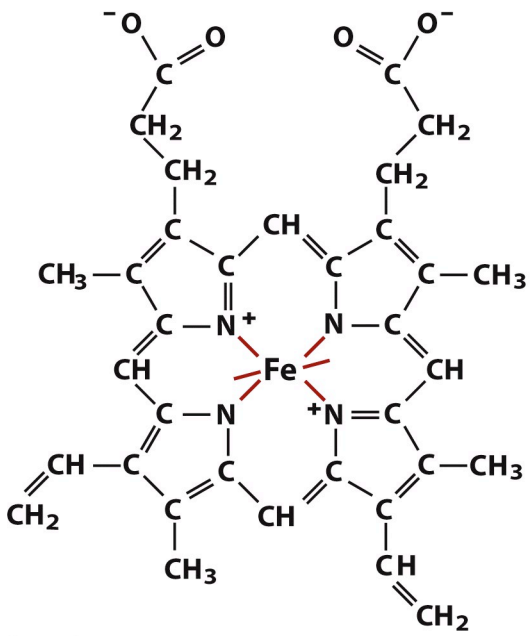

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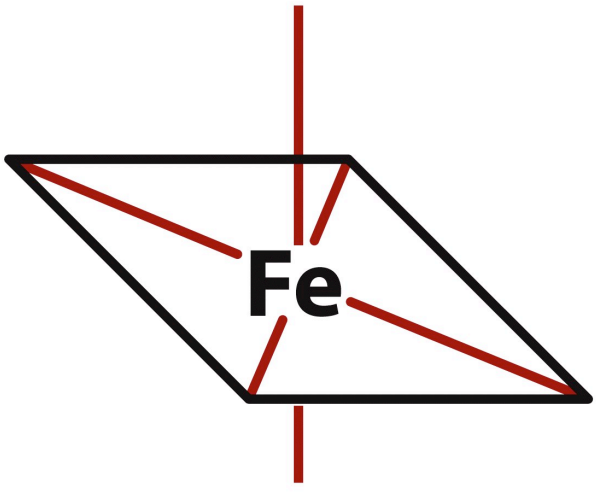

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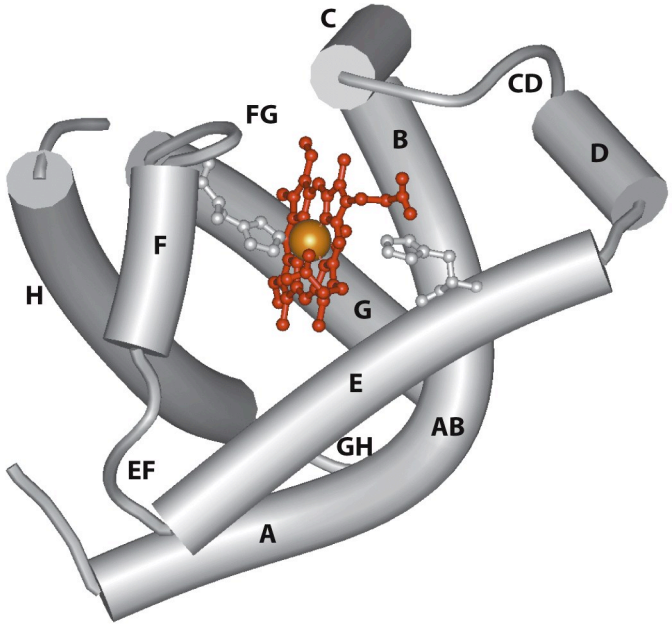
Role of Iron in Heme

- Fe^{2+} has six coordination positions.
- Four of the six are coordinated with nitrogens at the base of the five-membered rings.
- A fifth is coordinated with a N of His of the protein portion of the molecule.
- The sixth is coordinated with O_2.



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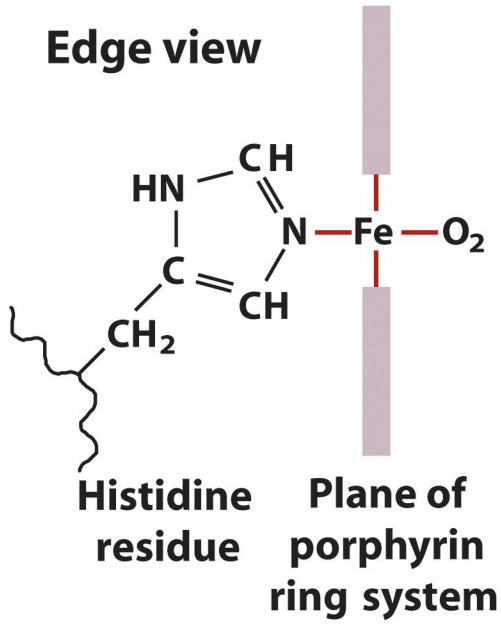

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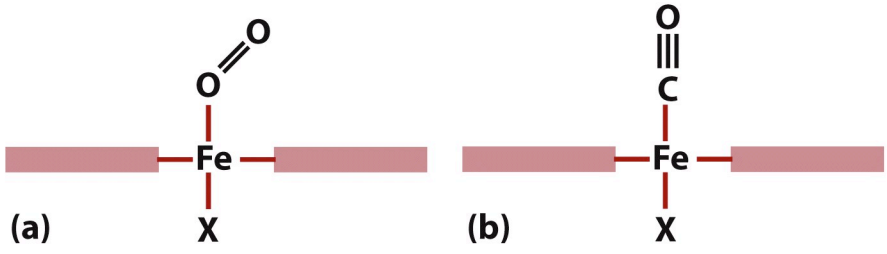

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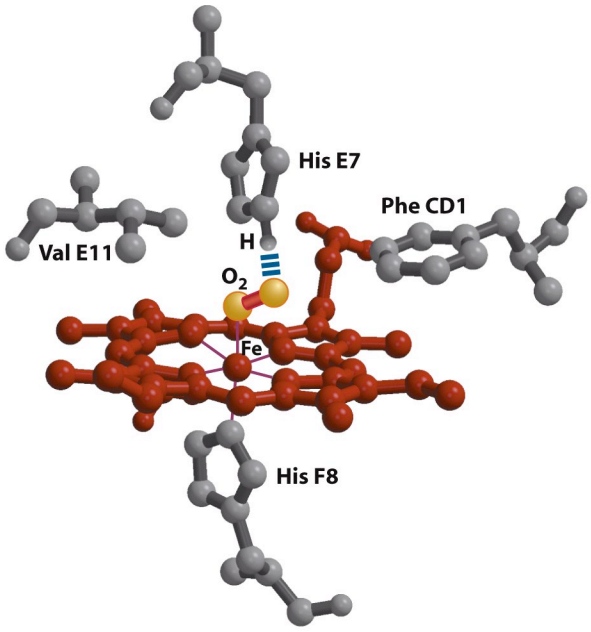

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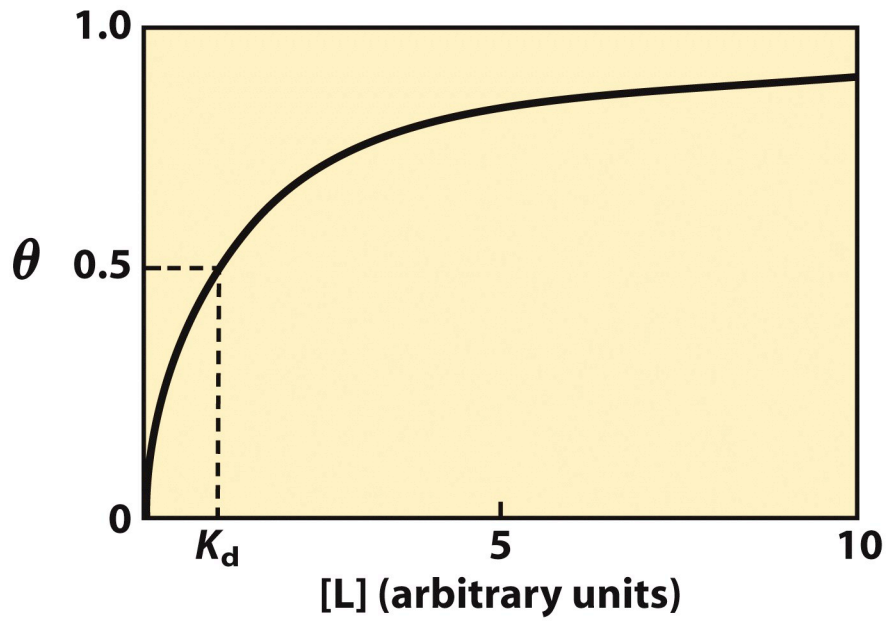

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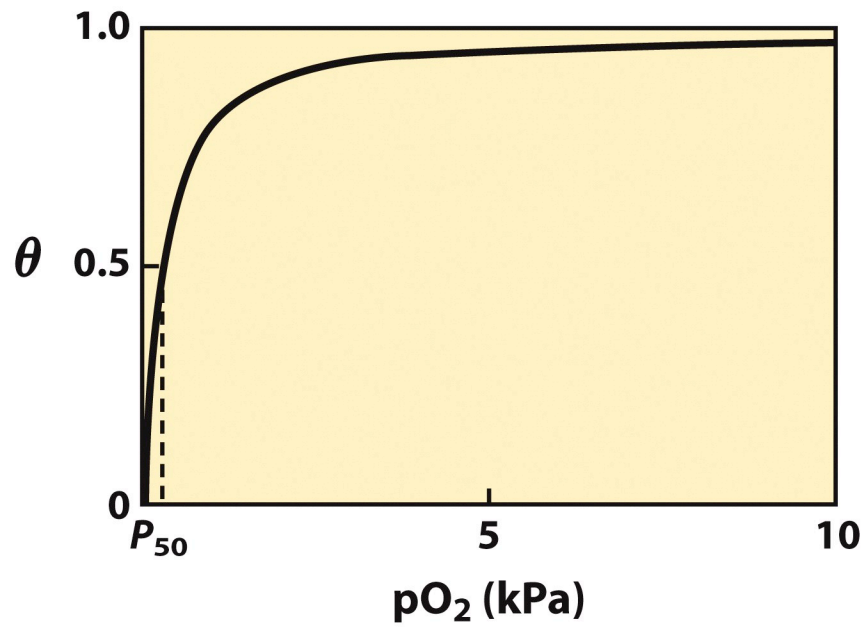

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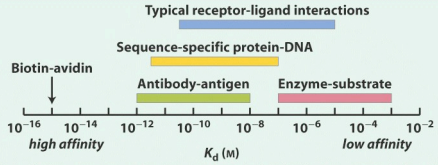
TABLE 5–1 Some Protein Dissociation Constants

Protein	Ligand	K_d (M)*
Avidin (egg white)†	Biotin	1×10^{-15}
Insulin receptor (human)	Insulin	1×10^{-10}
Anti-HIV immunoglobulin (human)‡	gp41 (HIV-1 surface protein)	4×10^{-10}
Nickel-binding protein (*E. coli*)	Ni^{2+}	1×10^{-7}
Calmodulin (rat)§	Ca^{2+}	3×10^{-6}
		2×10^{-5}



The range of dissociation constants for interactions in biological systems. Colors denote the range for each class of interaction. A few interactions, such as that between the protein avidin and the enzyme cofactor biotin, fall outside the normal ranges. The avidin-biotin interaction is so tight it may be considered irreversible. Sequence-specific protein-DNA interactions reflect proteins that bind to a particular sequence of nucleotides in DNA, as opposed to general binding to any DNA site.

*A reported dissociation constant is valid only for the particular solution conditions under which it was measured. K_d values for a protein-ligand interaction can be altered, sometimes by several orders of magnitude, by changes in the solution's salt concentration, pH, or other variables.

†This immunoglobulin was isolated as part of an effort to develop a vaccine against HIV. Immunoglobulins (described later in the chapter) are highly variable, and the K_d reported here should not be considered characteristic of all immunoglobulins.

‡Calmodulin has four binding sites for calcium. The values shown reflect the highest- and lowest-affinity binding sites observed in one set of measurements.

Table 5-1
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Myoglobin Structure

- Mb exists as a compact globular protein.
- There are eight helical regions (75% of Mb), with Pro or β turns typically separating the helical regions.
- Hydrophobic amino acid residues are on the interior.
- Hydrophilic amino acid residues are on the exterior where they hydrogen-bond with water.

Hemoglobin Chain Composition

- Rule: Adult human hemoglobin consists of two α and two non α chains.
- The predominant adult human hemoglobin is HbA. Composition: $\alpha_2\ \beta_2$
- A second adult human hemoglobin is HbA_2. Composition: $\alpha_2\ \delta_2$
- Fetal Hb: $\alpha_2\ \gamma_2$

Form	Chain composition	Fraction of total hemoglobin
HbA	$\alpha_2\beta_2$	90%
HbF	$\alpha_2\gamma_2$	<2%
HbA_2	$\alpha_2\delta_2$	2–5%
HbA_{1c}	$\alpha_2\beta_2$-glucose	3–9%

Figure 3.13
Normal adult human hemoglobins. [Note: The α-chains in these hemoglobins are identical.]

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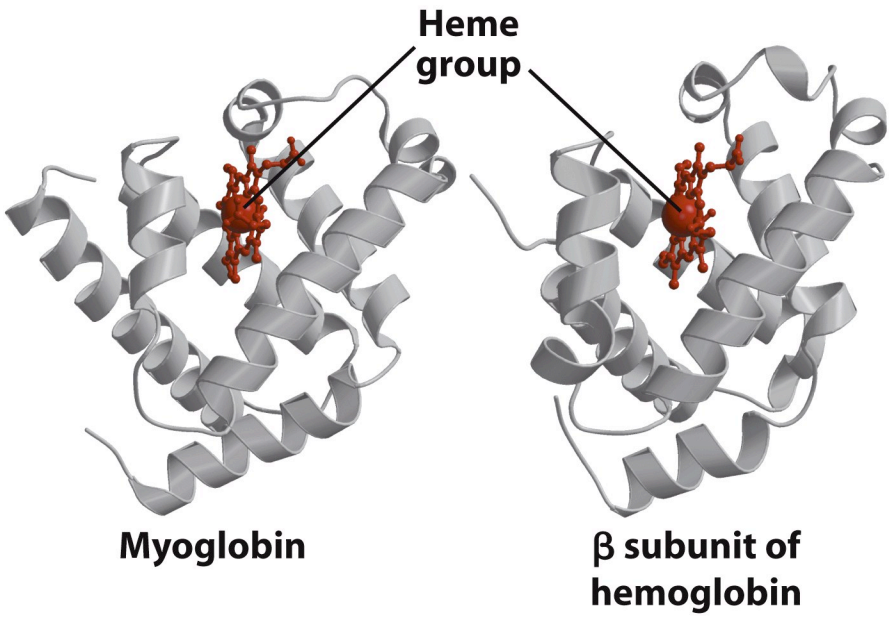
Hb F and Hb A

- Fetal Hb (HbF) has a higher affinity for oxygen than maternal Hb (HbA).
- This makes sense since the fetus must get its oxygen from the mother's blood.
- Fetal hemoglobin binds BPG less tightly than does maternal hemoglobin, thus explaining its higher affinity for oxygen.
- Lower affinity for BPG explained by two fewer positive charges in HbF than HbA.



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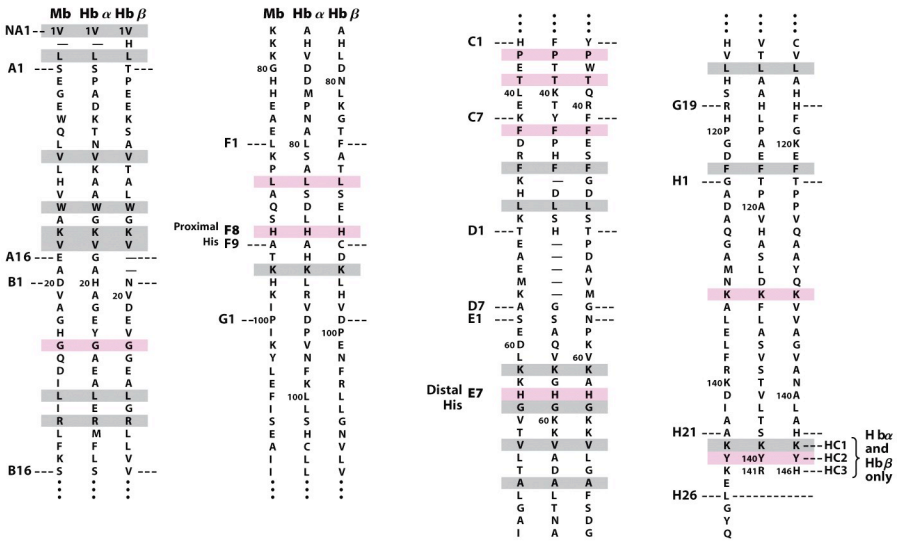

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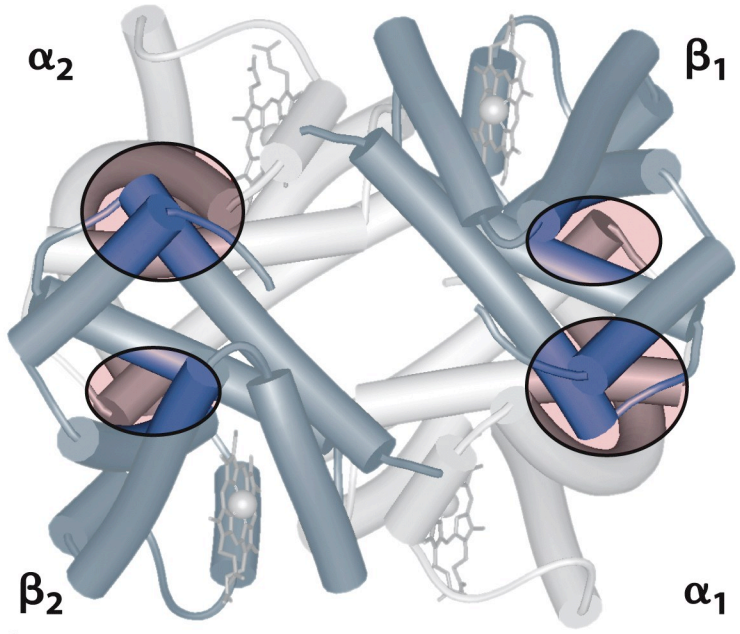

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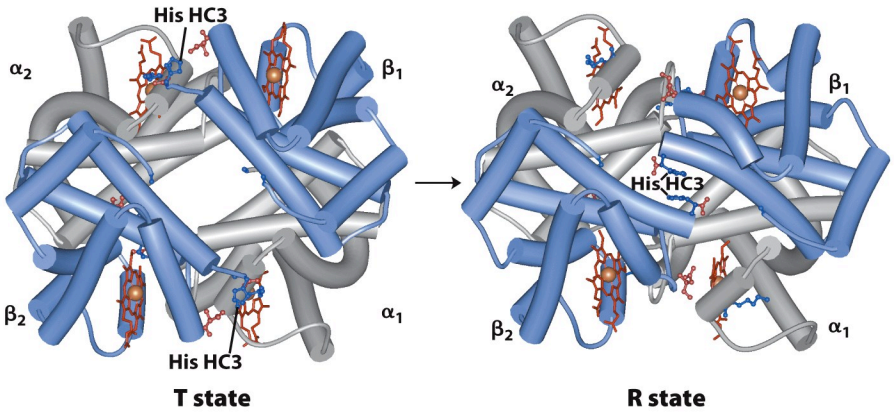

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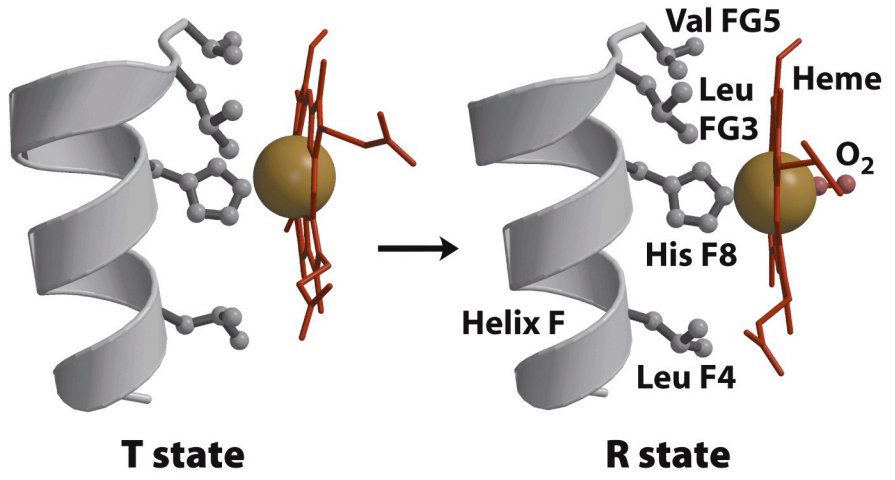

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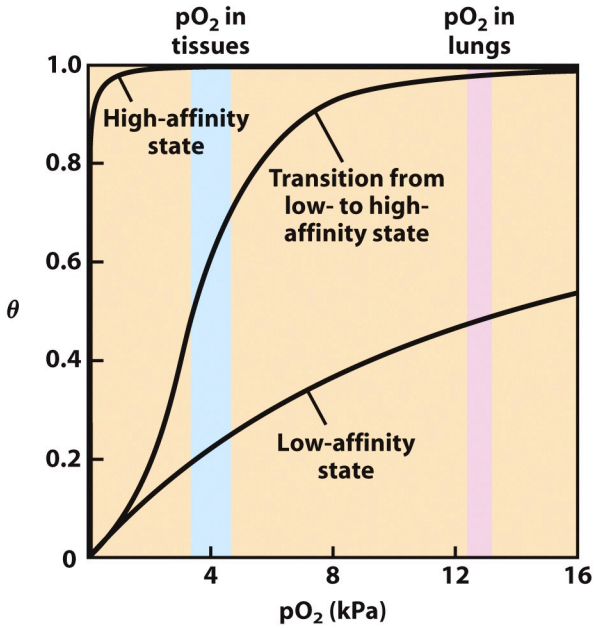

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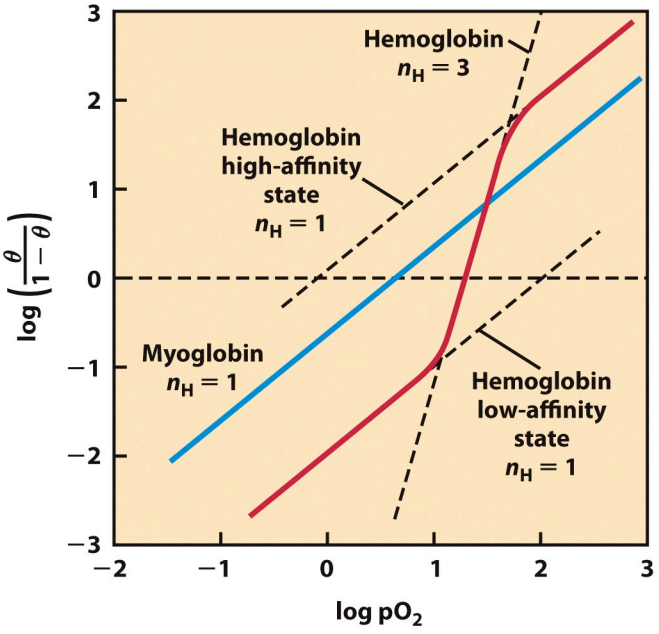

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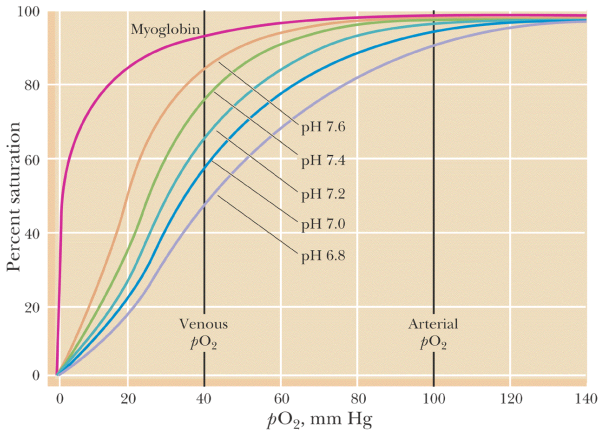
Effect of pH on Oxygen Binding to Hb

Garrett/Grisham, Biochemistry with a Human Focus
Figure 12.23



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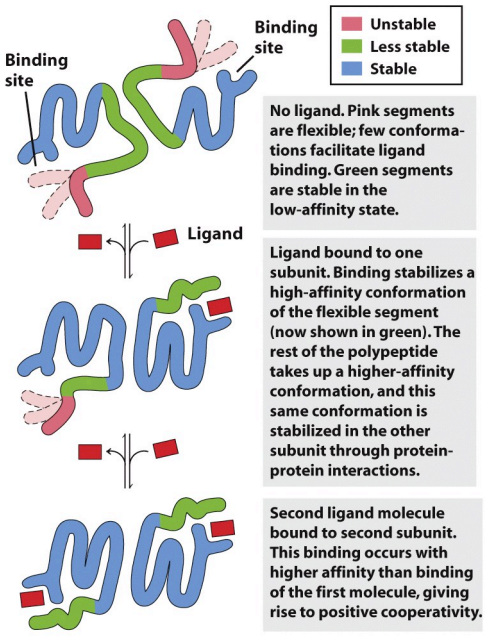
Allostery

- Allosteric proteins can exist in 2 conformational states (often denoted T and R)
  - States differ in ligand affinity or enzymatic activity
  - Conformational changes in tertiary structure and can also be in quaternary contacts
  - Effector binding shifts the distribution of states
  - Homotropic effectors (binding of one ligand or substrate affects the binding of the next of the same type)
  - Heterotropic effectors (different than the ligand or substrate)



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Hemoglobin

- In fact if the body had to depend upon dissolved oxygen in the plasma to supply oxygen to the cells
- The heart would have to pump 140 liters per minute - instead of 4 liters per minute.
- Each red blood cell can carry about one million molecules of oxygen
- Hemoglobin is 97% saturated when it leaves the lungs
- Under resting conditions is it about 75% saturated when it returns.

Hemoglobin

- Hemoglobin is a remarkable molecular machine that uses motion and small structural changes to regulate its action.
- Oxygen binding at the four heme sites in hemoglobin does not happen simultaneously.
- Once the first heme binds oxygen, it introduces small changes in the structure of the corresponding protein chain.

Hemoglobin

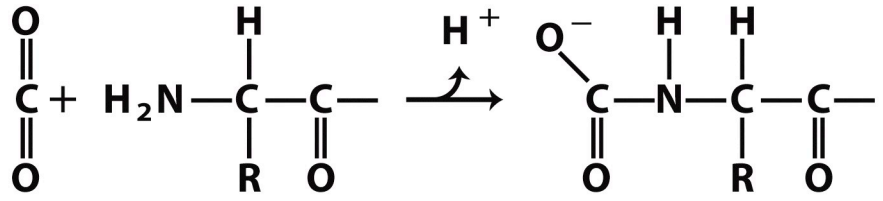
- These changes nudge the neighboring chains into a different shape, making them bind oxygen more easily.
- Thus, it is difficult to add the first oxygen molecule, but binding the second, third and fourth oxygen molecules gets progressively easier and easier.
- This provides a great advantage in hemoglobin function.

Hemoglobin

- When blood is in the lungs, where oxygen is plentiful, oxygen easily binds to the first subunit and then quickly fills up the remaining ones.
- Then, as blood circulates through the body, the oxygen level drops while that of carbon dioxide increases.

Hemoglobin

- In this environment, hemoglobin releases its bound oxygen. As soon as the first oxygen molecule drops off, the protein starts changing its shape.
- This prompts the remaining three oxygens to be quickly released.
- In this way, hemoglobin picks up the largest possible load of oxygen in the lungs, and delivers all of it where and when needed.



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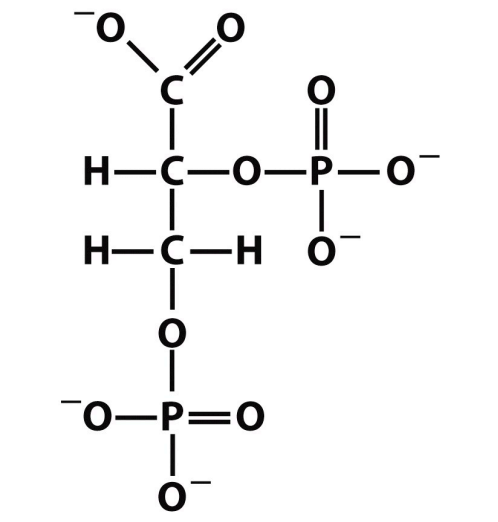

2,3-Bisphosphoglycerate

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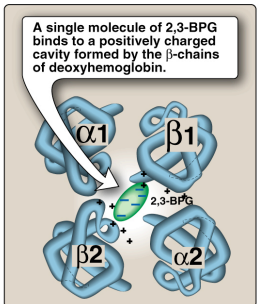
Effect of BPG Binding

- BPG is an allosteric regulator of Hb
- One BPG can be bound to Hb in a central cavity of the Hb molecule.
- The effect of BPG to "shift the dissociation curve to the right."
- Thus BPG promotes the unloading of oxygen.



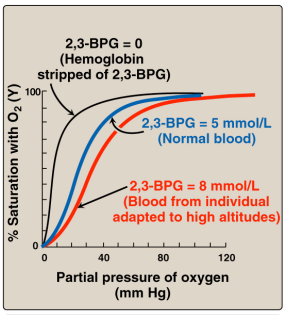


Figure 3.11
Effect of 2,3-BPG on the oxygen affinity of hemoglobin.

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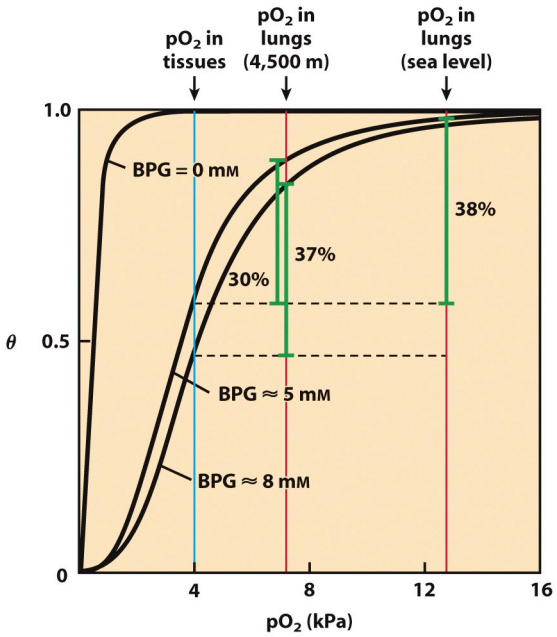

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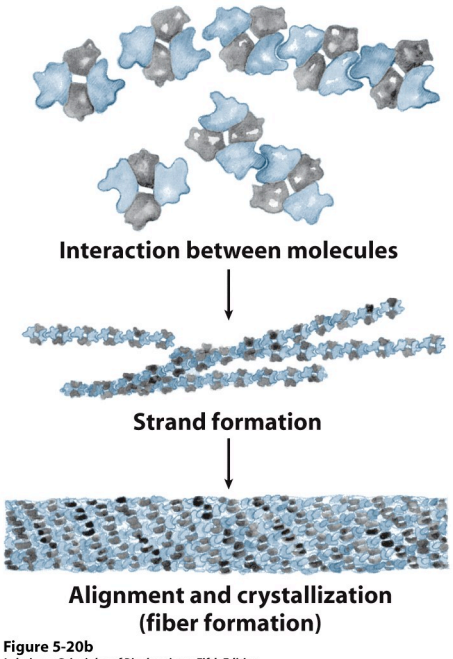

Figure 5-20b
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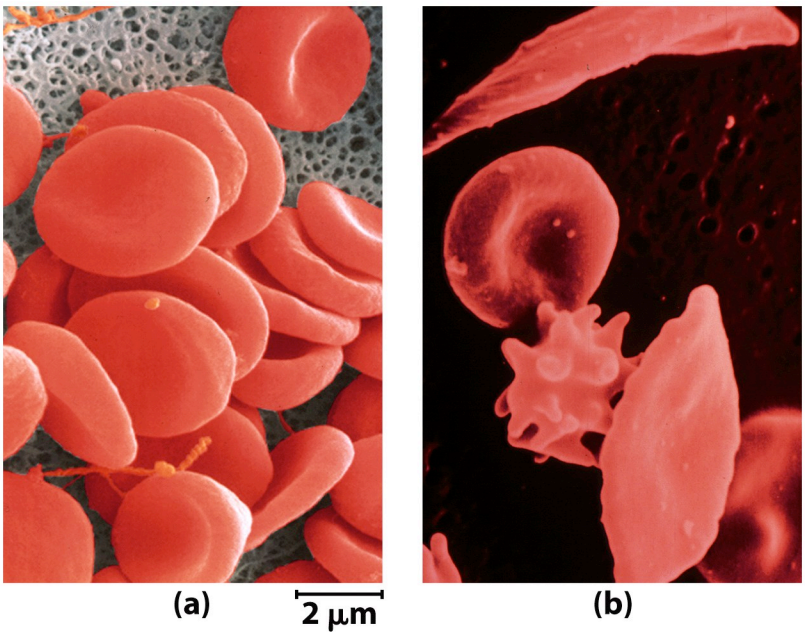

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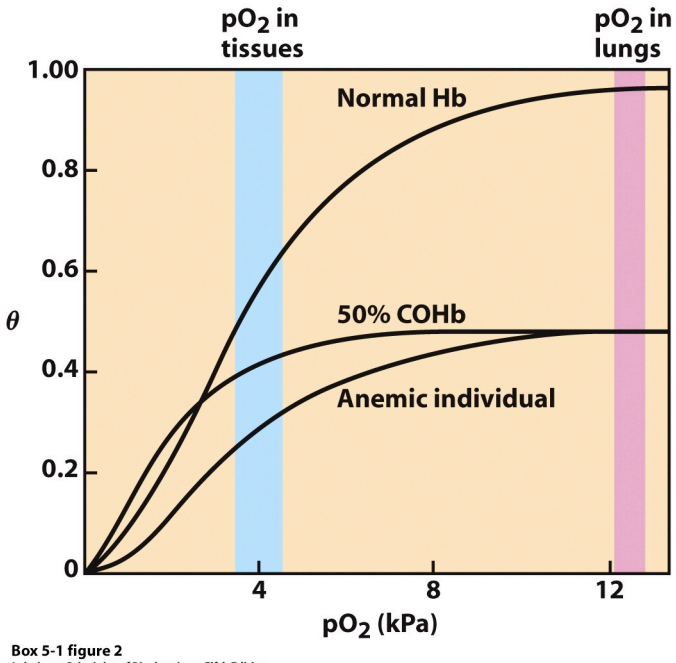

Box 5-1 figure 2
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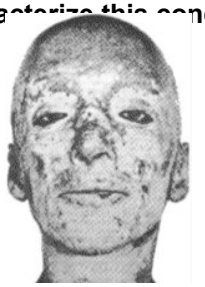
Thalassemia

- It consists of two different proteins, an alpha and a beta.
- If the body doesn't produce enough of either of these two proteins, the red blood cells do not form properly and cannot carry sufficient oxygen.
- The result is anemia that begins in early childhood and lasts throughout life.

Porphyria

- **Porphyria is a group of different disorders caused by abnormalities in the chemical steps leading to the production of heme**
- **It is characterized by extreme sensitivity to light (exposure to sunlight causes vesicular erythema), reddish-brown urine, reddish-brown teeth, and ulcers which destroy cartilage and bone, causing the deformation of the nose, ears, and fingers. Mental aberrations, such as hysteria, manic-depressive psychosis, and delirium, characterize this condition as well.**



What Is Immunity?

- Immunity is the body's ability to fight off harmful micro-organisms – PATHOGENS- that invade it.
- The immune system produces antibodies or cells that can deactivate pathogens.
- Fungi, protozoans, bacteria, and viruses are all potential pathogens.

Immune System

includes all parts of the body that help in the recognition and destruction of foreign materials. White blood cells, phagocytes and lymphocytes, bone marrow, lymph nodes, tonsils, thymus, and your spleen are all part of the immune system.

- Ø **Recognize and defense foreign substance**
- Ø **Immunosurveillance**

Time: Innate Immunity & Acquired Immunity

Location: Internal & External Immunity

Mechanism: Natural & Artificial Immunity

Strength of Response: Active & Passive

Mediator: Humoral & Cell-Mediated Immunity

Immune System, Continued

- Skin, mucous membranes, GI tract
- Organs of the immune system: Spleen, Lymph nodes, Thymus
- Cells of immune system: Phagocytes, Lymphocytes
- Mucosal immunity/Phagocytes
- Cell-mediated immunity/Lymphocytes

Immune System, Continued

- Operates through organ secretions/ interactions and white blood cells
- When invaded, body's WBC's move to area to defend
- White Blood Cells: includes phagocytes & lymphocytes

White Blood Cells (WBC's)

- Throughout the body
- Primarily in lymph tissue...thymus, lymph nodes, spleen, bone marrow, GI tract lining
- 3 types of WBC's:
  - Phagocytes
  - Lymphocytes:
    - T-cells
    - B-cells

WBC's, Continued

- Phagocytes
  - Scavenger cells
  - Digest microbes and secrete chemicals to activate T-cells
  - Detach antigen (on invader); placed on own cell surface --> activates lymphocytes

Lymphocytes

- T-cells
  - Stored in thymus gland
  - Specific for 1 antigen
  - Defend against:
    - fungi
    - viruses/parasites
    - some bacteria
    - Destroy some cancer cells

Lymphocytes, Cont'

- B-cells
  - Bone marrow derived
  - Produce antibodies --> kill or inactivate antigens --> phagocytes then eat invaders

- ***First-Line Defenses /Innate Immune System-*** The body's first line of defense against pathogens uses mostly physical and chemical barriers such as
- Skin – acts as a barrier to invasion
- Sweat – has chemicals which can kill different pathogens.
- Tears - have lysozyme which has powerful digestive abilities that render antigens harmless.
- Saliva – also has lysozyme.
- Mucus - can trap pathogens, which are then sneezed, coughed, washed away, or destroyed by chemicals.
- Stomach Acid – destroys pathogens

- ***Second-Line Defenses*** - If a pathogen is able to get past the body's first line of defense, and an infection starts, the body can rely on it's second line of defense. This will result in what is called an…….
- ***Inflammatory response*** causes
  - Redness - due to capillary dilation resulting in increased blood flow
  - Heat - due to capillary dilation resulting in increased blood flow
  - Swelling – due to passage of plasma from the blood stream into the damaged tissue
  - Pain – due mainly to tissue destruction and, to a lesser extent, swelling.

- ***Third-Line Defenses*** - Sometimes the second line of defense is still not enough and the pathogen is then heading for the body's last line of defense, the immune system.
- The immune system recognizes, attacks, destroys, and remembers each pathogen that enters the body. It does this by making specialized cells and antibodies that render the pathogens harmless.
- Unlike the first line and second line defense the immune system differentiates among pathogens.
- For each type of pathogen, the immune system produces cells that are specific for that particular pathogen.

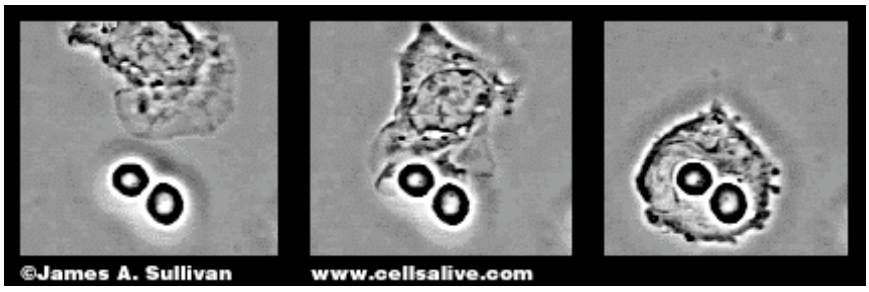
Lymph

Lymph is a milky body fluid that contains a type of white blood cells, called lymphocytes, along with proteins and fats.
Lymph seeps outside the blood vessels in spaces of body tissues and is stored in the lymphatic system to flow back into the bloodstream.

- **There are more than 100 tiny, oval structures called lymph nodes. These are mainly in the neck, groin and armpits, but are scattered all along the lymph vessels.**
- **They act as barriers to infection by filtering out and destroying toxins and germs. The largest body of lymphoid tissue in the human body is the spleen.**
- **Through the flow of blood in and out of arteries, and into the veins, and through the lymph nodes and into the lymph, the body is able to eliminate the products of cellular breakdown and bacterial invasion.**

- As the lymph flows through lymph vessels, it passes through lymph nodes.
- White blood cells called **macrophages** trap and engulf cell debris and pathogens. Other white blood cells, called
- **Lymphocytes** - are a type of white blood cell capable of producing a *specific immune response* to unique antigens. They produce antibodies which are chemicals that mark pathogens for destruction.

- Once a white cell has left the blood vessel and migrated to the enemy, the next job is to EAT the microbe.
- The macrophage is a large phagocyte. A **phagocyte** is an eating cell (phago = "eating", cyte = "cell") which engulfs invaders.



Secretory Functions of Macrophages

- Binding proteins (transferrin, fibronectin)
- Complement components
- Proteolytic enzymes (lysozyme)
- Enzyme inhibitors (a_2-macroglobulin)
- Endogenous pyrogen (IL-1)
- ROS (superoxide, hydrogen peroxide, hydroxyl radical)
- RNS (nitric oxide, peroxynitrite)
- Bioactive lipids (PAF, PG, LT, TBX)
- Chemokines (C-C and C-X-C)
- Growth factors (FGF, EGF, CSF)
- Proinflammatory cytokines (IL-1, TNFα, IL-6)
- Angiogenic factors: VEGF
- Matrix remodeling proteins: TGFβ, MMP

- Immunity is the result of the action of two types lymphocytes, the *B lymphocytes* and the *T lymphocytes*.
- B cells produce antibodies that are secreted into the blood and lymph.
- T cells attack the cells that have antigens that they recognize.

T cell responses differ from B cell responses in two crucial ways

- T cells are activated by foreign antigen to proliferate and differentiate into effector cells only when the antigen is displayed on the surface of antigen-presenting cells in peripheral lymphoid organs. Whereas B cells recognize intact antigen, T cells recognize fragments of protein antigens that have been partly degraded inside the antigen-presenting cell. The peptide fragments are then carried to the surface of the presenting cell on special molecules called MHC proteins;
- The second difference is that, once activated, effector T cells act only at short range, either within a secondary lymphoid organ or after they have migrated into a site of infection. They interact directly with another cell in the body, which they either kill or signal in some way. Activated B cells, by contrast, secrete antibodies that can act far away.

Two main classes of T cells

- Effector cytotoxic T cells directly kill cells that are infected with a virus or some other intracellular pathogen.
- Effector helper T cells, by contrast, help stimulate the responses of other cellsmainly macrophages, B cells, and cytotoxic T cells

TABLE 5–2 Some Types of Leukocytes Associated with the Immune System

Cell type	Function
Macrophages	Ingest large particles and cells by phagocytosis
B lymphocytes (B cells)	Produce and secrete antibodies
T lymphocytes (T cells)	
Cytotoxic (killer) T cells (T_C)	Interact with infected host cells through receptors on T-cell surface
Helper T cells (T_H)	Interact with macrophages and secrete cytokines (interleukins) that stimulate T_C, T_H, and B cells to proliferate.

Table 5-2
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What is the Innate Immune Response?

- Universal and evolutionarily conserved mechanism of host defense against infection; first line of defense;
- Predates adaptive immune response
  - Found in all multicellular organisms (adaptive only in vertebrates)
  - Uses receptors and effectors that are ancient in their lineage
  - Provides protection against a wide variety of pathogens
- Distinguishes self from non-self perfectly
- Defects in innate immunity are very rare and almost always lethal

Innate Immunity: Functions

- Provides a barrier to prevent the spread of infection
  - Physical
    - Skin (epithelial cells); Wounds, burns, insect bites
    - Mucosal surfaces (respiratory, GI, Reproductive)
  - Mechanical (tight junctions, movement)
  - Chemical (fatty acids, enzymes, pH, antimicrobial peptides)
  - Microbiological (normal flora)

Innate Immunity: Functions

- Identifies and eliminates pathogens
  - Non-adaptive recognition systems
  - Activates molecules that target the microbe and aid in it's identification
    - These factors may be surface expressed (TLR), released from immune cells (antibodies) or present within circulatory system (complement)

Innate Immunity: Functions

- Initiates an inflammatory response
  - Reaction to injury or infection
    - Trauma to tissues or cells
    - Presence of foreign material (splinter)
    - Infectious agents (viruses, bacteria, fungi)
  - Delivers immune cells and effector molecules to the site of injury/infection
  - Components
    - Granulocytes, MP, inflammatory mediators
    - Blood vessels (endothelium)
    - Plasma proteins

Innate Immunity: Functions

- Provides signals to alert the adaptive immune system to activate an effective specific immune response
  - Antigen processing and presentation (activation of T helper cells)
  - Upregulation of co-stimulatory molecules
    - MHC class II, CD80/86
  - Induction of cytokine/chemokine response
    - IL-4, IL-12

Innate Immunity: Cellular Components

- **Granulocytes**
  - Polymorphonuclear leukocytes (PMN, neutrophils)
  - Eosinophils
  - Basophils (blood)
  - Mast Cells (tissues)
- **Mononuclear Phagocytes (RES)**
  - Monocytes (blood)
  - Macrophages (tissue)

Innate Immunity Features

- **Preformed: Rapid-Available on Short Notice**
- **No Memory:Not Enhanced by Prior Exposure:**
- **Broad Specificity**
- **Early Phase of Immune Response**
- **Dependent on species, strain, sex.**

  Human: no hog cholera, cunine distemper

  Dog: no anthrax

  Human, cattle, sheep: anthrax

  African & native American: TB

  Cancasians: diphtheria & influenza

Acquired/Specific Immunity

- Acquired Following Exposure to the Microorganism.

Acquired/Adaptive/Specific Immunity Features

- Specificity
- Memory
- Specialization
- Self/Nonself recognition
- Inducibility
- Diversity
- Self-Limiting

Innate vs. Acquired Immunity

- Innate/Natural/ Nonspecific
  - present from birth
  - operates against any substance
  - not enhanced by prior exposure
- Acquired/Adaptive/Specific
  - defense mechanisms tailored to individual pathogens
  - enhanced by prior exposure

Natural & Artificial immunity (vaccine)

Active & Passive Immunity

Active: generated slowly, highly protective, last years

Passive: response fast, no memory, moderative protection, last days to month

Vaccination: A vaccination is an injection of a weakened form of the actual antigen that causes the disease. The injection is too weak to make you sick, but your B lymphocytes will recognize the antigen and react as if it were the "real thing". Thus, you produce MEMORY cells for long term immunity.

•**Active Immunity** occurs when when one makes his/her own antibodies. This type of immunity is long term.

•**Getting the disease** : If you get an infectious disease (like Chicken Pox), often times, that stimulates the production of MEMORY cells which are then stored to prevent the infection in the future.

Passive Immunity occurs when the antibodies come from some other source. This type of immunity is short term.

Breastmilk : Milk from a mother's breast contains antibodies. The baby is acquiring passive immunity. These antibodies will only last several weeks.

Characters of Internal Immunity

- ü **Preformed**
- ü **Standarized**
- ü **Without Memory**
- ü **Nonspecific**

Inflammation: red, swell, heat, pain

- v **clotting mechanism activation**
- v **increased blood flow**
- v **increased capillary permeability**
- v **increased influx of phagocytic cells**

External Immunity

- **Skin**
- **Body secretion**
- **Mucos membrane**
- **Cilia (sputum or phlegm from respiratory tract)**

Antigens & Antibodies

- Antigens:
  - Molecules that stimulate the production of specific antibodies and combine specifically with the antibodies produced. Most antigens are foreign to the blood and other bodily fluids.
- Antibodies:
  - Antibody proteins (immunoglobulins) are found in the gamma globulin class of plasma proteins. There are five main subclasses : IgG, IgA, IgM, IgD, and IgE. (ex. Most antibodies in serum are from the class IgG).

- antigens can be generated within the cells of the body. These include
  - proteins encoded by the genes of viruses that have infected a cell
  - aberrant proteins that are encoded by mutant genes; such as mutated genes in cancer cells

- An antibody is a protein produced in response to an antigen.
- Antigens are macromolecules that elicit an immune response in the body. The most common antigens are proteins and polysaccharides. Antigens can enter the body from the environment. These include
  - inhaled macromolecules (e.g., proteins on cat hairs that can trigger an attack of asthma in susceptible people)
  - ingested macromolecules (e.g., shellfish proteins that trigger an allergic response in susceptible people)
  - molecules that are introduced beneath the skin (e.g., on a splinter or in an injected vaccine)

There Are Five Classes of Heavy Chains

- IgM, which has μ heavy chains, is always the first class of antibody made by a developing B cell;
- After leaving the bone marrow, the B cell starts to produce cell-surface IgD molecules as well, with the same antigen-binding site as the IgM molecules.
- The major class of immunoglobulin in the blood is IgG, which is a four-chain monomer produced in large quantities during secondary immune responses;
- IgA is the principal class of antibody in secretions, including saliva, tears, milk, and respiratory and intestinal secretions;
- The tail region of IgE molecules, which are four-chain monomers, binds with unusually high affinity (Ka ~ 1010 liters/ mole) to yet another class of Fc receptors;

Functions of immunoglobulins

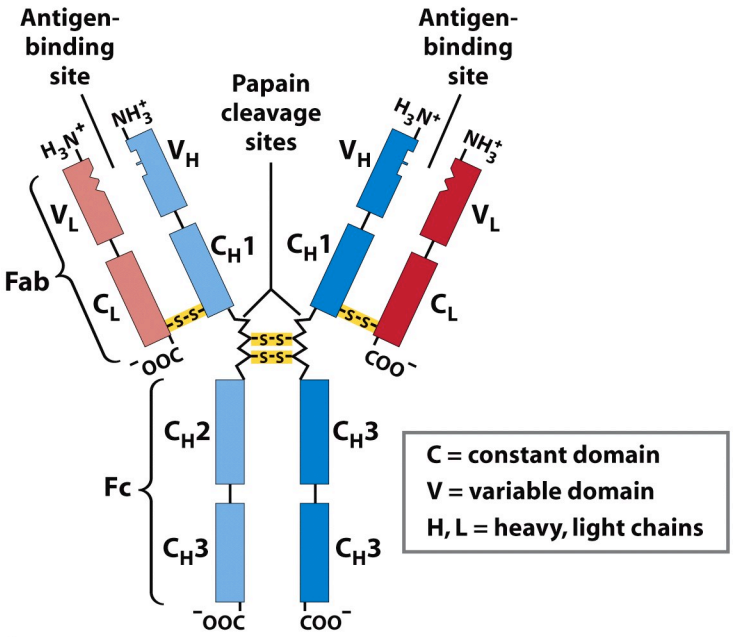
Function	IgM	IgD	IgG1	IgG2	IgG3	IgG4	IgA	IgE
Neutralization	+	–	+++	+++	+++	+++	+++	–
Opsonization	–	–	+++	*	++	+	+	–
Sensitization for killing by NK cells	–	–	++	–	++	–	–	–
Sensitization of mast cells	–	–	+	–	+	–	–	+++
Activation of complement system	+++	–	++	+	+++	–	+	–

Property	IgM	IgD	IgG1	IgG2	IgG3	IgG4	IgA	IgE
Transport across epithelium	+	–	–	–	–	–	+++ (dimer)	–
Transport across placenta	–	–	+++	+	++	++	–	–
Diffusion into extravascular sites	+/–	–	+++	+++	+++	+++	++ (monomer)	+
Mean serum level (mg/ml)	1.5	0.03	9	3	1	0.5	2.5	5×10^{-5}

Figure 4.32 The Immune System, 3ed. (© Garland Science 2009)

Changes in immunoglobulin genes during a B cell's life			
	Event	**Mechanism**	**Permanence of change to the B cell's genome**
1	V-region assembly from gene fragments	Somatic recombination of genomic DNA	Irreversible
2	Generation of junctional diversity	Imprecision in joining rearranged DNA segments adds nongermline nucleotides (P and N) and deletes germline nucleotides	Irreversible
3	Assembly of transcriptional controlling elements	Promoter and enhancer are brought closer together by V-region assembly	Irreversible
4	Transcription activated with coexpression of surface IgM and IgD	Two patterns of splicing and processing RNA are used	Reversible and regulated
5	Synthesis changes from membrane Ig to secreted antibody	Two patterns of splicing and processing RNA are used	Reversible and regulated
6	Somatic hypermutation	Point mutation of genomic DNA	Irreversible
7	Isotype switch	Somatic recombination of genomic DNA	Irreversible

Figure 4.35 The Immune System, 3ed. (© Garland Science 2009)



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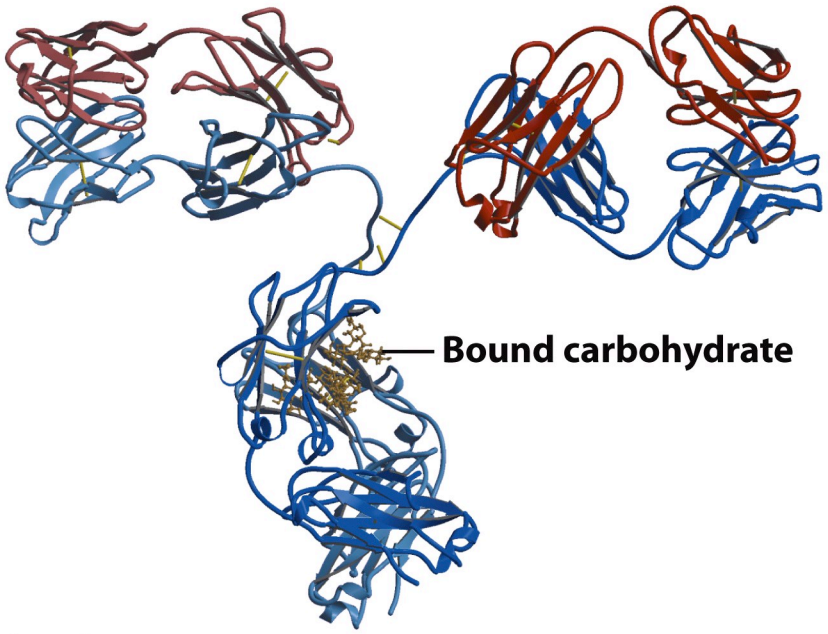

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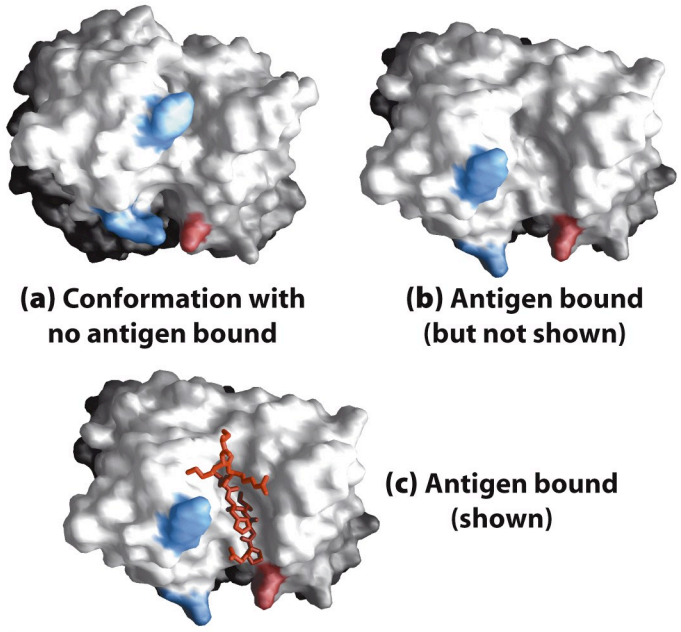

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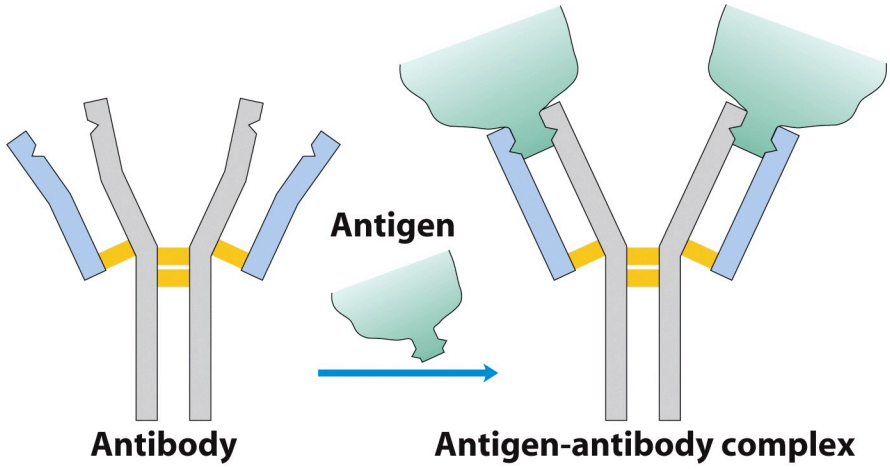

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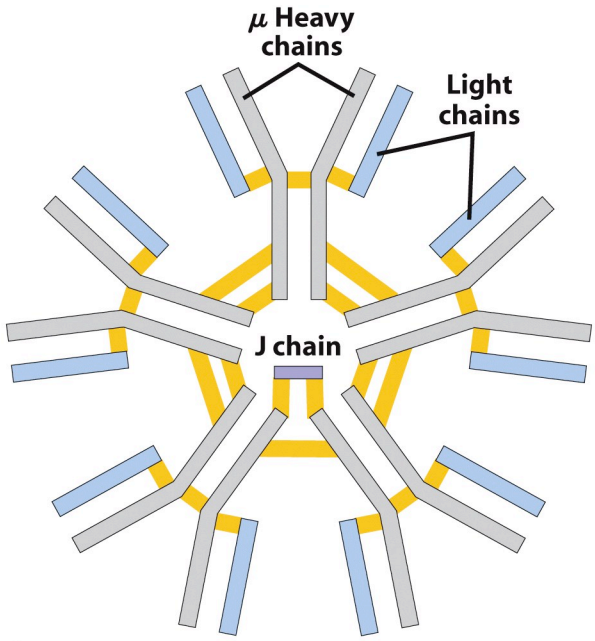

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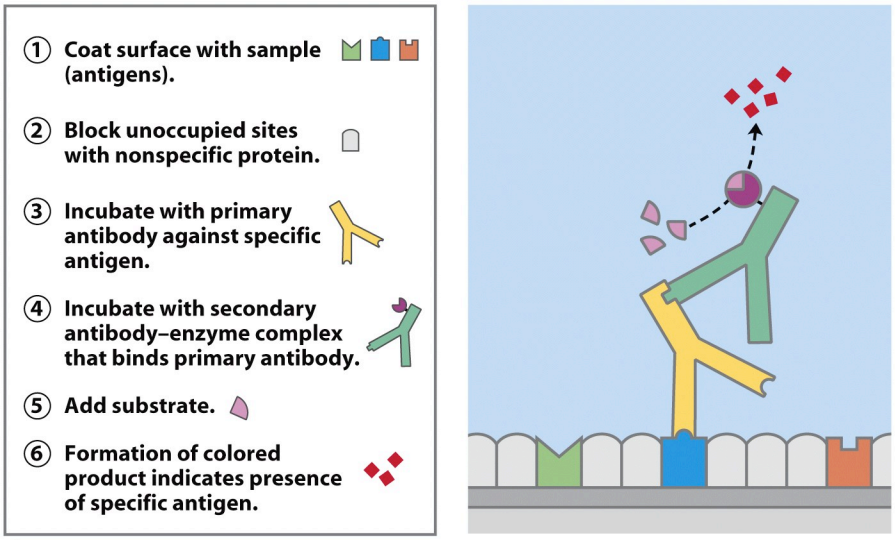

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