MEMBRANES:

- **LIPID BILAYER - provides the basic fluid <u>structure</u> of the membrane - relatively impermeable barrier (5 nm thick).**

- **PROTEIN MOLECULES - span the lipid bilayer mediate nearly all of the other <u>functions</u>.**

30% of the proteins that are encoded in an animal cell's genome are membrane proteins

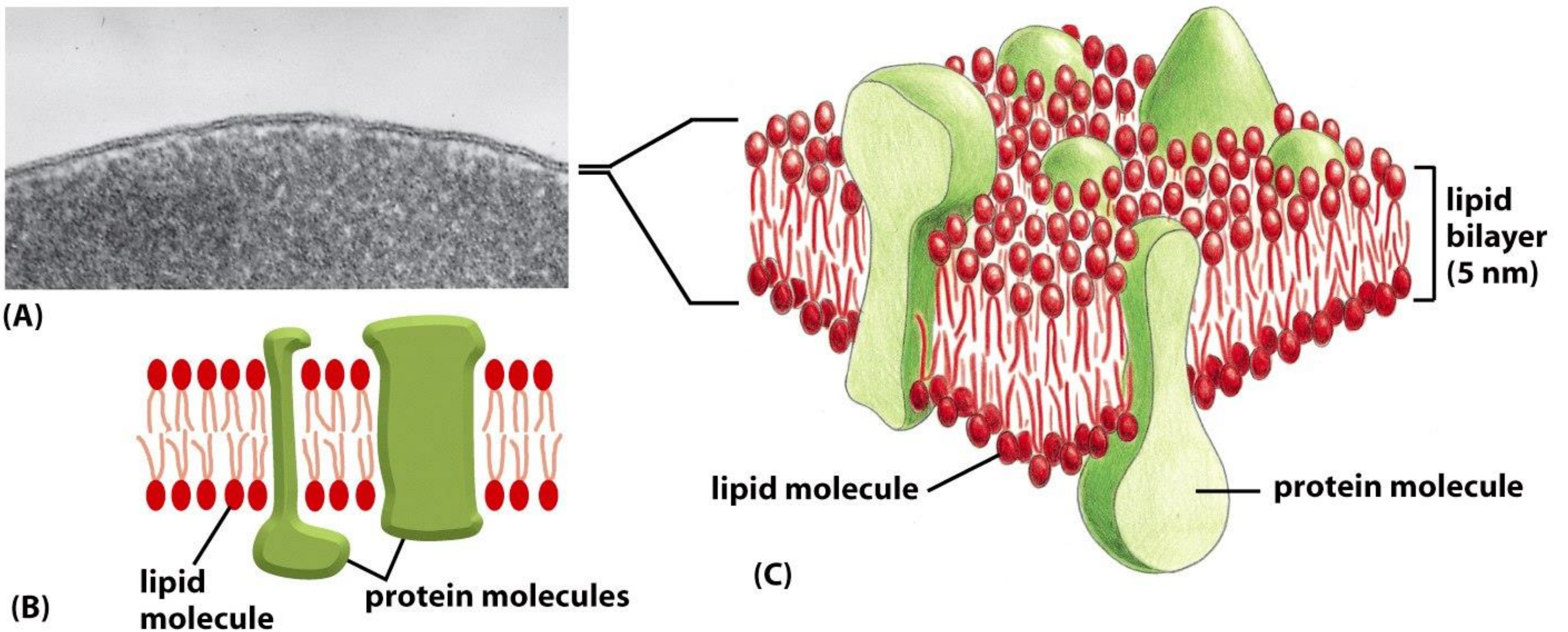
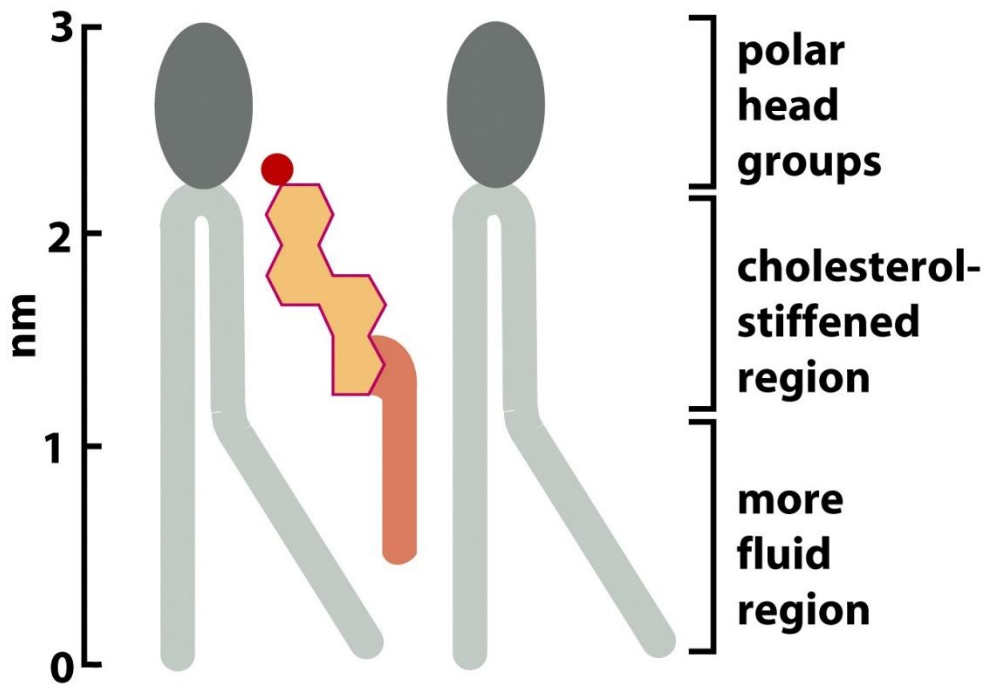


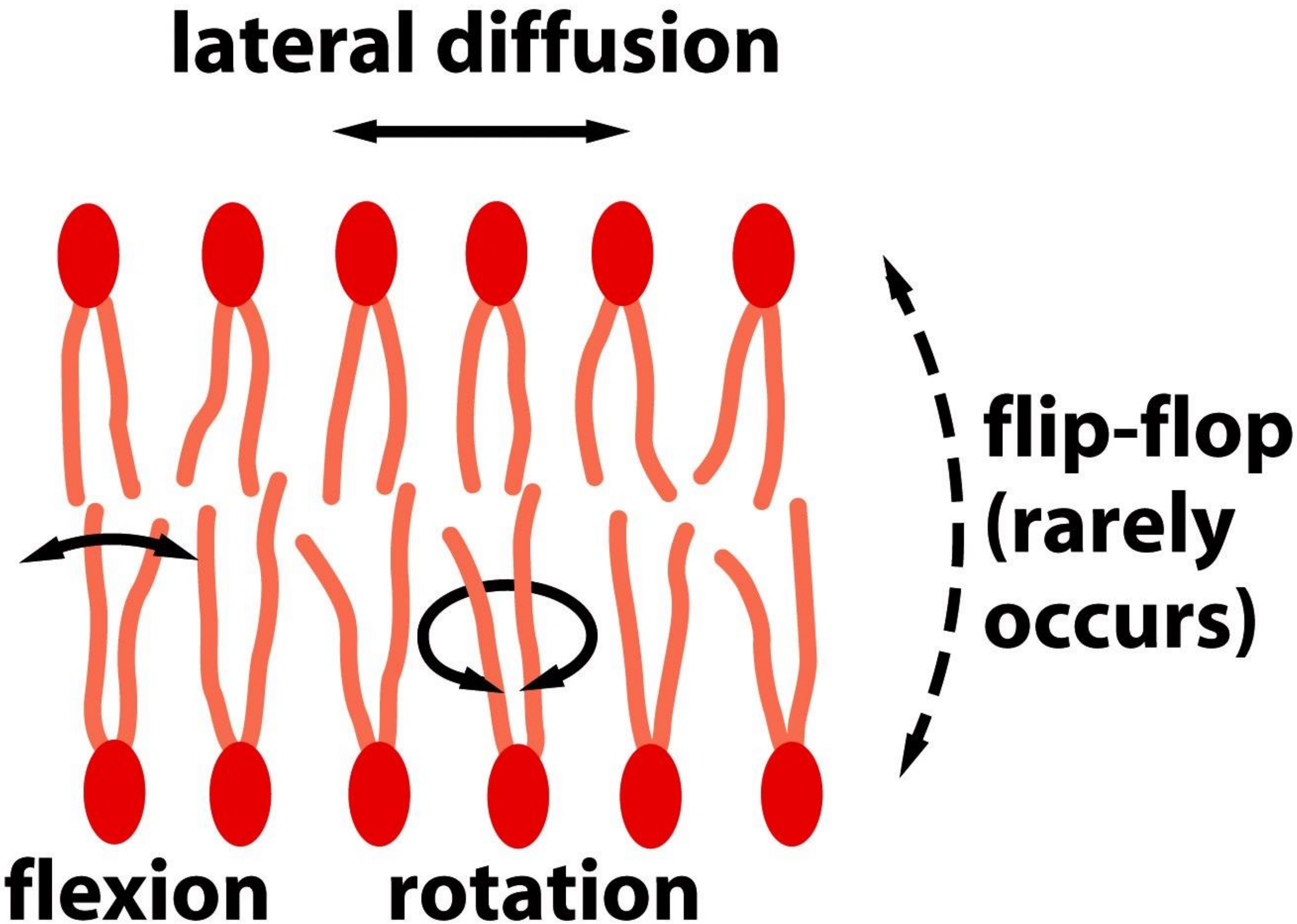
Figure 10-1 *Molecular Biology of the Cell* (© Garland Science 2008)

MEMBRANE LIPIDS:

- phospholipids
- glycolipids
- Cholesterol - up to one molecule for every phospholipid molecule (permeability).



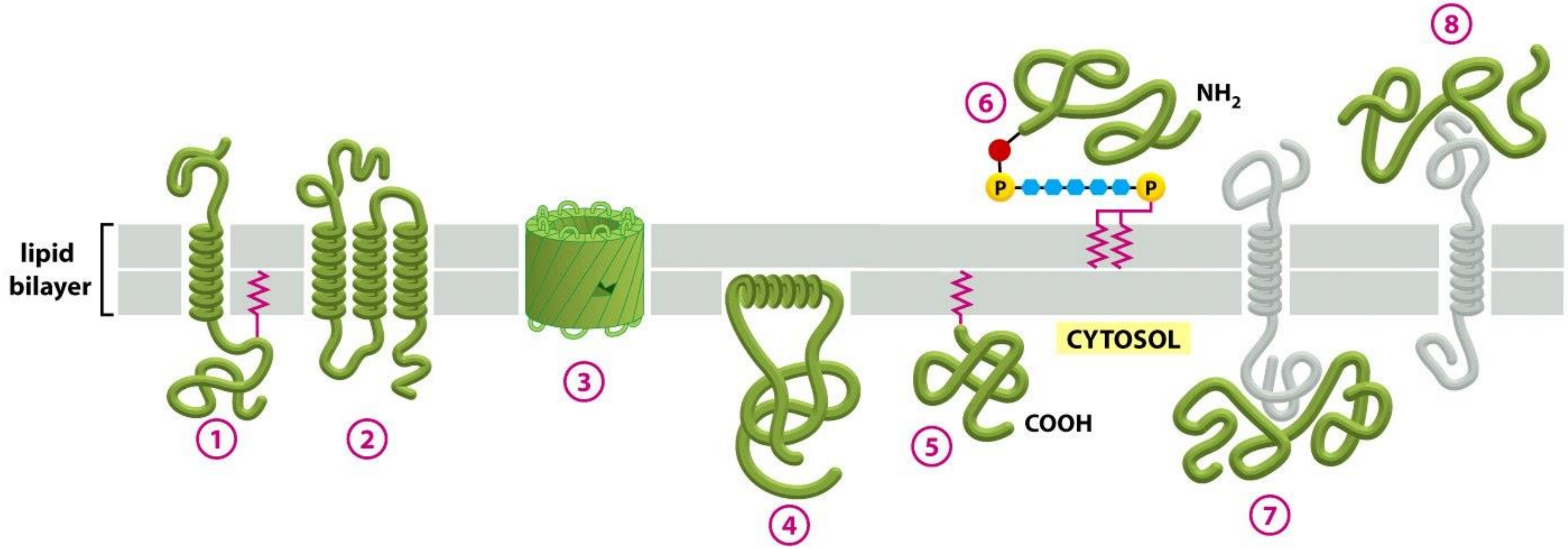
The Lipid Bilayer Is a Two-dimensional Fluid



Membrane Proteins

- perform most of the specific functions of membranes;
- give each type of membrane in the cell its characteristic functional properties;
- the amounts and types of proteins in a membrane are highly variable (eg: myelin membrane< 25% of the mb. Mass, internal membranes of mitochondria – aprox. 75%)

Membrane Proteins - Associated with the Lipid Bilayer



- Extend across the bilayer as (1) a single α helix, (2) as multiple α helices, or (3) β sheet.
- Exposed at only one side of the membrane - anchored to the cytosolic surface (4)
- Attached to the bilayer solely by a covalently attached lipid chain (5),
- Attached via an oligosaccharide linker to phosphatidylinositol in the noncytosolic monolayer (6).
- Attached to the membrane only by noncovalent interactions with other membrane proteins. (7, 8)

1. MEMBRANE TRANSPORT

- **small soluble molecules**;

- **inorganic ions and small water-soluble molecules**;

- **large particles**.

2. CELL JUNCTIONS

MEMBRANE TRANSPORT

- **WHAT?**
- **HOW +/- proteins?**
- **active/passive?**

<u>MEMBRANE</u> Transport of Small Molecules

- LIPID BILAYER (hydrophobic interior) - a barrier to the passage of most polar molecules.

- allows the cell to maintain concentrations of solutes (<u>extracell</u> *vs* <u>cytosol</u> *vs* each of the intracellular membrane-enclosed <u>compartments</u>)

Table 11–1 A Comparison of Ion Concentrations Inside and Outside a Typical Mammalian Cell

COMPONENT	INTRACELLULAR CONCENTRATION (mM)	EXTRACELLULAR CONCENTRATION (mM)
Cations		
Na^+	5–15	145
K^+	140	5
Mg^{2+}	0.5	1–2
Ca^{2+}	10^{-4}	1–2
H^+	7×10^{-5} ($10^{-7.2}$ M or pH 7.2)	4×10^{-5} ($10^{-7.4}$ M or pH 7.4)
Anions*		
Cl^-	5–15	110

*The cell must contain equal quantities of positive and negative charges (that is, it must be electrically neutral). Thus, in addition to Cl^-, the cell contains many other anions not listed in this table; in fact, most cell constituents are negatively charged (HCO_3^-, PO_4^{3-}, proteins, nucleic acids, metabolites carrying phosphate and carboxyl groups, etc.). The concentrations of Ca^{2+} and Mg^{2+} given are for the free ions. There is a total of about 20 mM Mg^{2+} and 1–2 mM Ca^{2+} in cells, but both are mostly bound to proteins and other substances and, for Ca^{2+}, stored within various organelles.

MEMBRANE TRANSPORT

I. small soluble molecules (hydrophobic/nonpolar) -<u>without</u> specialized transmembrane proteins (simple DIFFUSION)

II. inorganic ions and small water-soluble molecules – <u>with</u> specialized transmembrane proteins:

- “carrier” p.–moving parts (active/passive);

Energy source - ATP/ions gradients;

- “channel” p .–form a narrow hydrophilic pore (passive – facilitate diffussion);

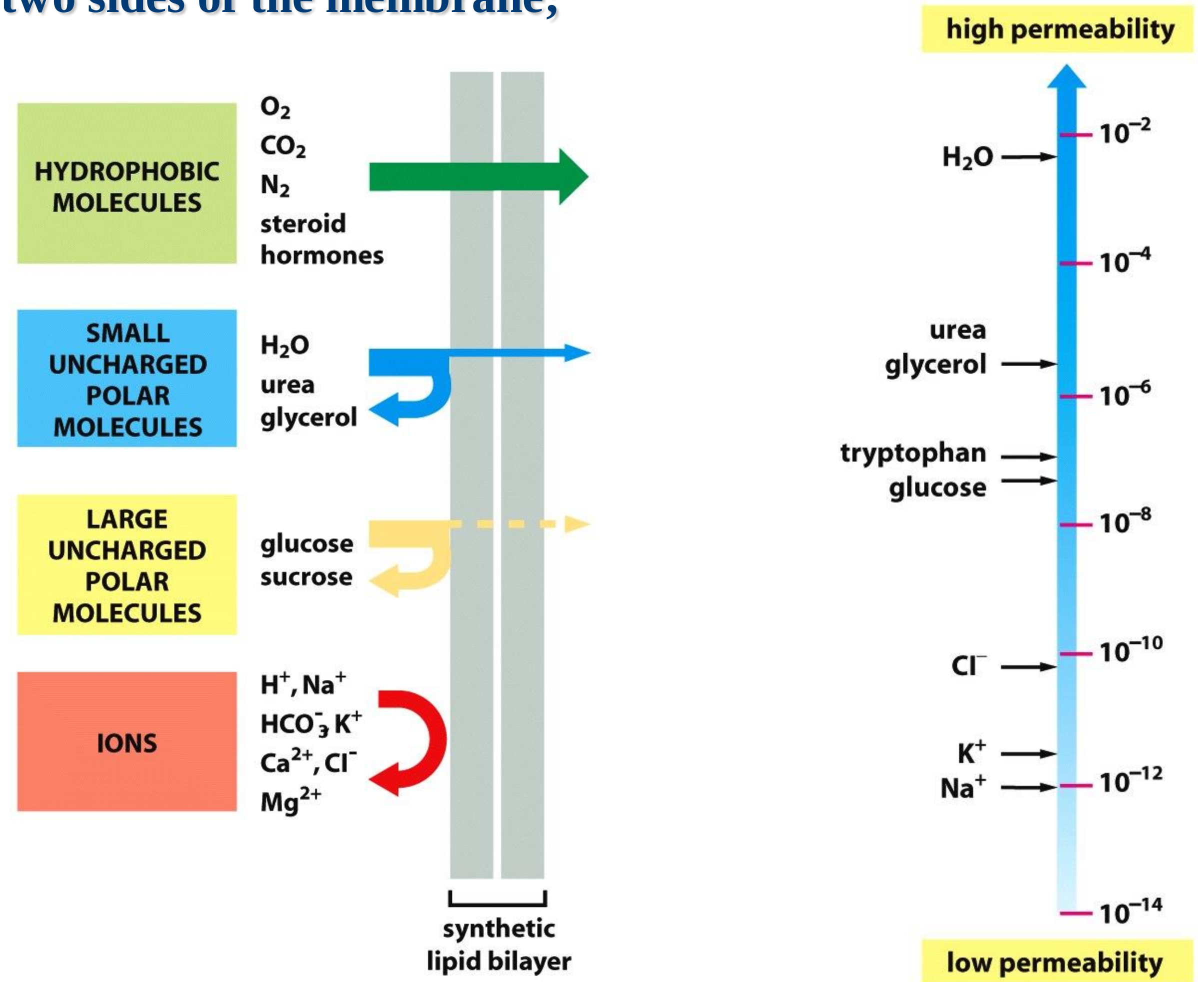
III. large particles <= vesicules

- endocytosis;

- exocytosis;

I. simple DIFFUSION across a protein-free lipid bilayer down its concentration gradient

- the rate of flow of a solute across the bilayer is directly proportional to the difference in its concentration on the two sides of the membrane;
- reduced specificity;



II. A. <u>TRANSPORTERS</u> (Carriers/Permeases)

- <u>multipass</u> transmembrane proteins;
- form a continuous protein <u>pathway</u> across the membrane;
- enable specific <u>hydrophilic solutes to cross</u> the membrane without coming into direct contact with the hydrophobic interior of the lipid bilayer;
- <u>bind the specific solute</u> to be transported;
- undergo a series of <u>reversible conformational changes</u> to transfer the bound solute across the membrane.

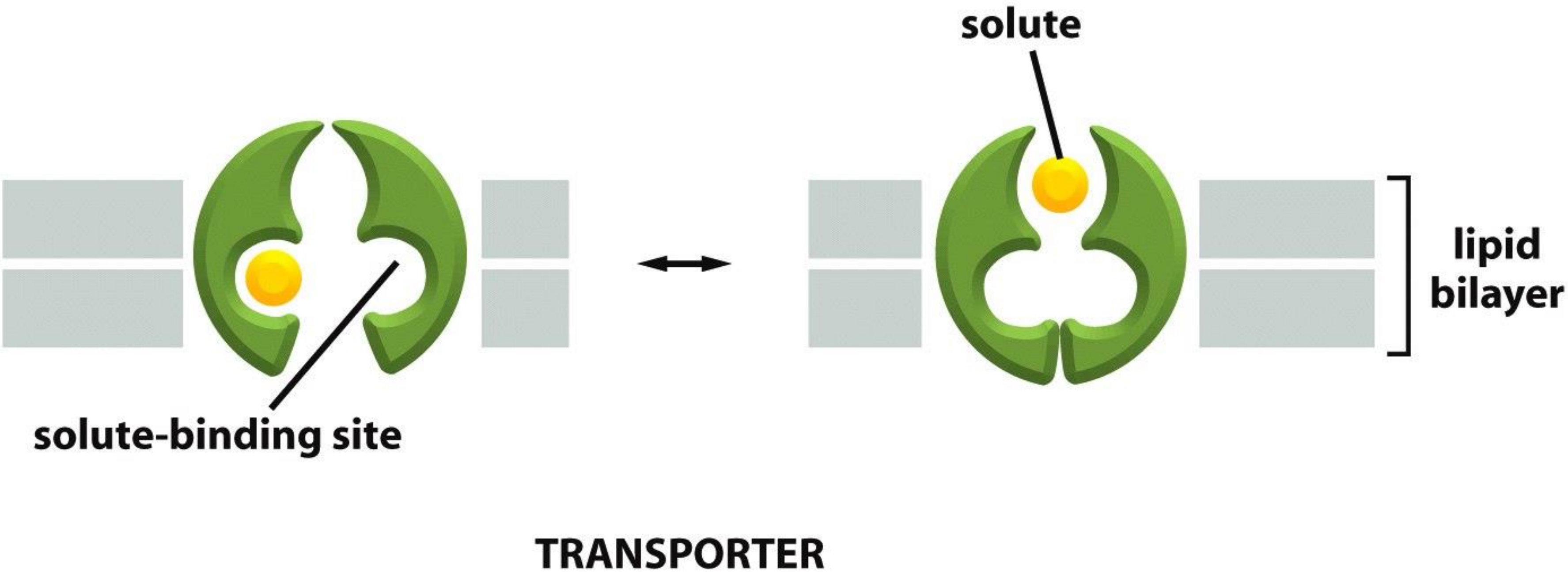


Figure 11-3a *Molecular Biology of the Cell* (© Garland Science 2008)

II. B. CHANNELS

- interact with the solute to be transported much more weakly;
- transport through channels occurs at a much faster rate;
- form aqueous pores that extend across the lipid bilayer;
- when open, these pores allow specific solutes (usually inorganic ions of appropriate size and charge) to pass through them and thereby cross the membrane;
- all cells contain specific channel proteins (called water channels, or aquaporins) that greatly increase the permeability of these membranes to water

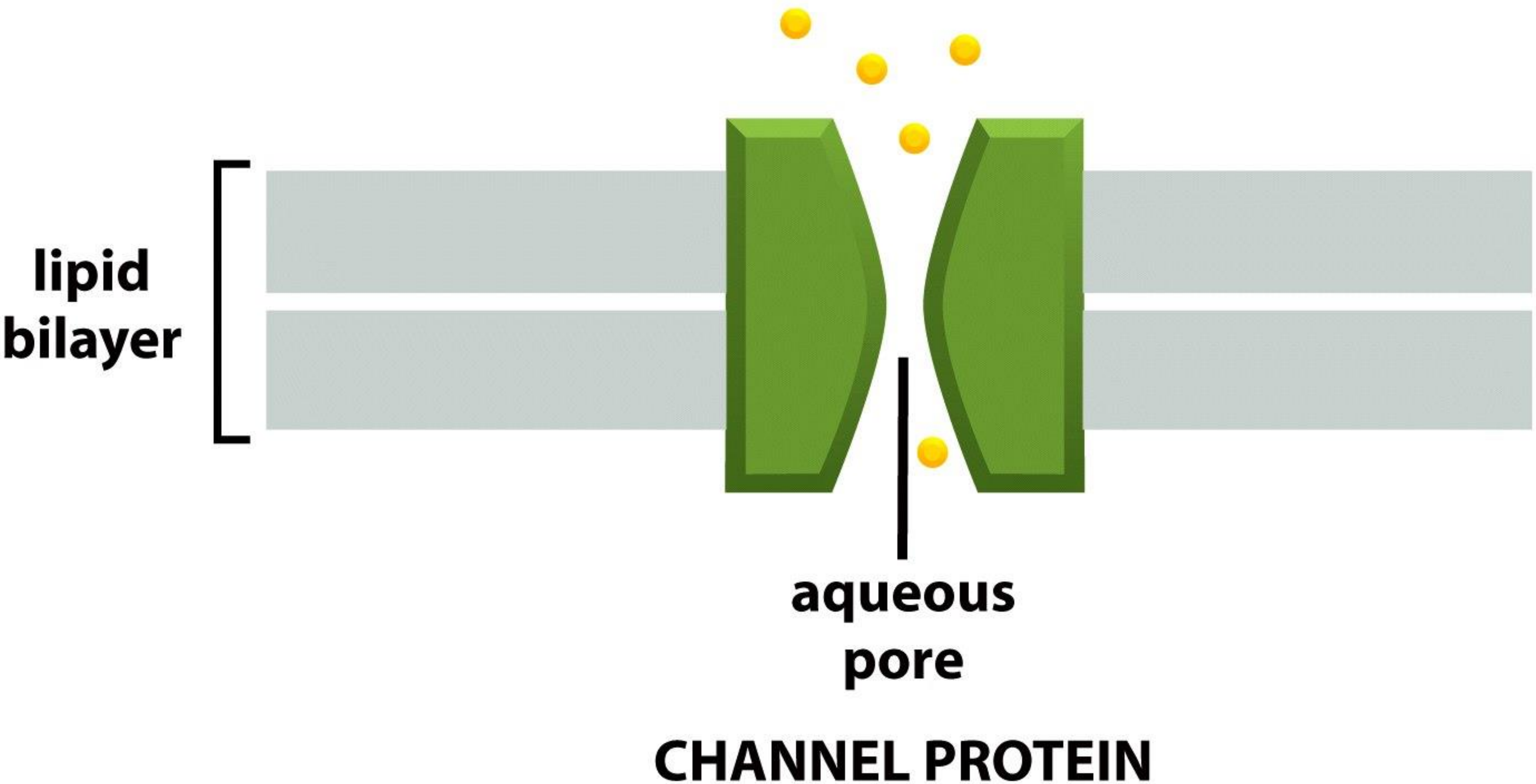


Figure 11-3b *Molecular Biology of the Cell* (© Garland Science 2008)

water channels/aquaporins

In 1986, Benga and coworkers (1) clearly demonstrated for the first time the presence and location of a water channel protein in the human red blood cell (RBC).

1. Benga Gh, Popescu O, Pop VI, Holmes RP, 1986. *p*-(Chloromercuri) benzenesulfonate binding by membranes proteins and the inhibiton of water transport in human erythrocytes. *Biochemistry* **25**: 1535-1538

In 1988, Agre and coworkers purified a new protein from the RBC membrane (9), nick-named CHIP28 (channel-forming integral membrane protein of 28 kDa) (10).

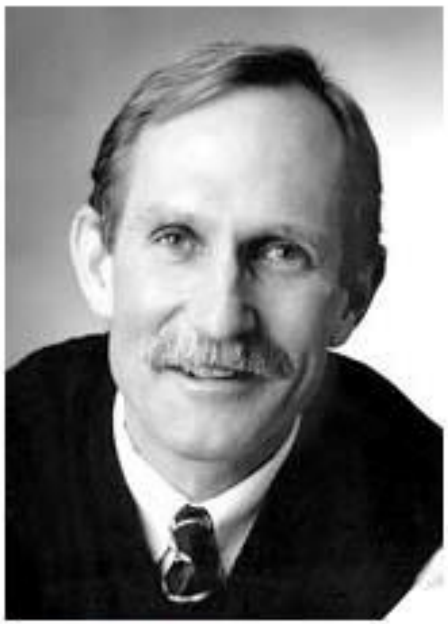
10. Smith BL, Agre P. Erythrocyte Mv 28,000 transmembrane protein exists. as a multisubunit oligomer similar to channel proteins. *J. Biol. Chem*. 1991, **266**:6407-6415.

The Nobel Prize in Chemistry 2003

Nobel Prize Award Ceremony

Peter Agre

Roderick MacKinnon



Peter Agre

Roderick MacKinnon

The Nobel Prize in Chemistry 2003 was awarded *"for discoveries concerning channels in cell membranes"* jointly with one half to Peter Agre *"for the discovery of water channels"* and with one half to Roderick MacKinnon *"for structural and mechanistic studies of ion channels"*.

II.A. TRANSPORTERS (Carriers/Permeases)

A. +/- energy source - transport

- active ("uphill") – "pumps" (ATP/ions gradient)
- passive ("downhill") – passive transport, or facilitated diffusion, concentration gradient;

B. Systems

- uniport: one type of molecule;
- coupled → Symport – *Co-transporters*
  → Antiport – *Exchangers*

A. +/- energy source - transport

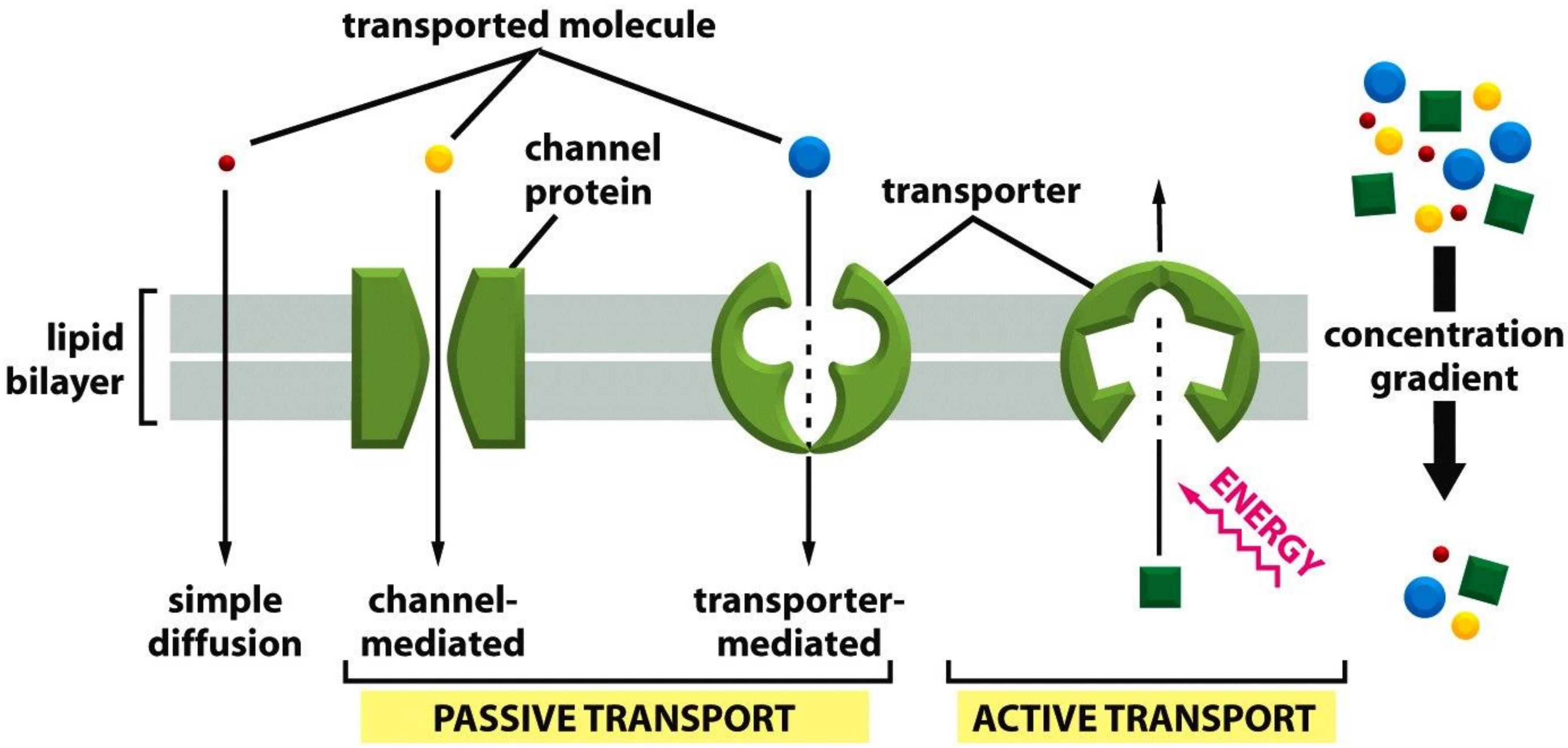


Figure 11-4a *Molecular Biology of the Cell* (© Garland Science 2008)

B. Uniport/coupled

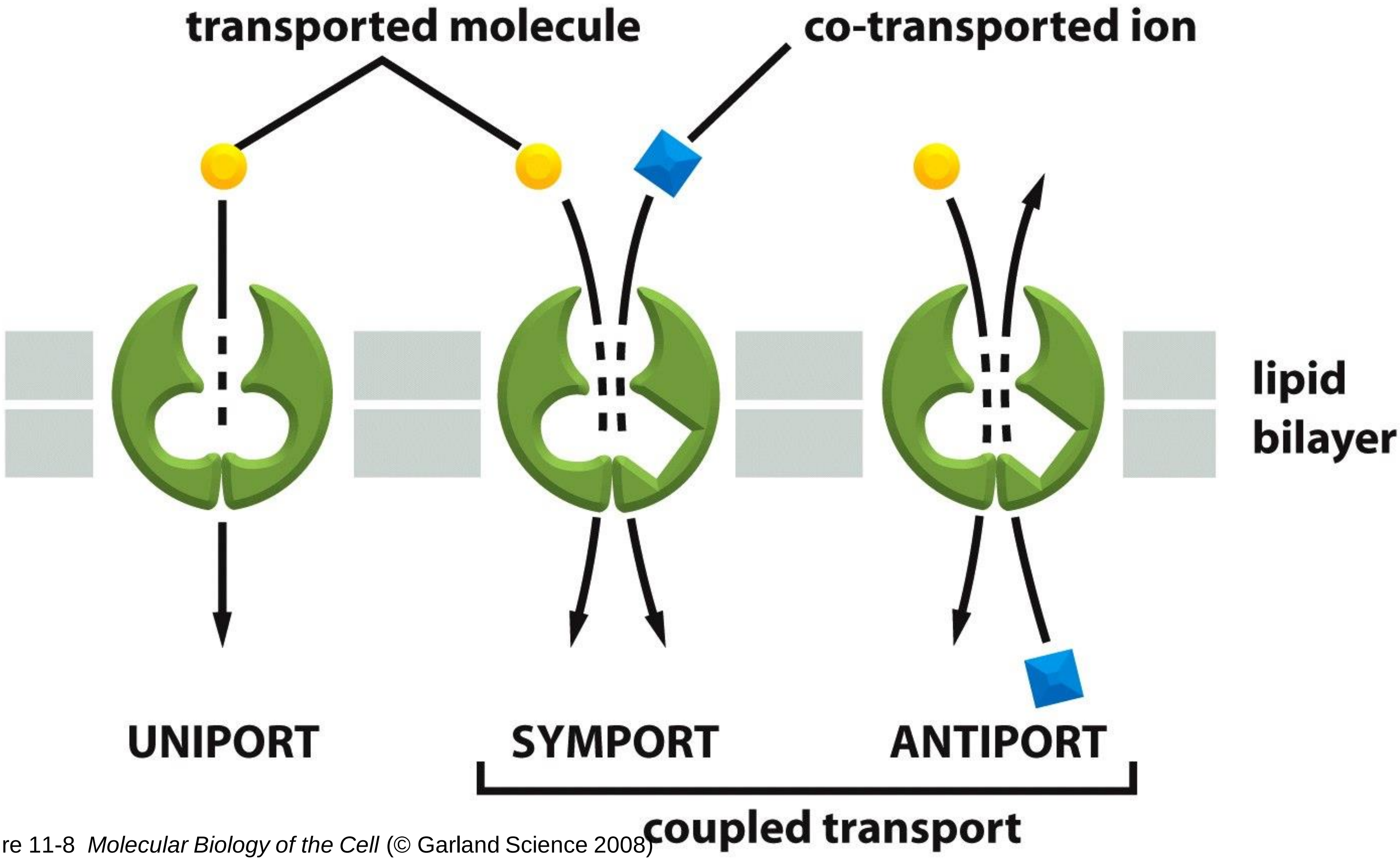
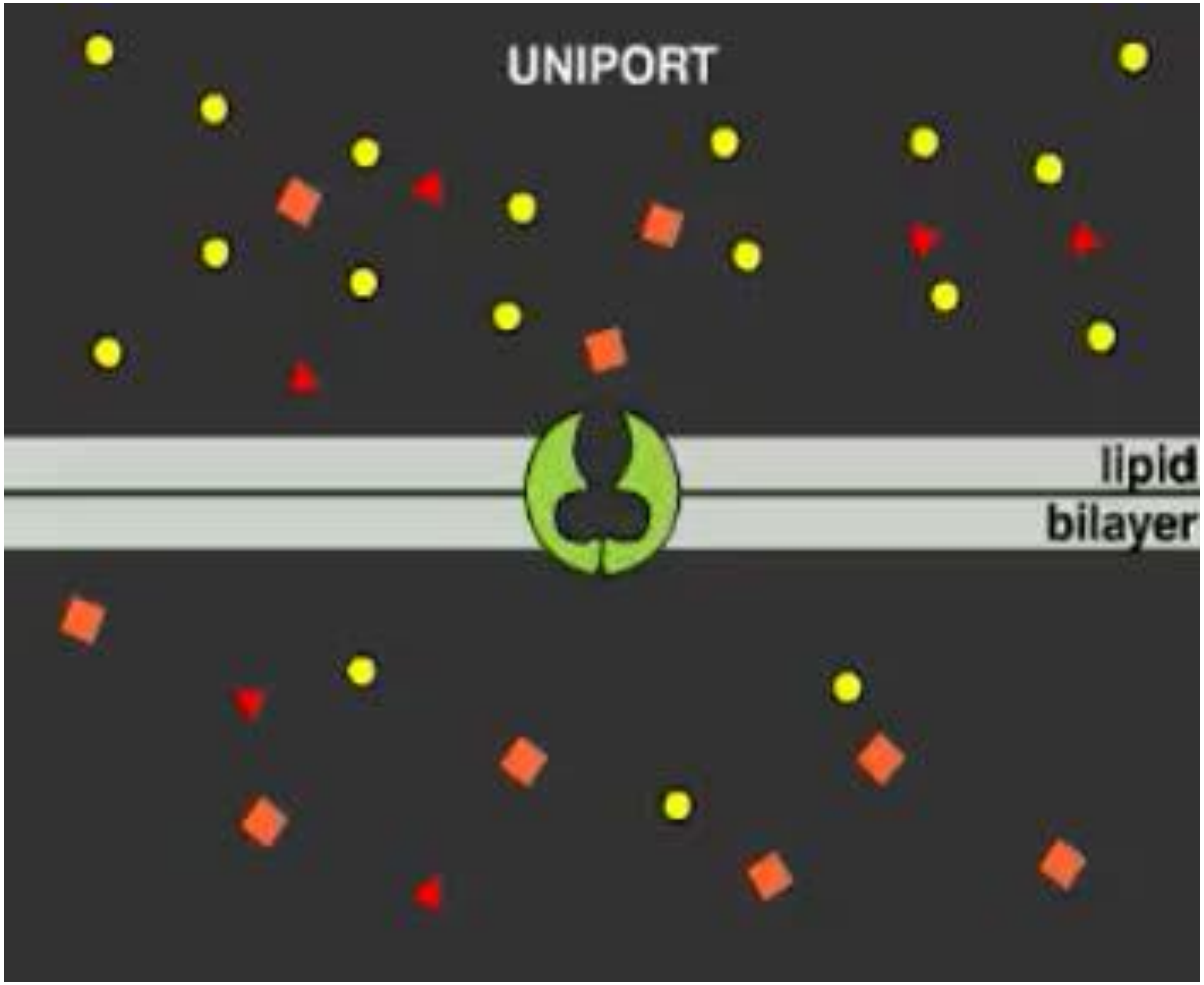


Figure 11-8 *Molecular Biology of the Cell* (© Garland Science 2008)

II.A. TRANSPORTERS (Carriers/Permeases)



II.A. TRANSPORTERS (Carriers/Permeases)

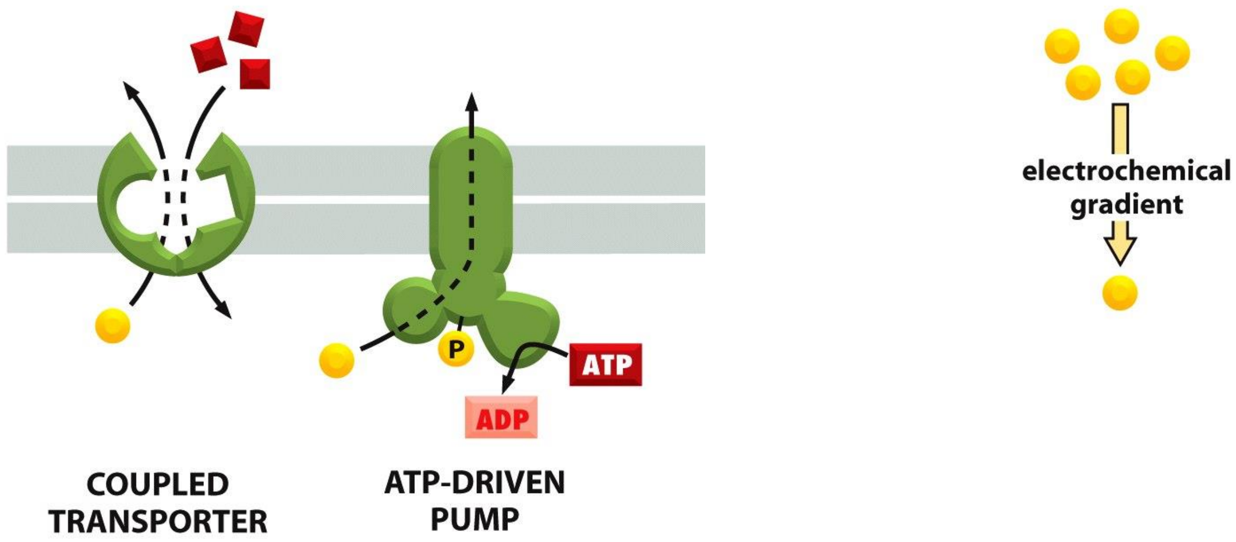
- behave like enzymes (the transfer process - enzyme-substrate reaction);
- do not modify the transported solute but instead delivers it unchanged to the other side of the membrane;
- undergo a series of reversible conformational changes;

II.A. TRANSPORTERS (Carriers/Permeases)

ACTIVE MEMBRANE TRANSPORT

1. **ATP-driven pumps** couple uphill transport to the hydrolysis of ATP

2. **Coupled transporters** couple the uphill transport of one solute across the membrane to the downhill transport of another;



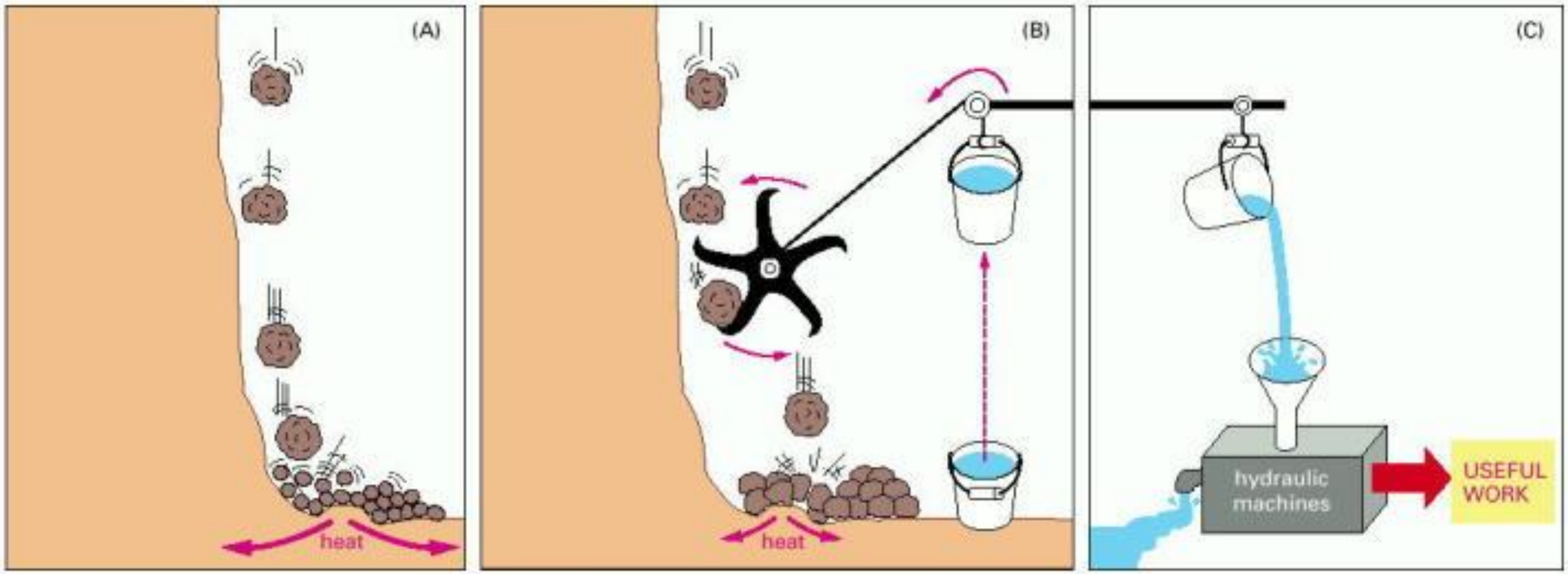
II.A. TRANSPORTERS (Carriers/Permeases)

ACTIVE MEMBRANE TRANSPORT

1. ATP-driven carriers mediate primary active transport;

2. ion-driven carriers mediate secondary active transport;

Energy conversion



kinetic energy transformed into heat energy only

part of the kinetic energy is used to lift a bucket of water, and a correspondingly smaller amount is transformed into heat

the potential kinetic energy stored in the raised bucket of water can be used to drive hydraulic machines that carry out a variety of useful tasks

1. ATP-driven carriers mediate primary active transport;

Table 11–1 A Comparison of Ion Concentrations Inside and Outside a Typical Mammalian Cell

COMPONENT	INTRACELLULAR CONCENTRATION (mM)	EXTRACELLULAR CONCENTRATION (mM)
Cations		
Na^+	5–15	145
K^+	140	5
Mg^{2+}	0.5	1–2
Ca^{2+}	10^{-4}	1–2
H^+	7×10^{-5} ($10^{-7.2}$ M or pH 7.2)	4×10^{-5} ($10^{-7.4}$ M or pH 7.4)
Anions*		
Cl^-	5–15	110

*The cell must contain equal quantities of positive and negative charges (that is, it must be electrically neutral). Thus, in addition to Cl^-, the cell contains many other anions not listed in this table; in fact, most cell constituents are negatively charged (HCO_3^-, PO_4^{3-}, proteins, nucleic acids, metabolites carrying phosphate and carboxyl groups, etc.). The concentrations of Ca^{2+} and Mg^{2+} given are for the free ions. There is a total of about 20 mM Mg^{2+} and 1–2 mM Ca^{2+} in cells, but both are mostly bound to proteins and other substances and, for Ca^{2+}, stored within various organelles.

Table 11-1 *Molecular Biology of the Cell*

1. ATP-driven carriers mediate primary active transport;

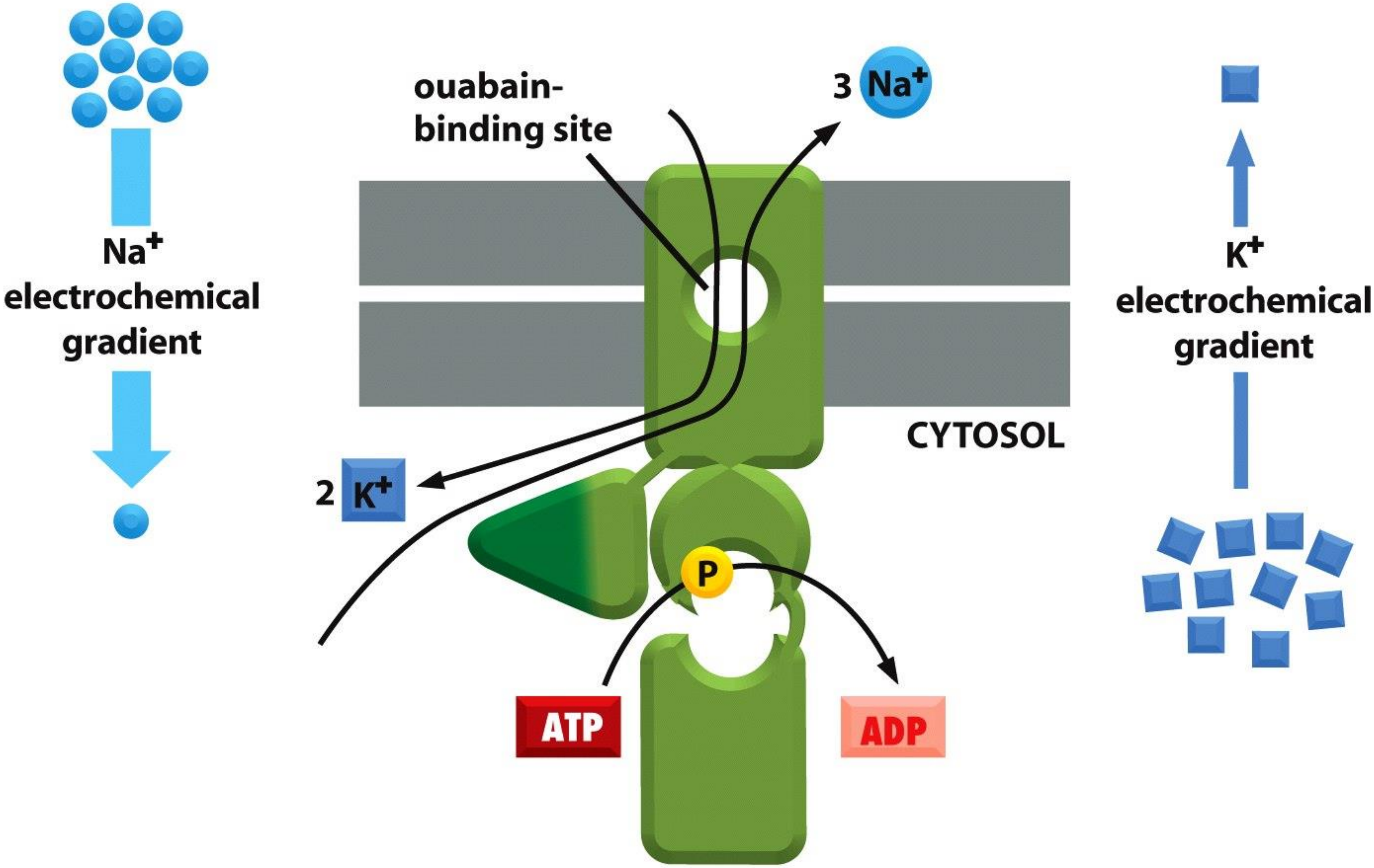
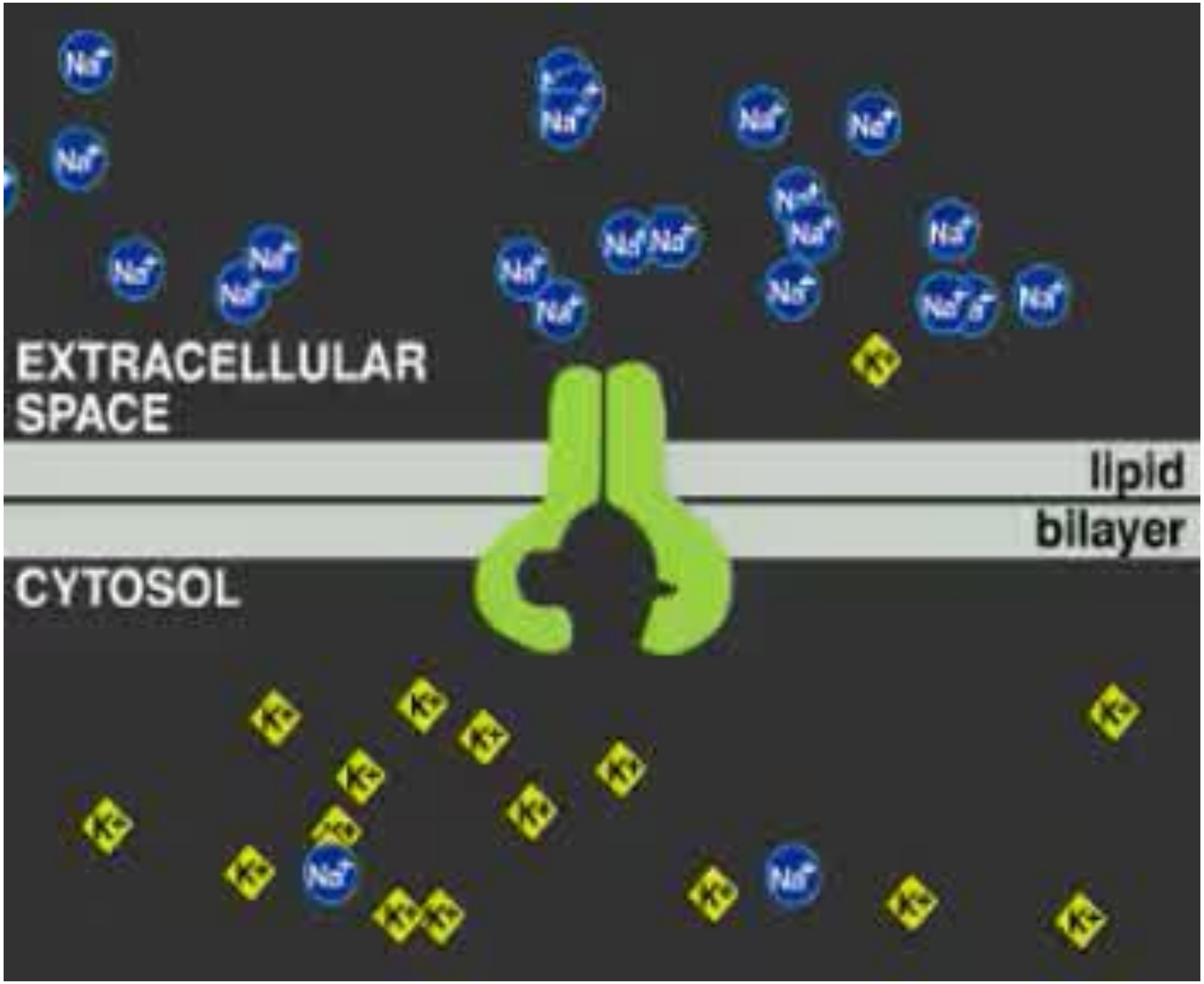


Figure 11-14 *Molecular Biology of the Cell* (© Garland Science 2008)

1. ATP-driven carriers mediate primary active transport;



2. ion-driven carriers mediate secondary active transport;

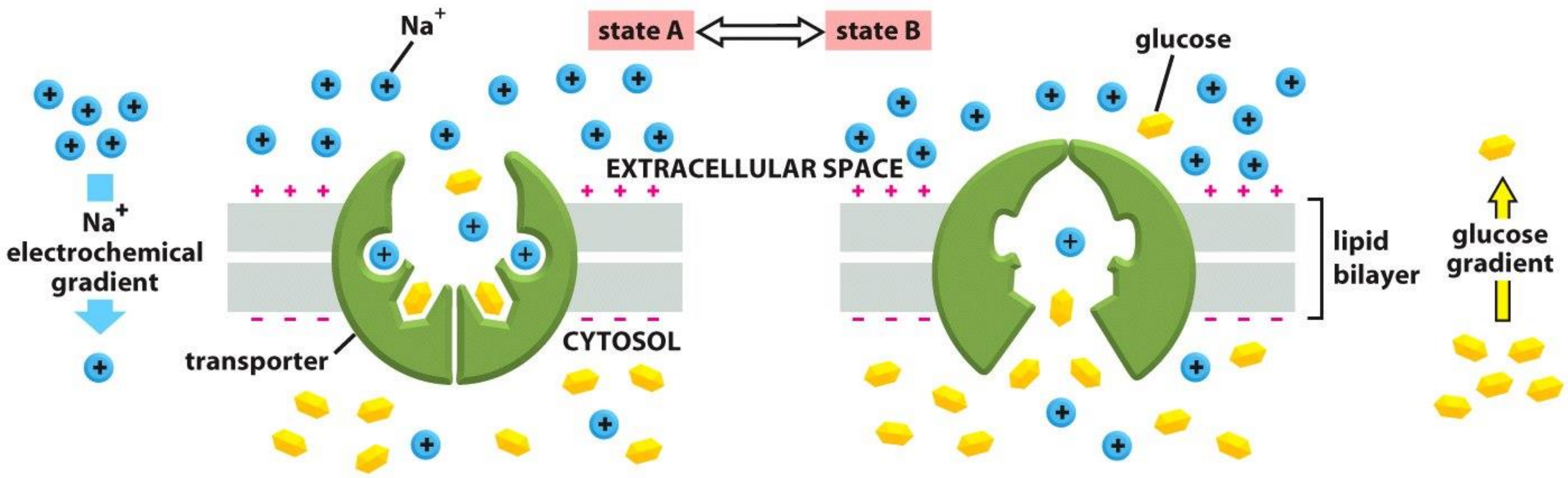


Figure 11-9 *Molecular Biology of the Cell* (© Garland Science 2008)

An asymmetric distribution of transporters in epithelial cells underlies the transcellular transport of solutes

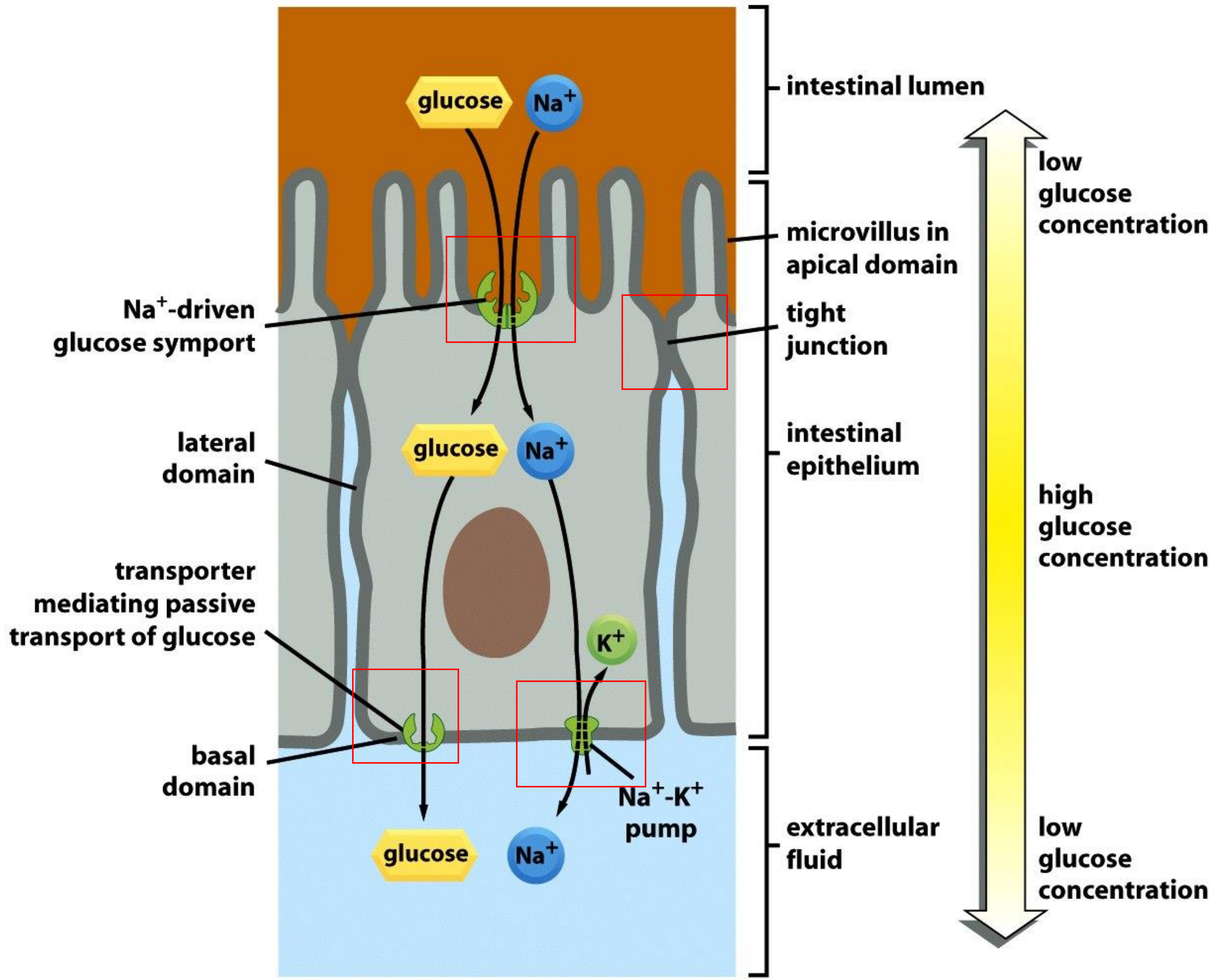
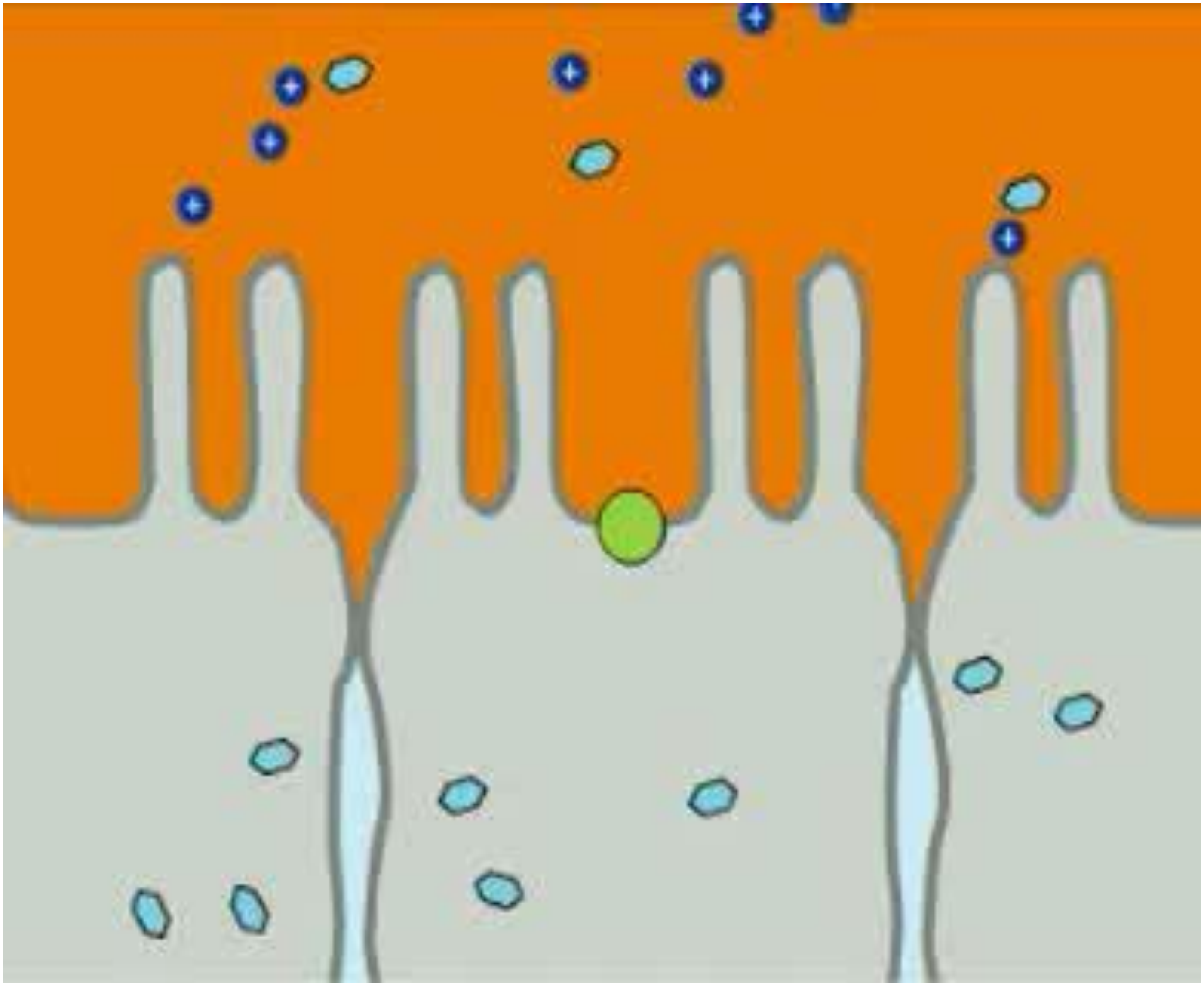


Figure 11-11 *Molecular Biology of the Cell* (© Garland Science 2008)



II.A. TRANSPORTERS (Carriers/Permeases)

ACTIVE MEMBRANE TRANSPORT

ATP-driven carriers mediate primary active transport:

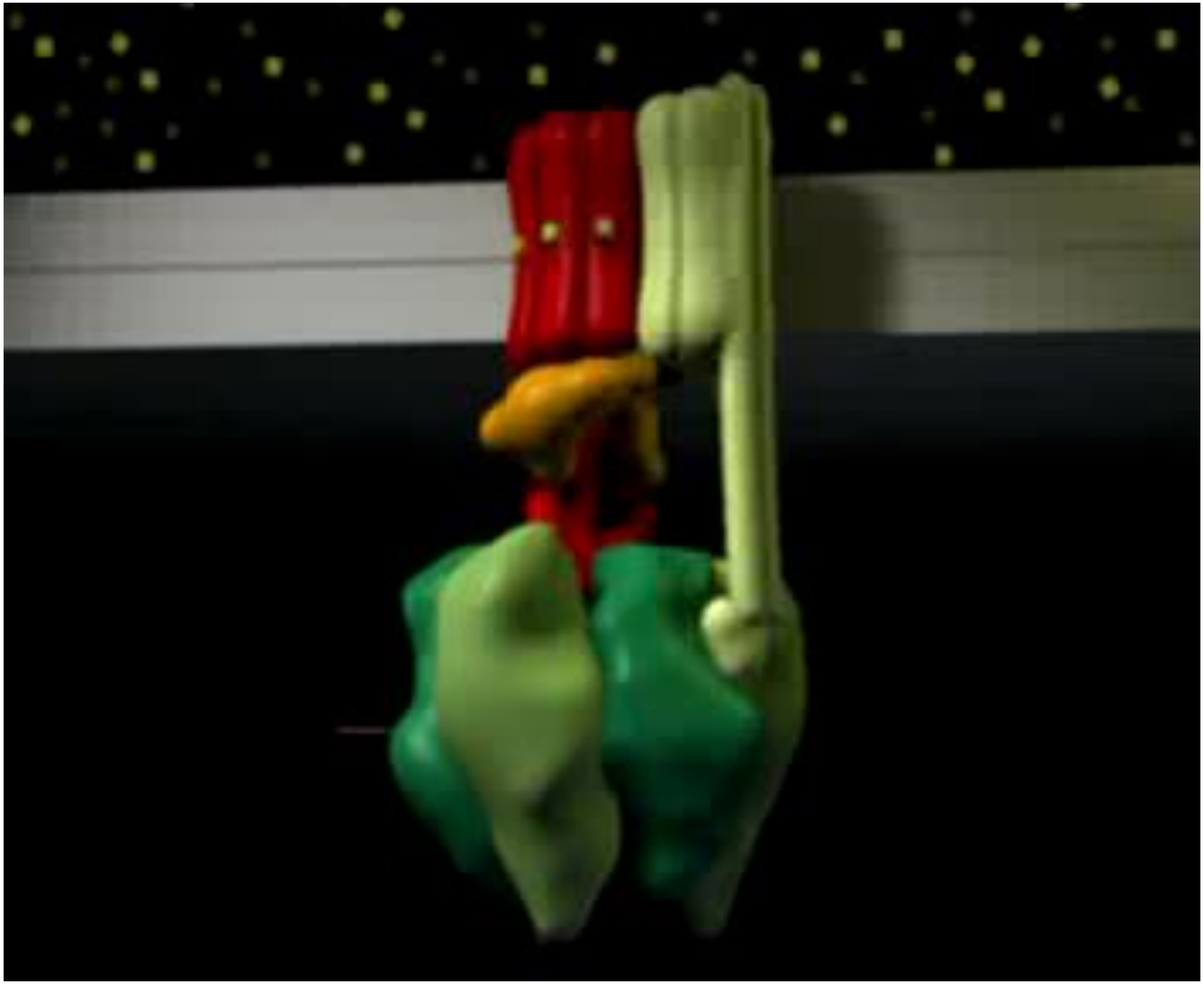
1. - P-type pumps – phosphorylate themselves – pumping cycle (Ca+, Na+, K+, H+);

2. - F-type pumps – multiple different subunits – *ATP synthase* (mitochondria)

- V-type ATP*ases* –multiple normaly pump H+

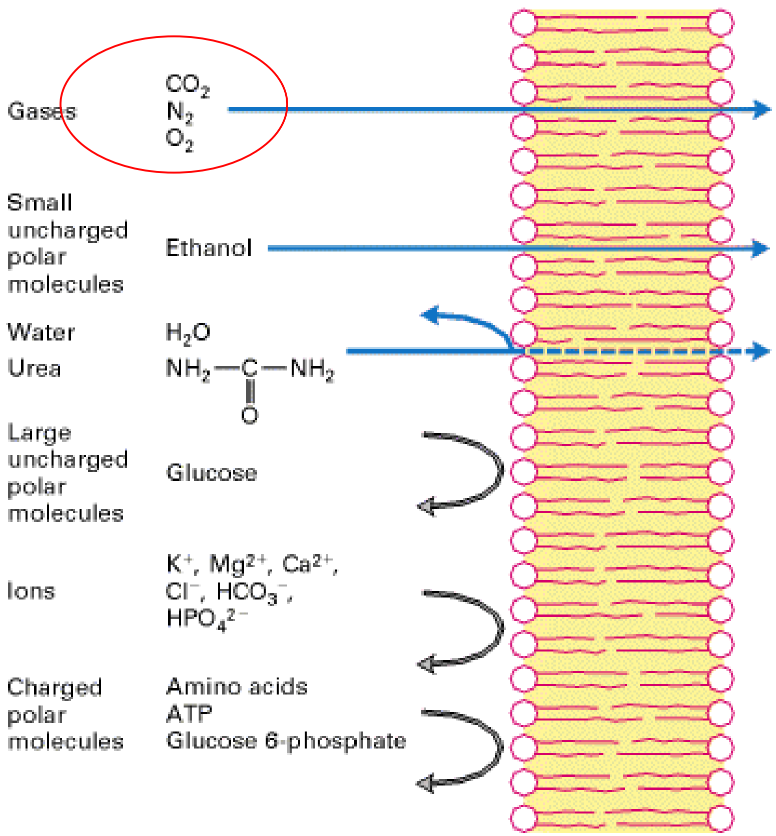
3. – ABC transportes – normally transport small molecules

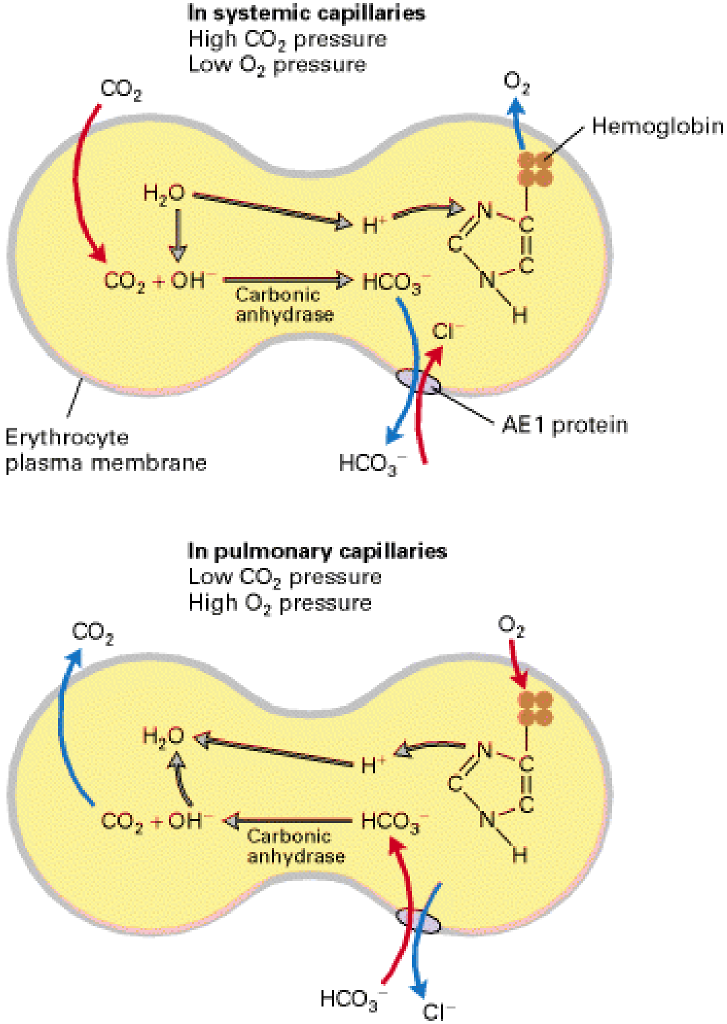
F-type pumps –*ATP synthase* (mitochondria)



band 3 protein (RBC) acts as an anion transporter

Cl-/HCO3- exchanger





Gastric acid (HCl) - the stomach epithelium

Parietal cells, or oxyntic cells - secrete HCl and intrinsic factor in response to:

- histamine (H2 receptor);
- acetylcholine (M3 receptors);
- gastrin (CCK2 receptors).