Medicinal Chemistry/ CHEM 458/658

Chapter 7- Biological Membranes

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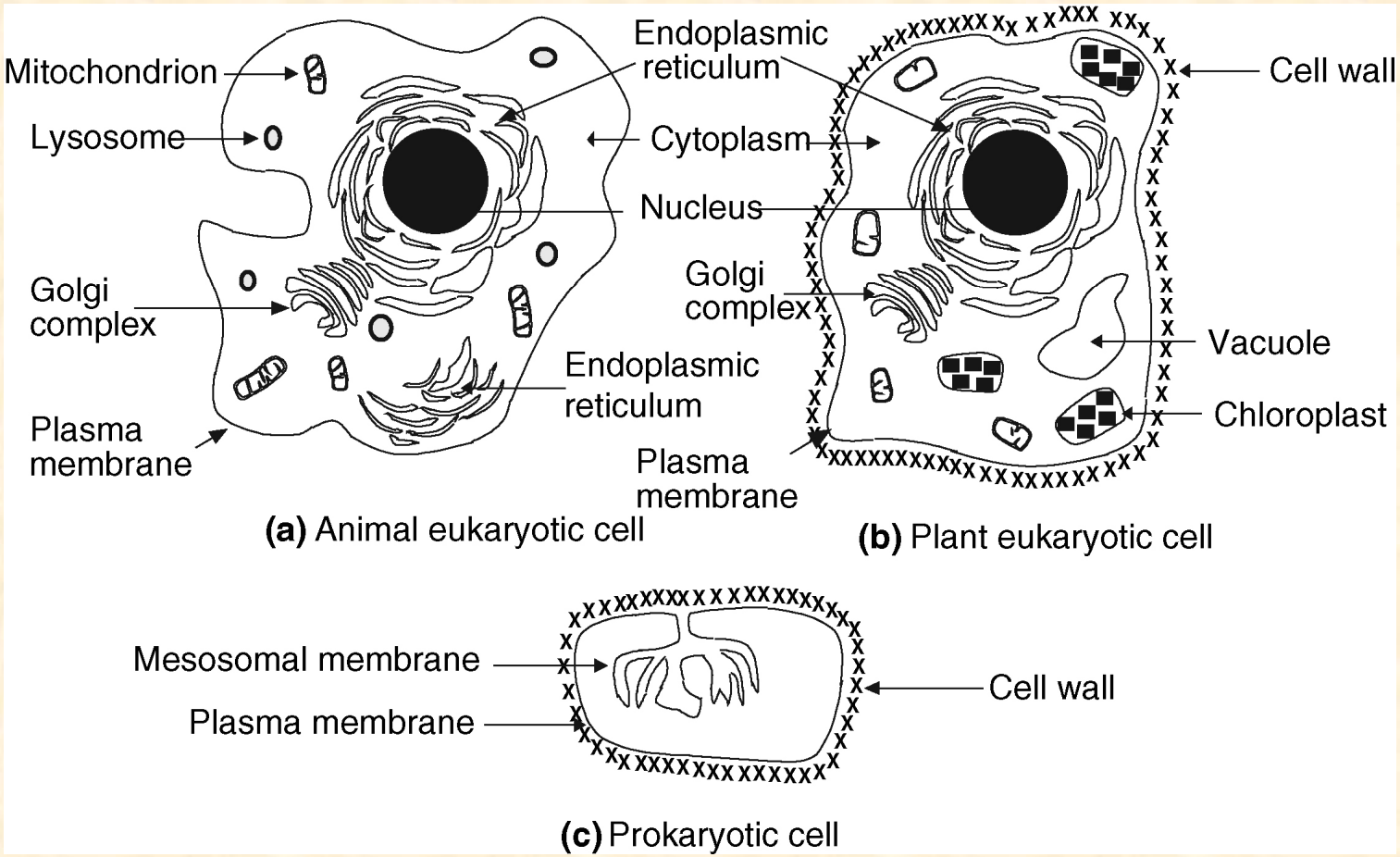
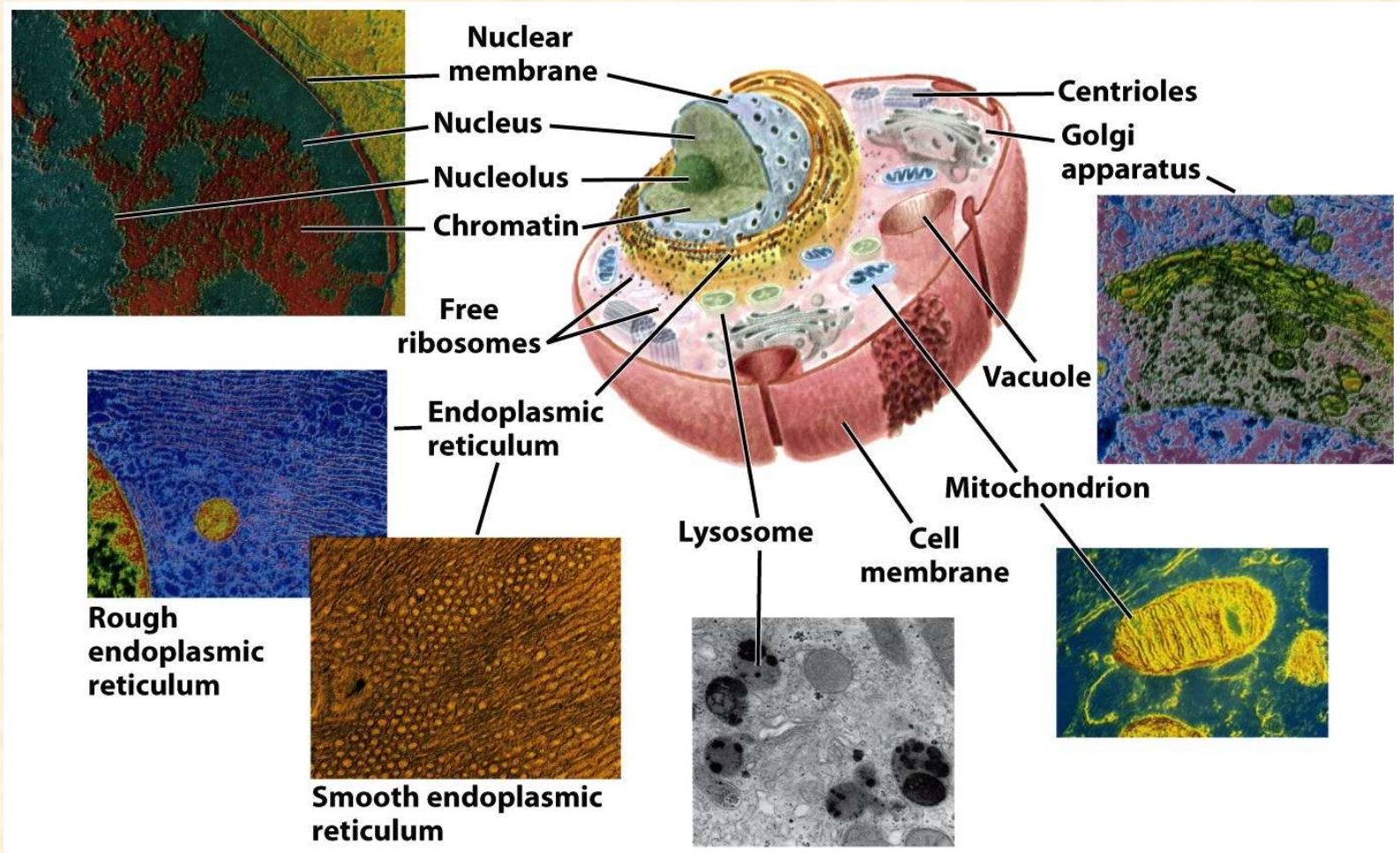
Introduction

- The cell membrane separates the cell the intracellular fluid from the surrounding medium (extracellular fluid).



Introduction

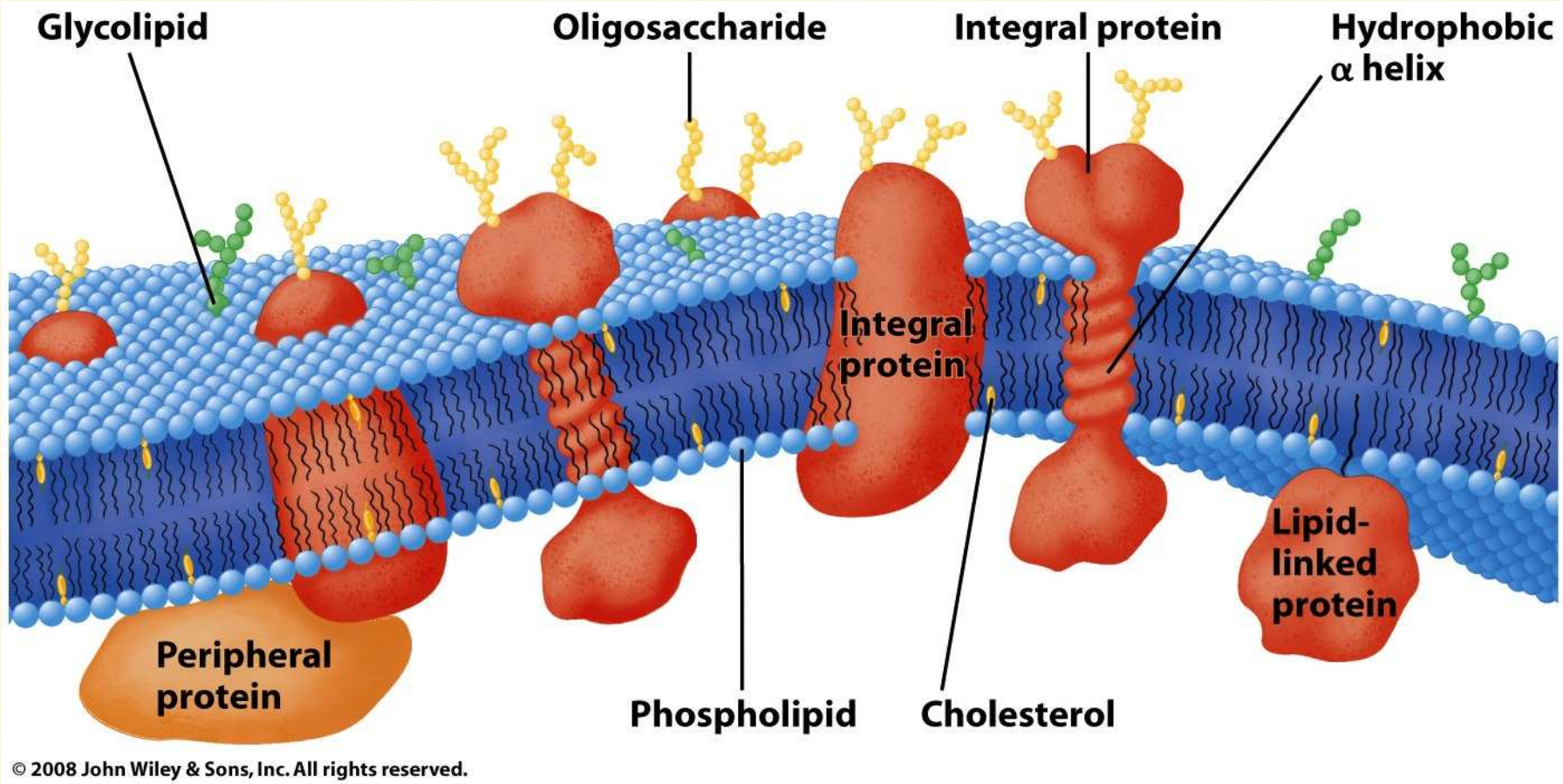
- Eukaryotic cell



Nucleus: Tektoff-RM, CNRI/Photo Researchers; rough endoplasmic reticulum and Golgi apparatus: Secchi-Lecaque/Roussel-UCLAF/ CNRI/Photo Researchers; smooth endoplasmic reticulum: David M. Phillips/Visuals Unlimited; mitochondrion: CNRI/Photo Researchers; lysosome: Biophoto Associates/Photo Researchers.

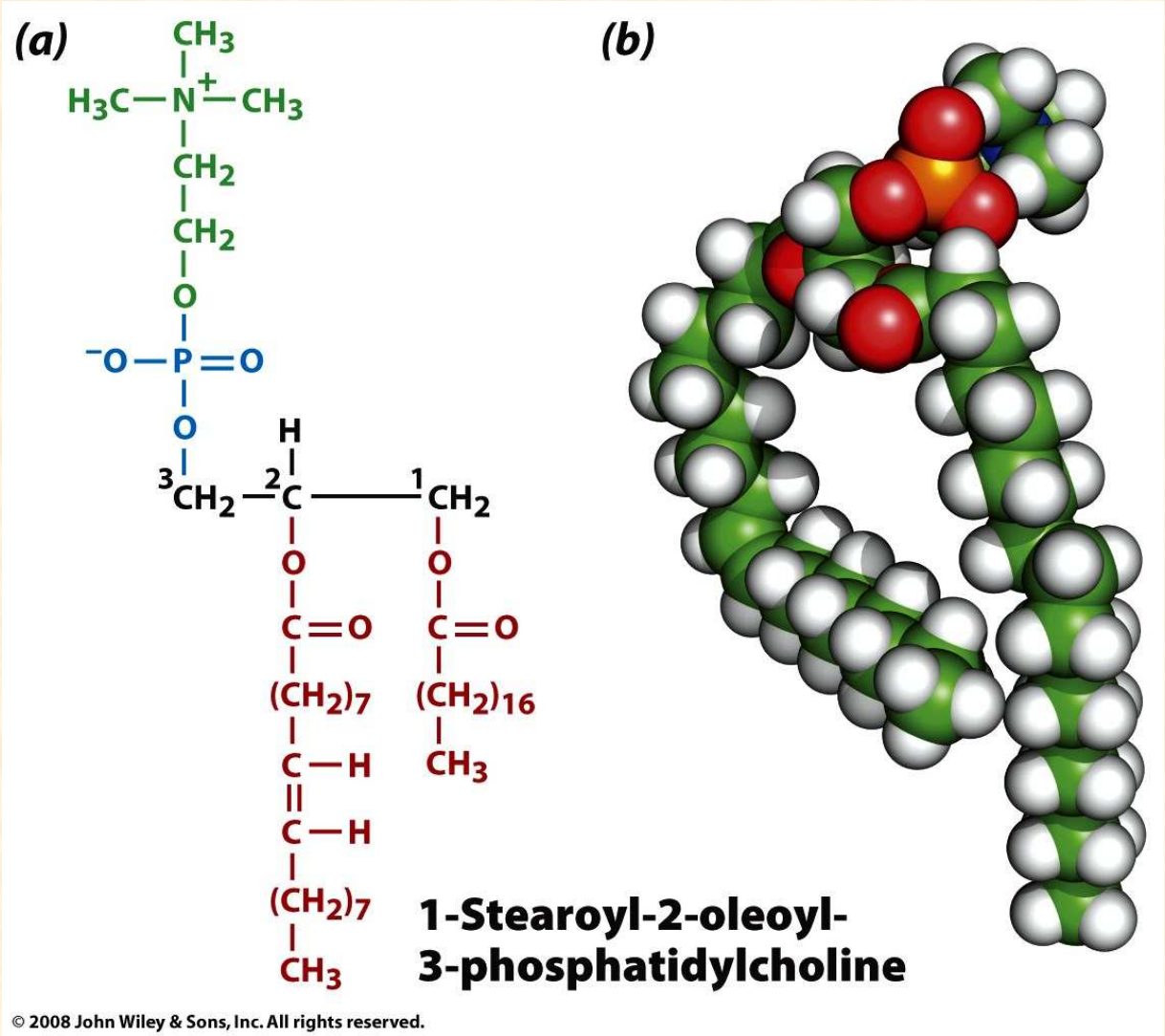
The Plasma Membrane

- Fluid Mosaic model



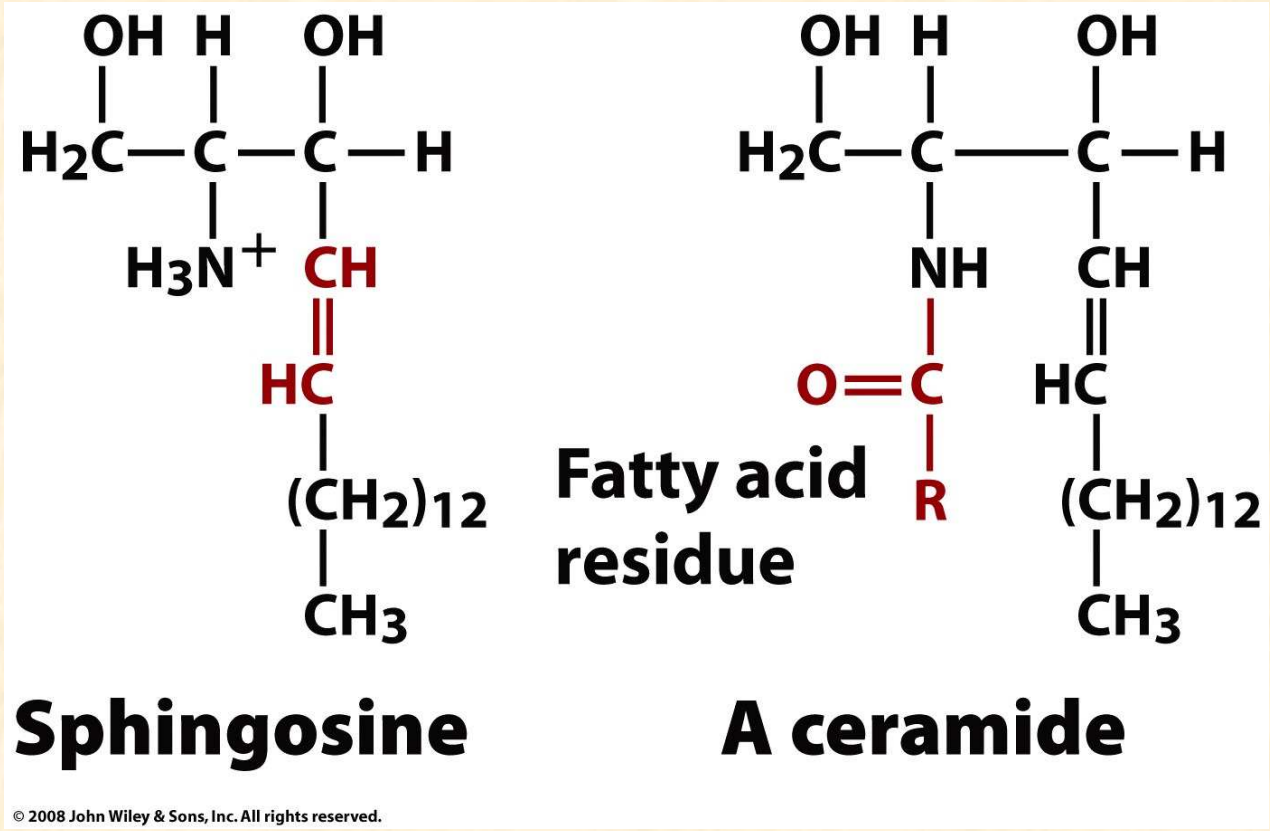
The Plasma Membrane

- Lipid components - glycerophospholipids



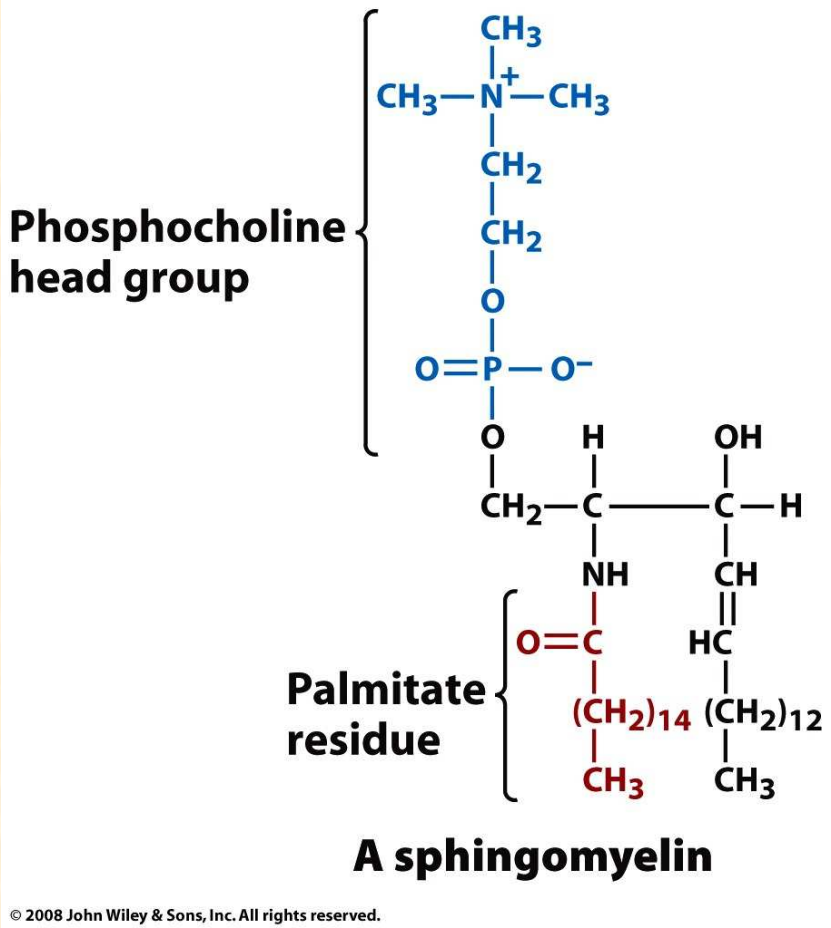
The Plasma Membrane

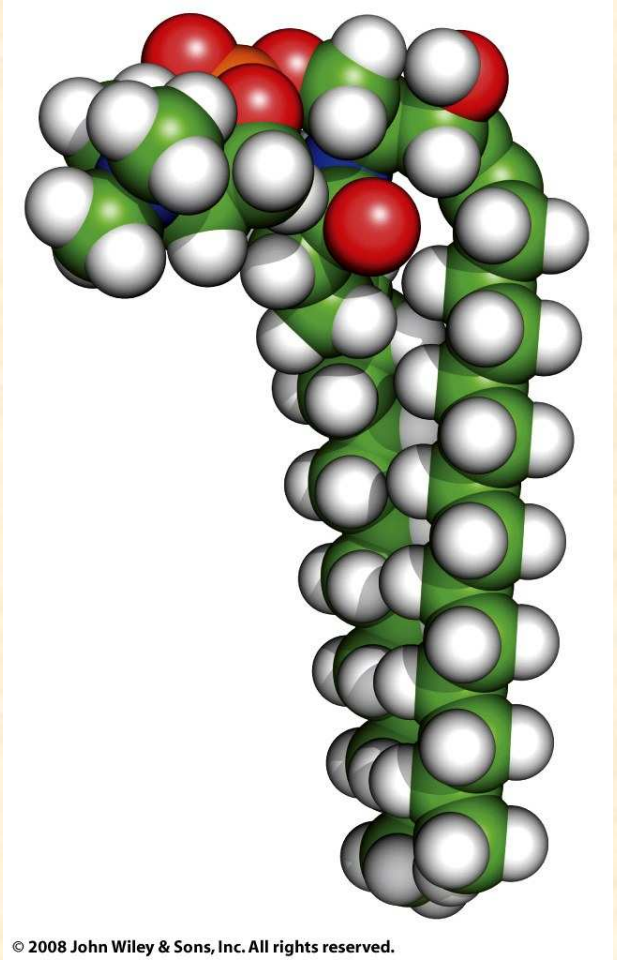
- Lipid components - sphingolipids



The Plasma Membrane

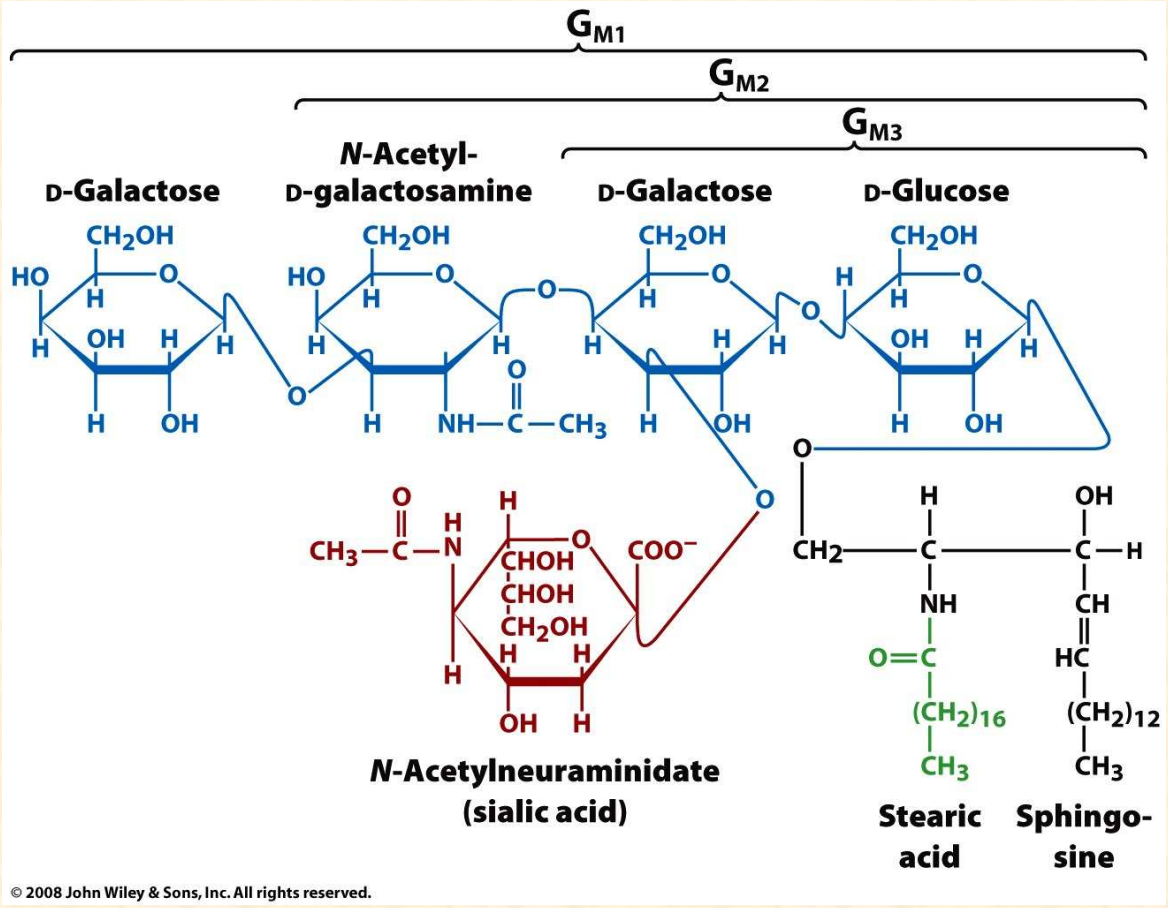
- Lipid components - sphingolipids

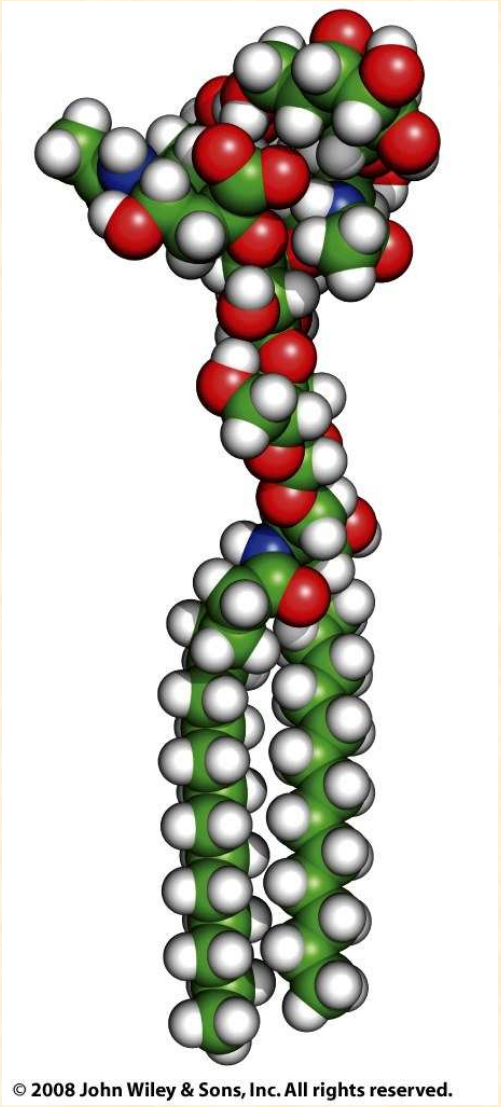




The Plasma Membrane

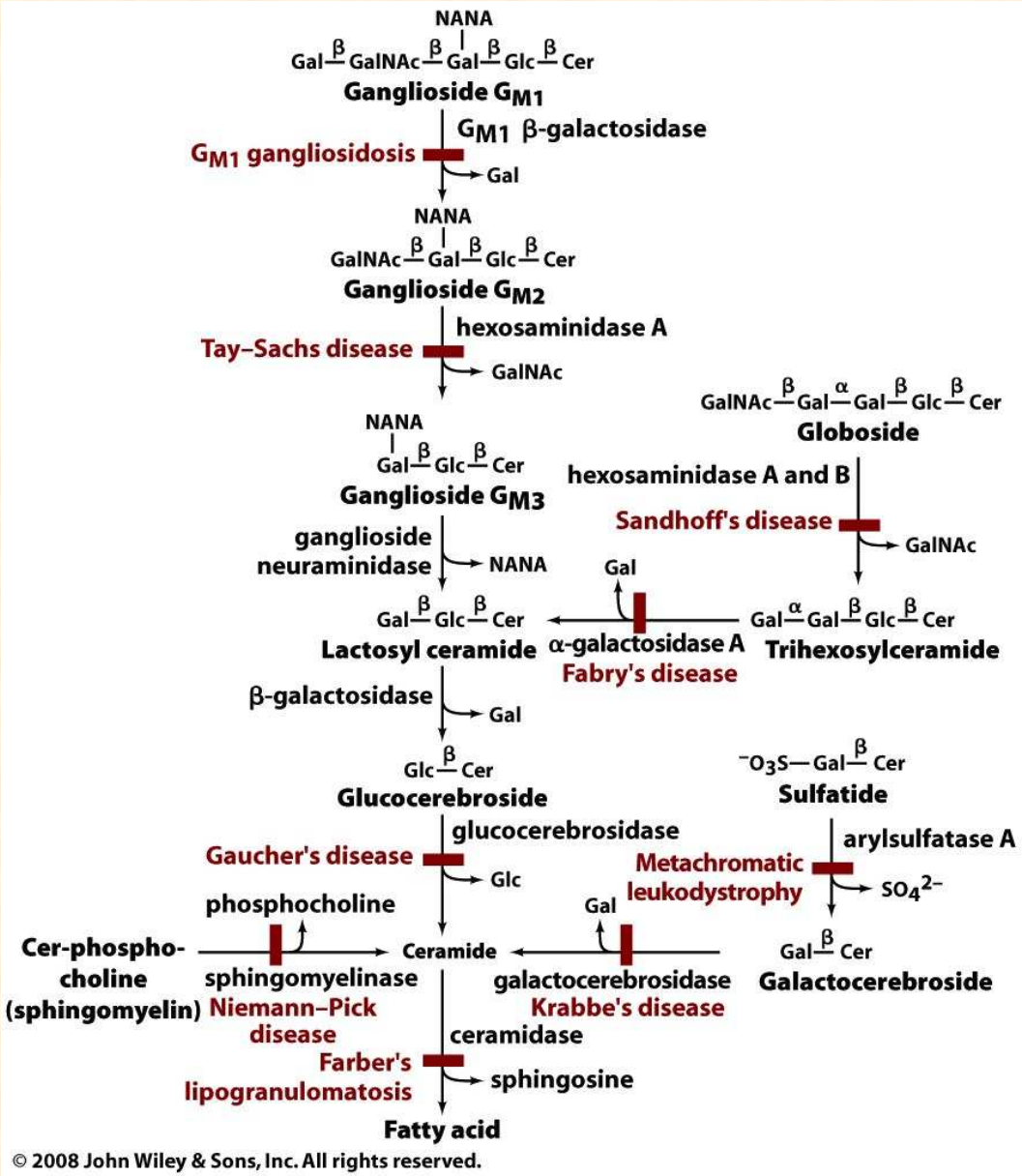
- Lipid components - glycosphingolipids





Tay-Sachs-, Gaucher-, Krabbe's-, Fabry's and Niemann-Pick diseases

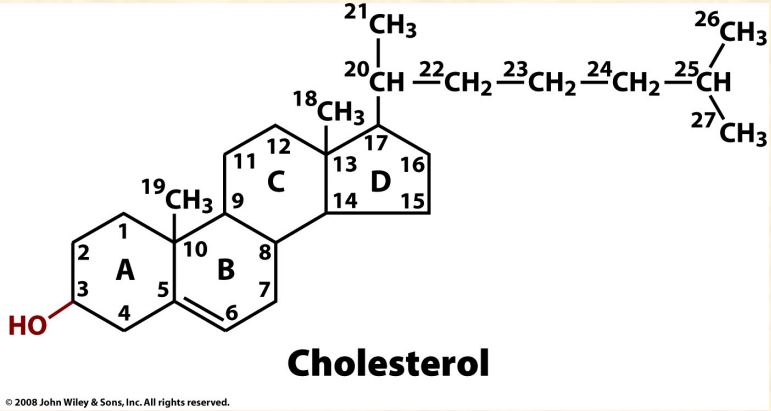
The Plasma Membrane

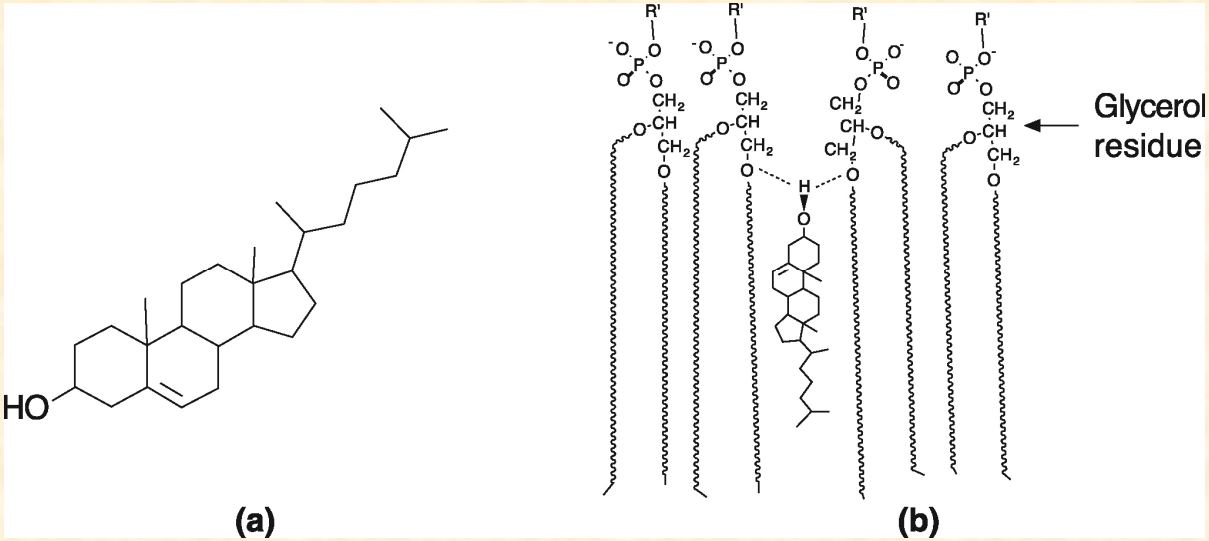


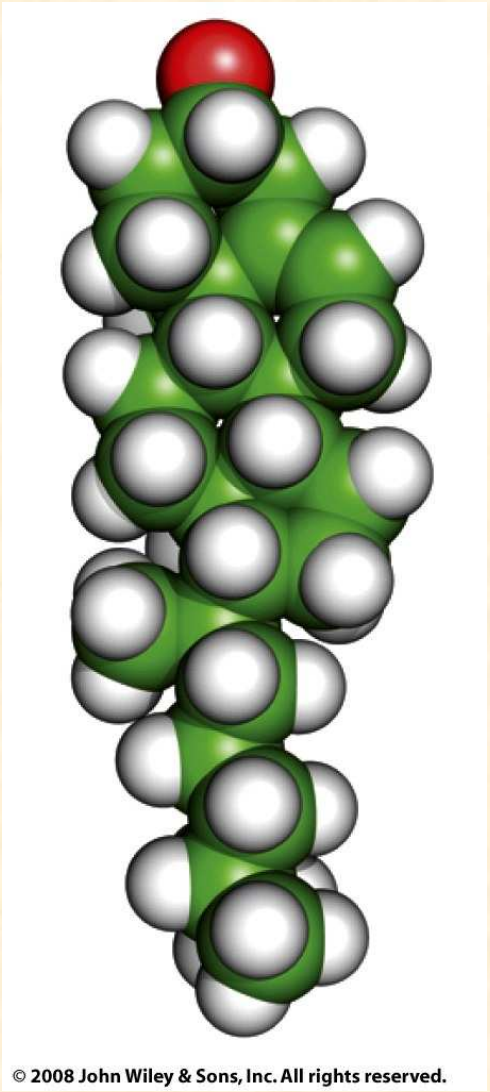
- Lipid components - glycosphingolipids

The Plasma Membrane

- Lipid components - cholesterol

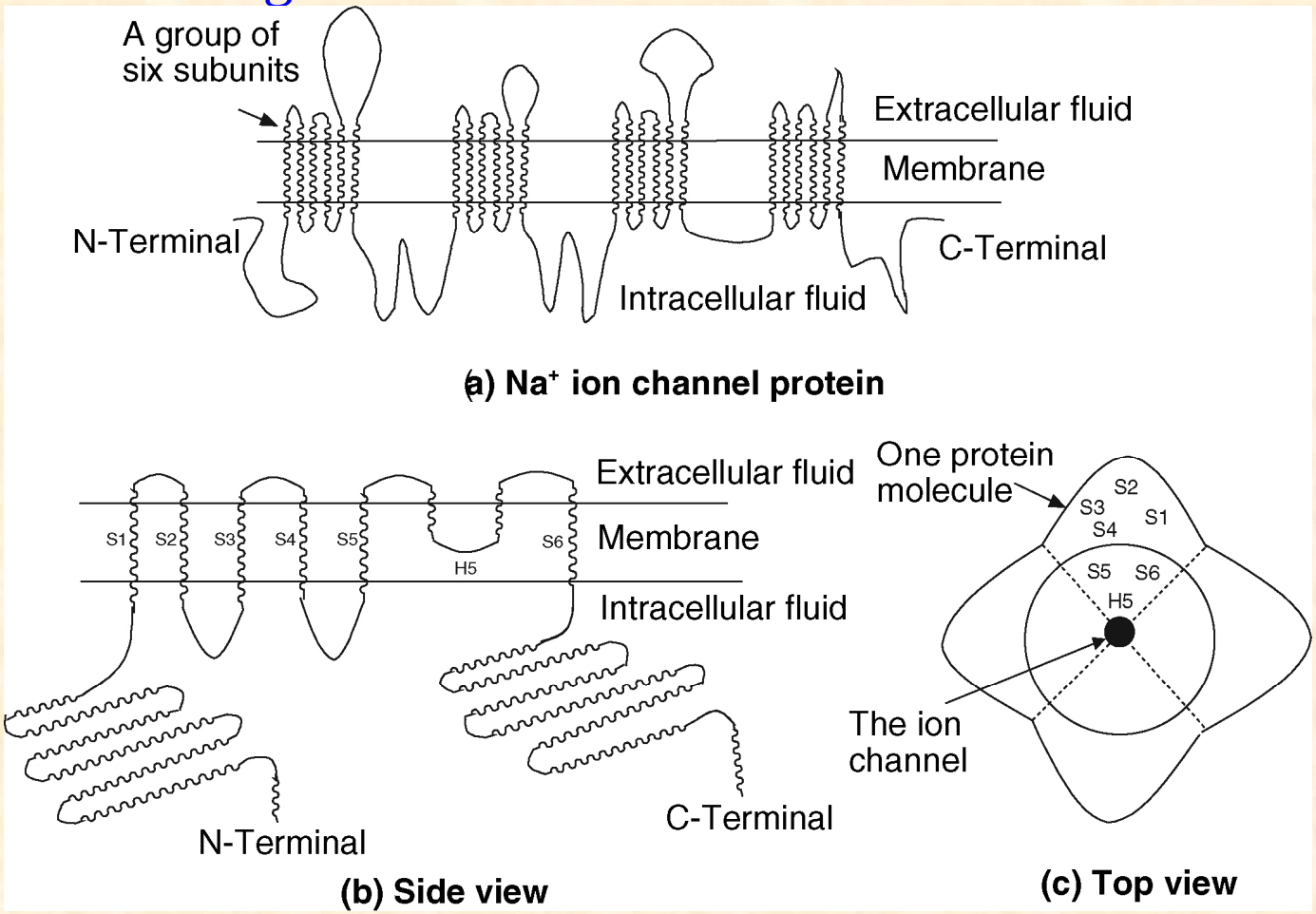


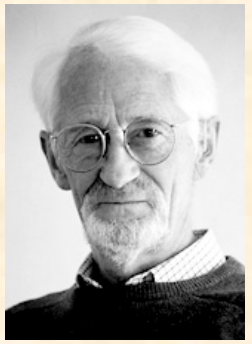




The Plasma Membrane

- Protein components - Integral proteins
  e.g ion- or water-channels



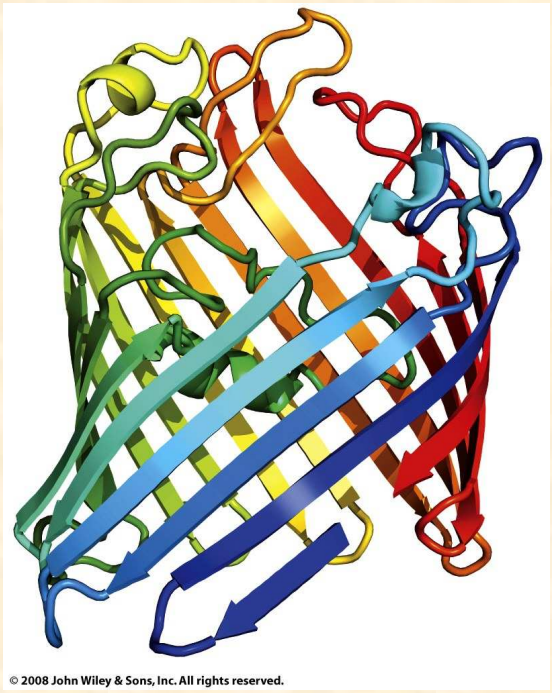


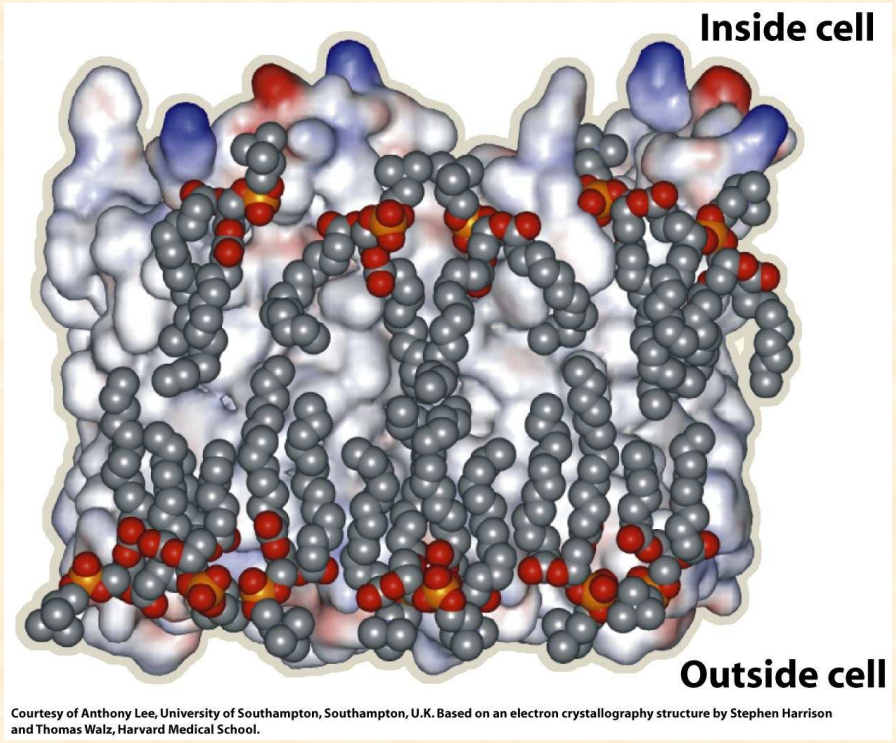
Jens C. Skou
1997

Roderick MacKinnon
2003

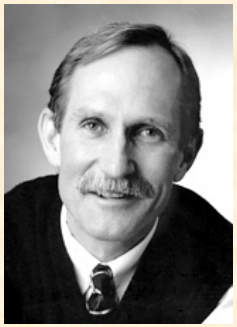
The Plasma Membrane

- Protein components - Integral proteins
  e.g porins, aquaporins





Courtesy of Anthony Lee, University of Southampton, Southampton, U.K. Based on an electron crystallography structure by Stephen Harrison and Thomas Walz, Harvard Medical School.

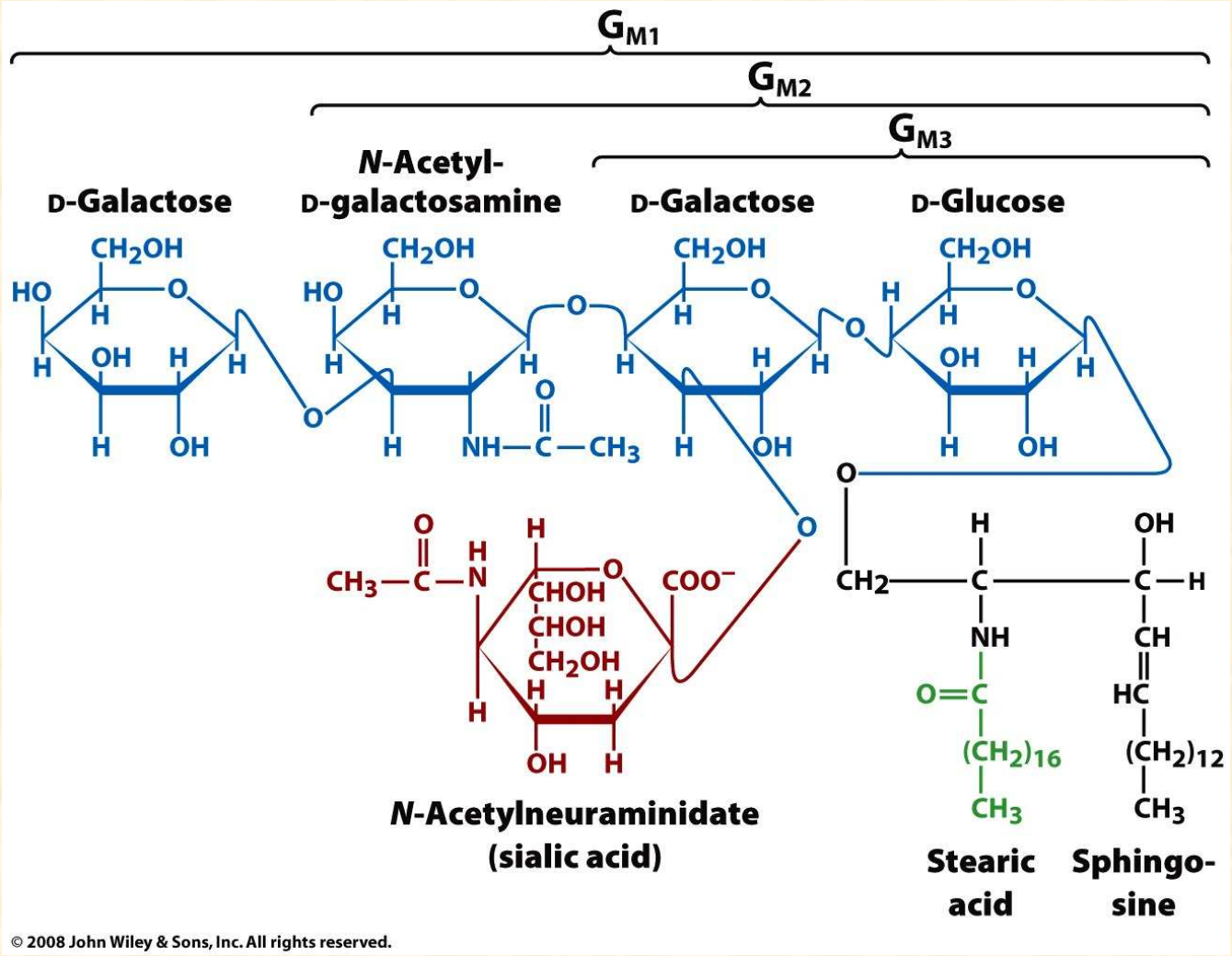


Peter Agre

2003

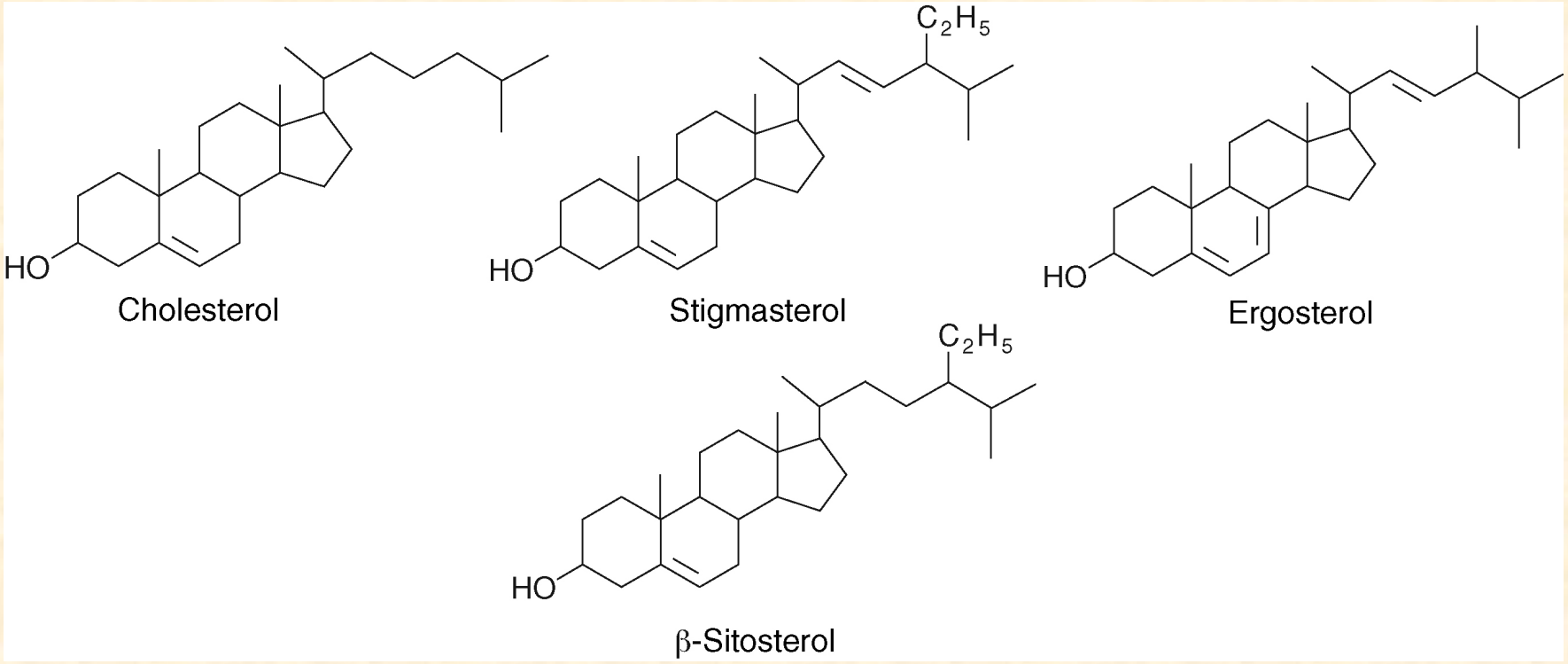
The Plasma Membrane

- The carbohydrate component



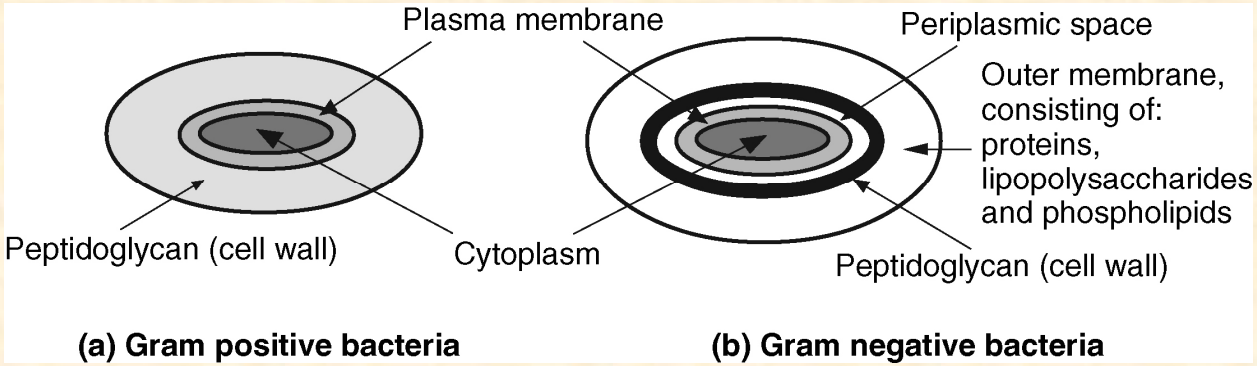
The Plasma Membrane

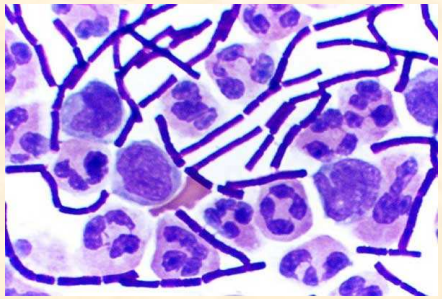
- Similarities and differences between plasma membranes in different cells



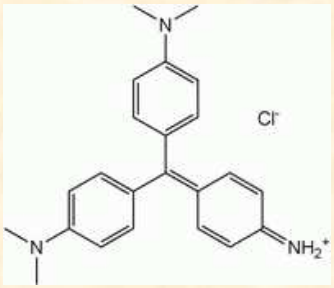
The Plasma Membrane

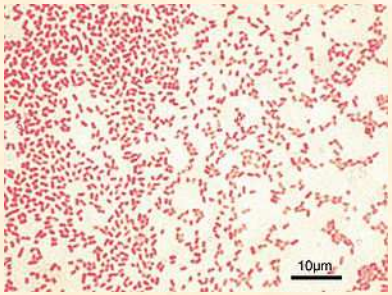
- Bacterial cell walls - peptidoglycans



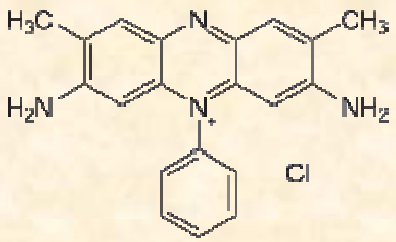


Crystal violet



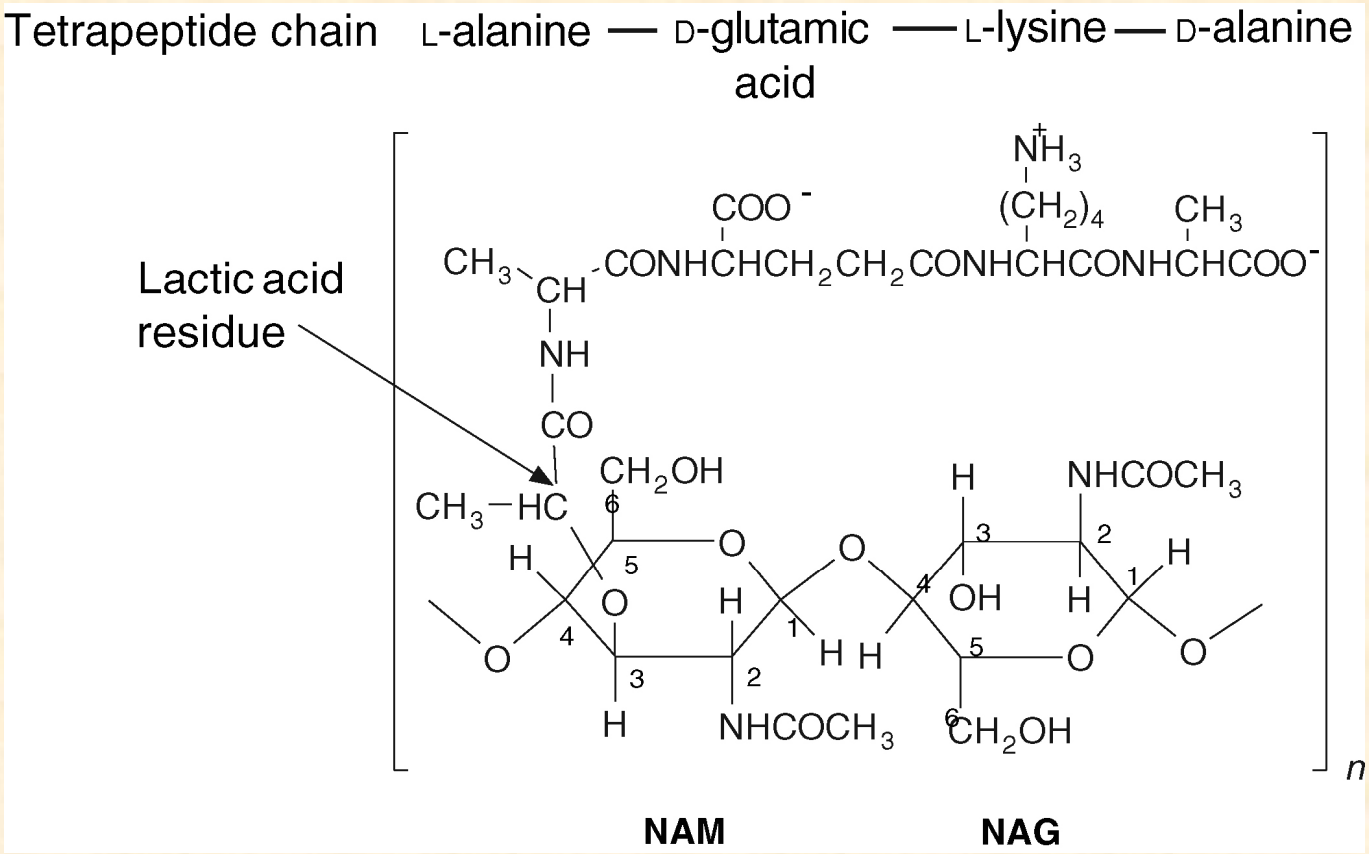


Safranin



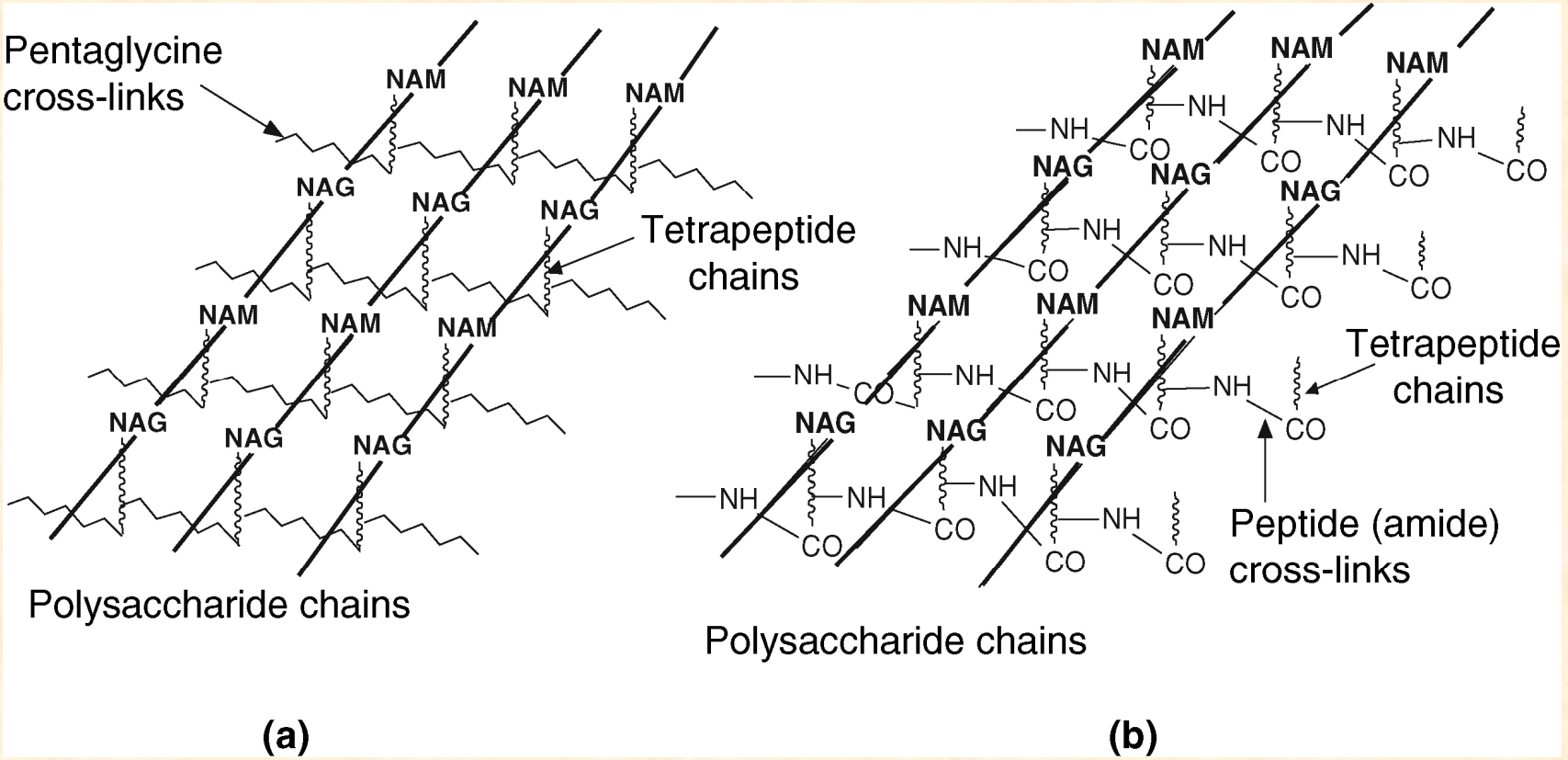
The Plasma Membrane

- Bacterial cell walls - peptidoglycans



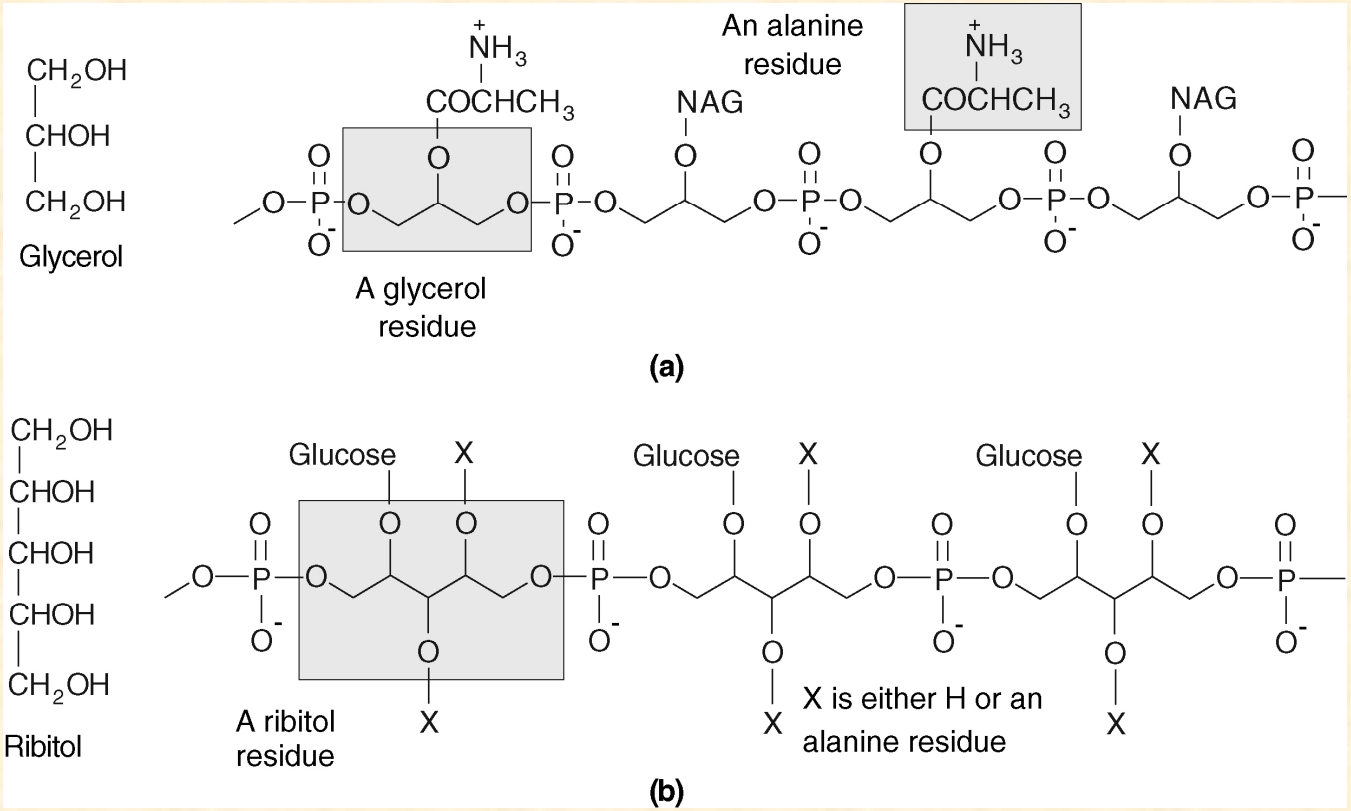
The Plasma Membrane

- Bacterial cell walls - peptidoglycans



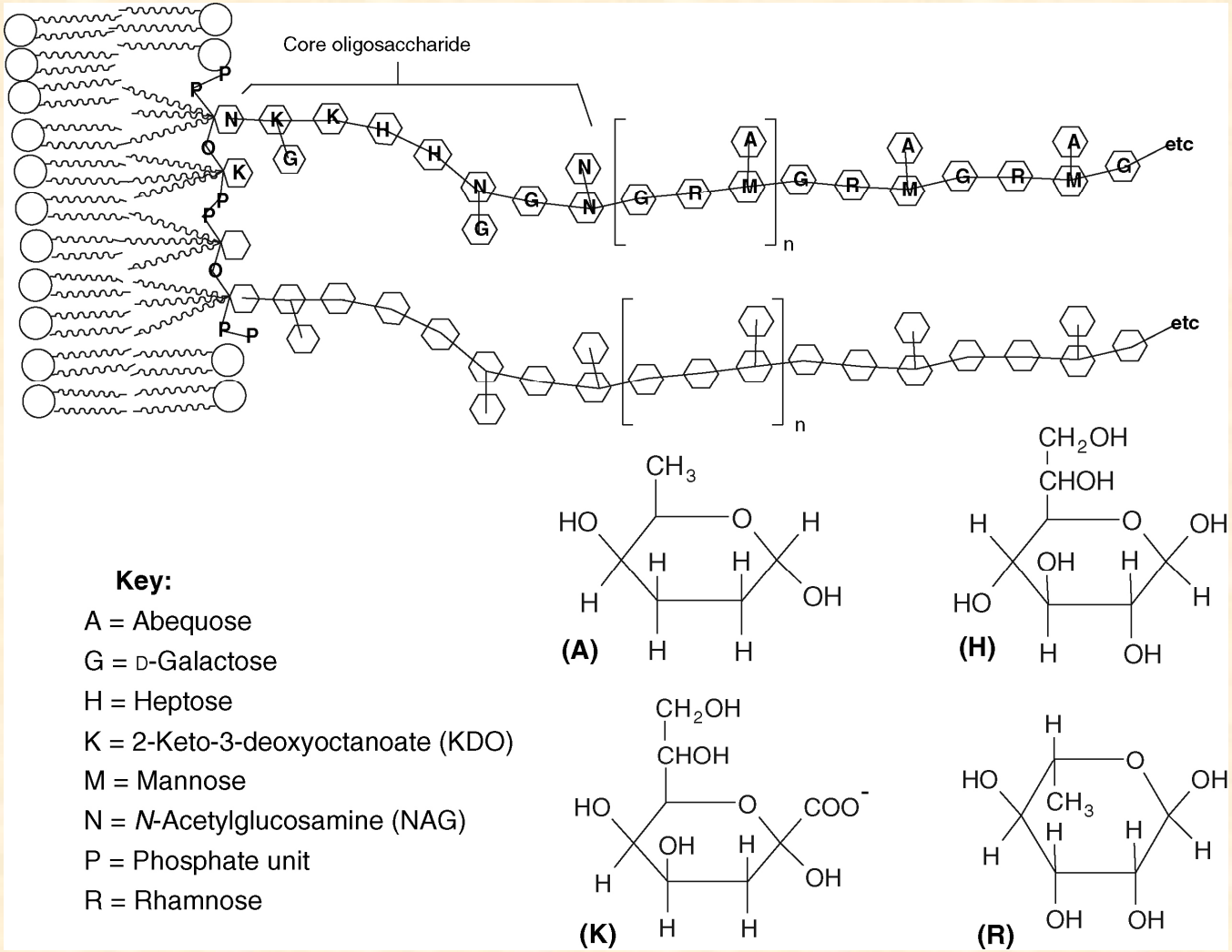
The Plasma Membrane

- Bacterial cell exterior surfaces – teichoic acids



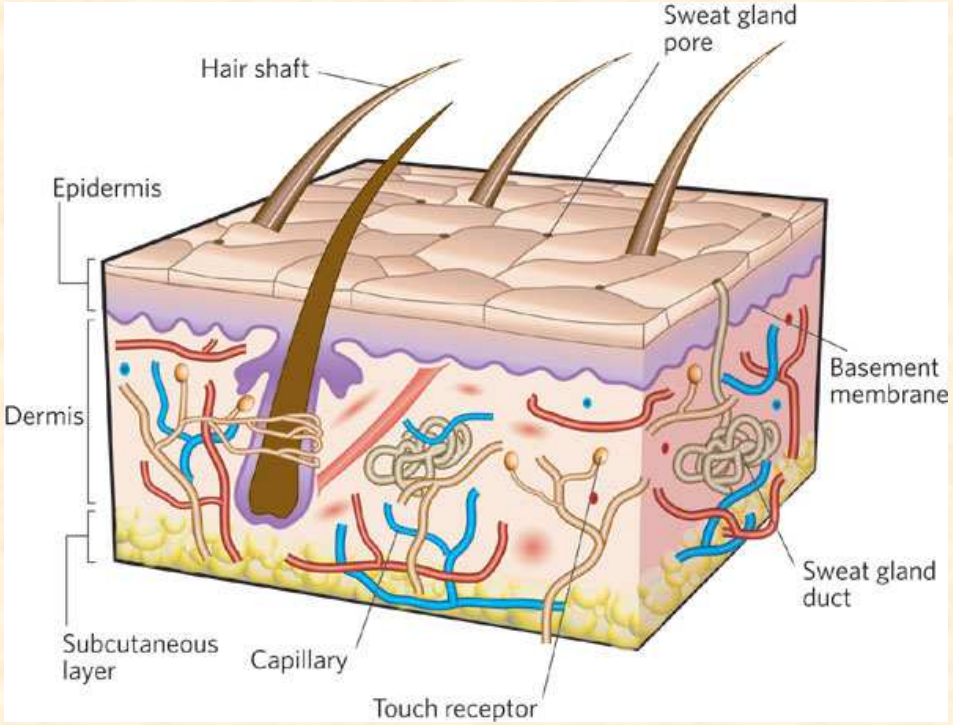
The Plasma Membrane

- Bacterial cell exterior surfaces



The Plasma Membrane

- Animal cell exterior surfaces
- Virus
- Tissue
- Human Skin



The Transfer of Species through Membranes

- Energetics of membrane transport

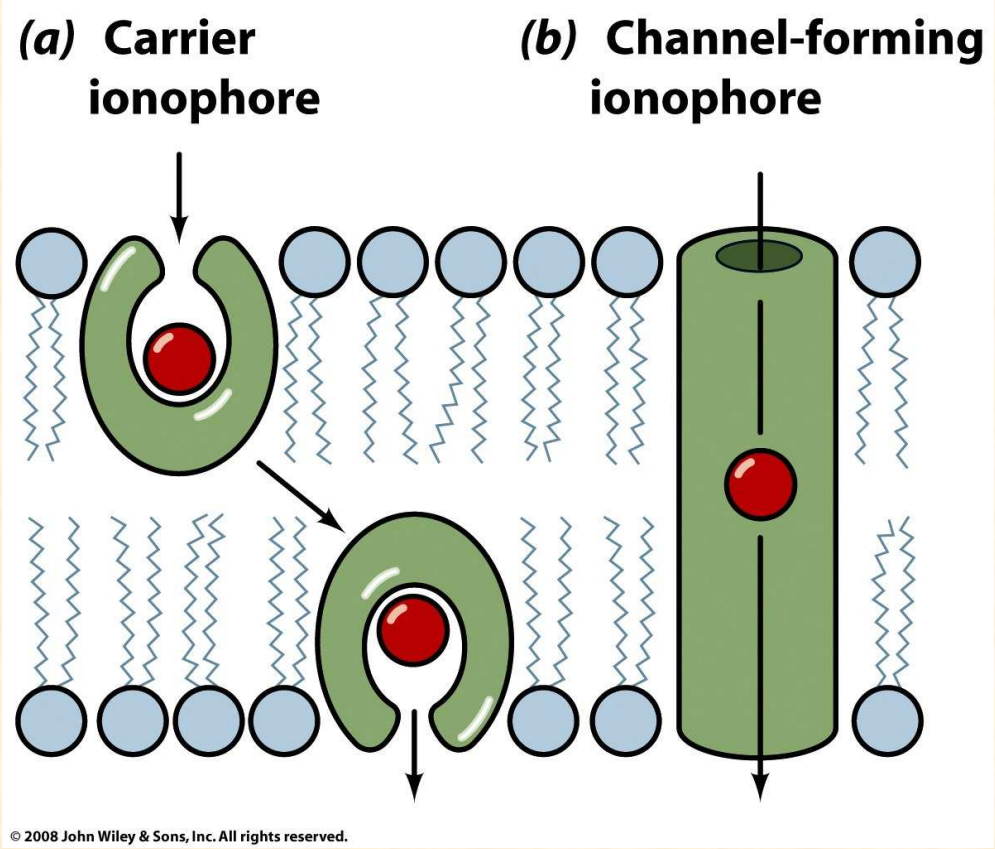
$$\Delta G = RT\ln(c_2/c_1) + ZF\Delta V$$

ΔG can predict whether a transport process must be active ($\Delta G > 0$) or passive ($\Delta G < 0$).

- Osmosis
- Filtration
- Passive diffusion

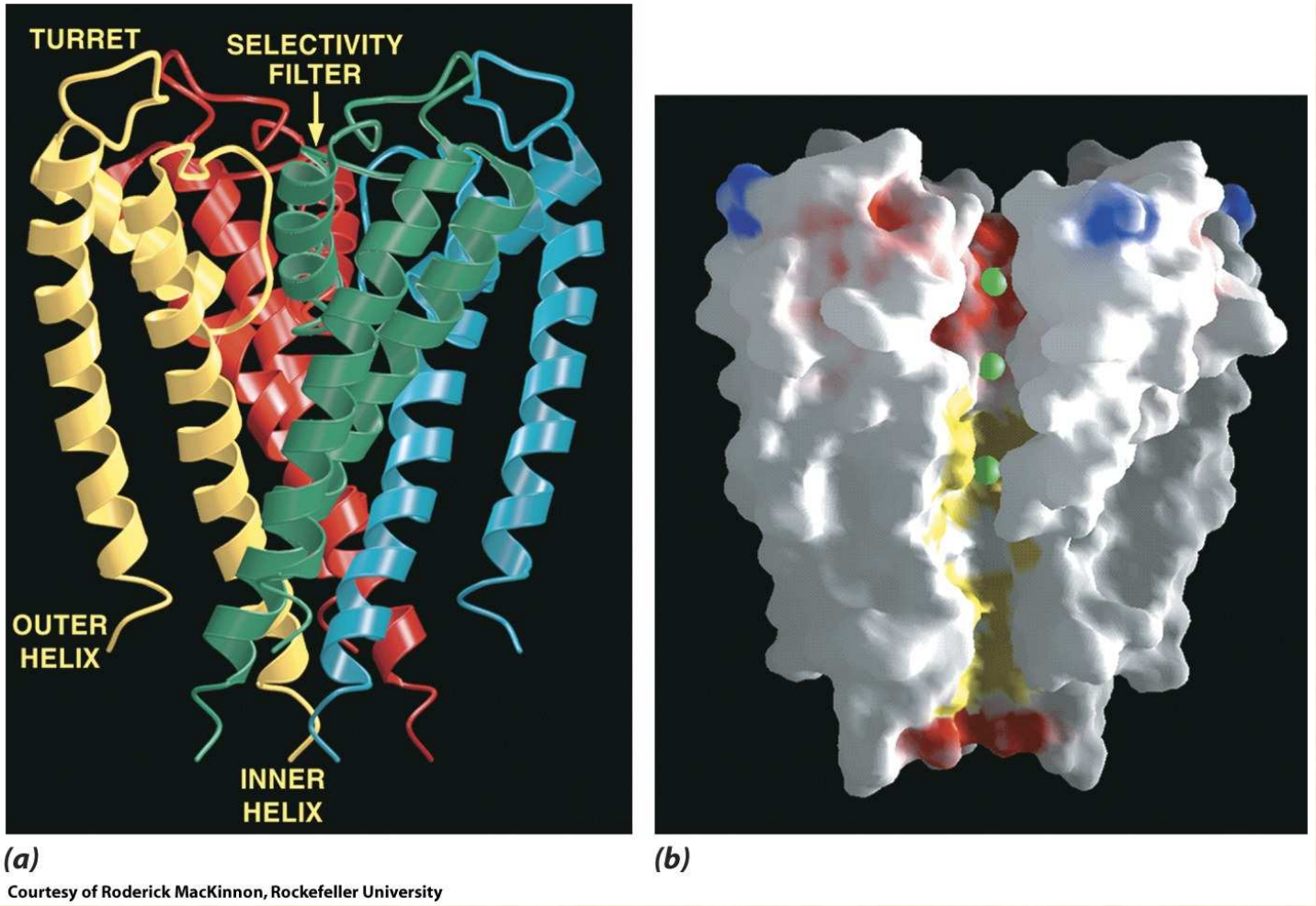
The Transfer of Species through Membranes

- Facilitated diffusion/transport



The Transfer of Species through Membranes

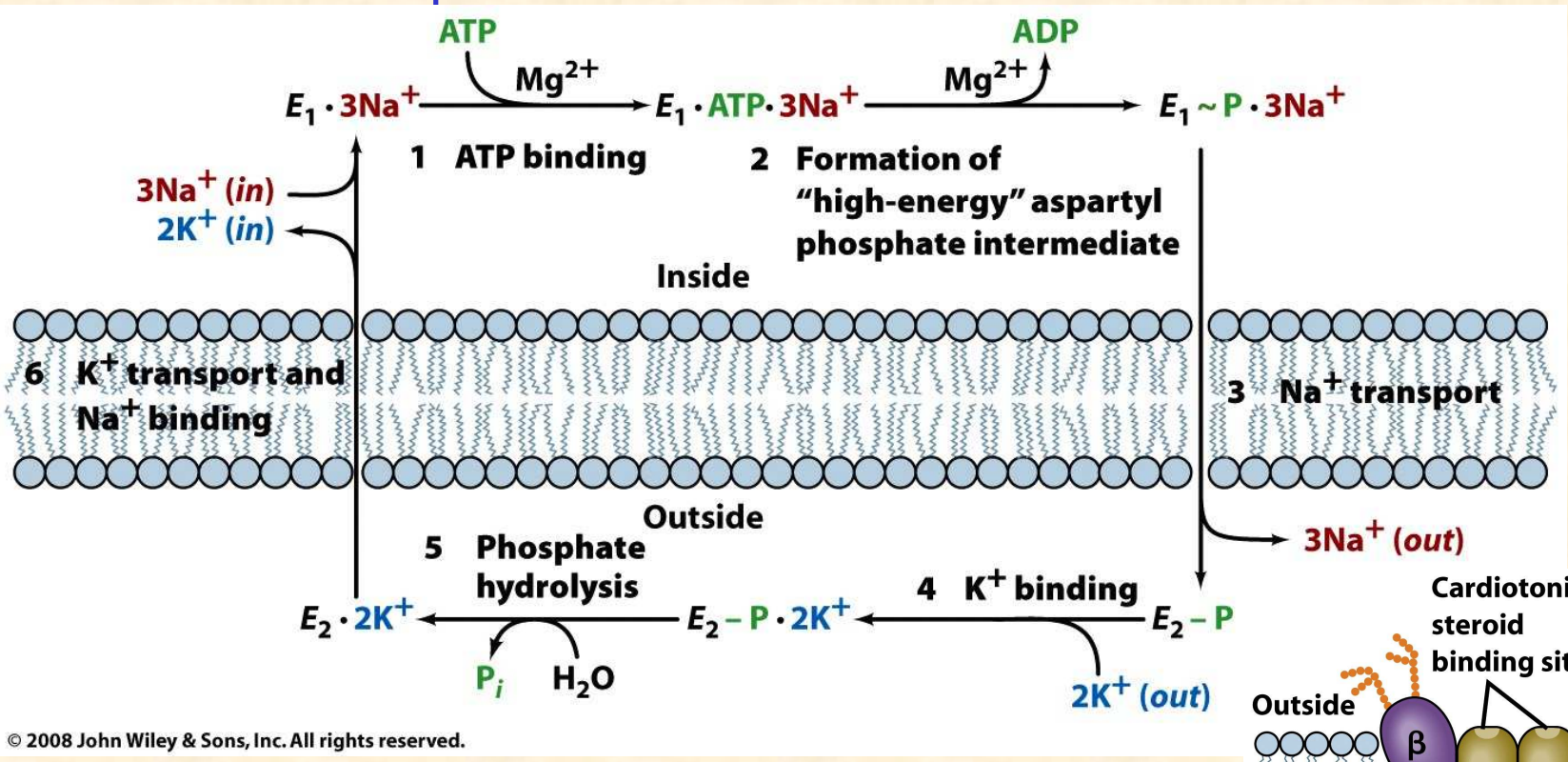
- Facilitated diffusion/transport - Ion Channels

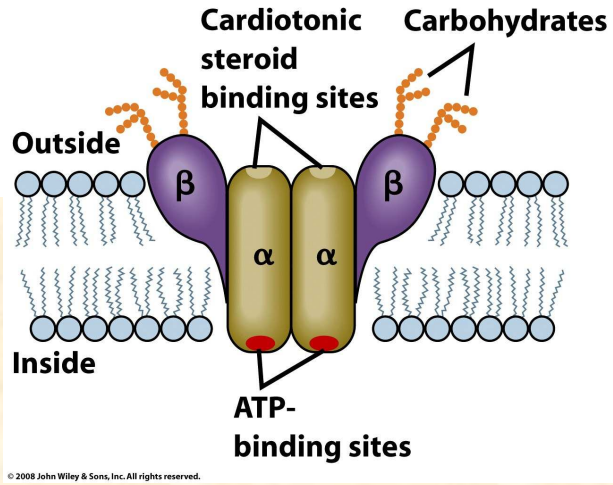


X-Ray structure of the KcsA K^+ channel

The Transfer of Species through Membranes

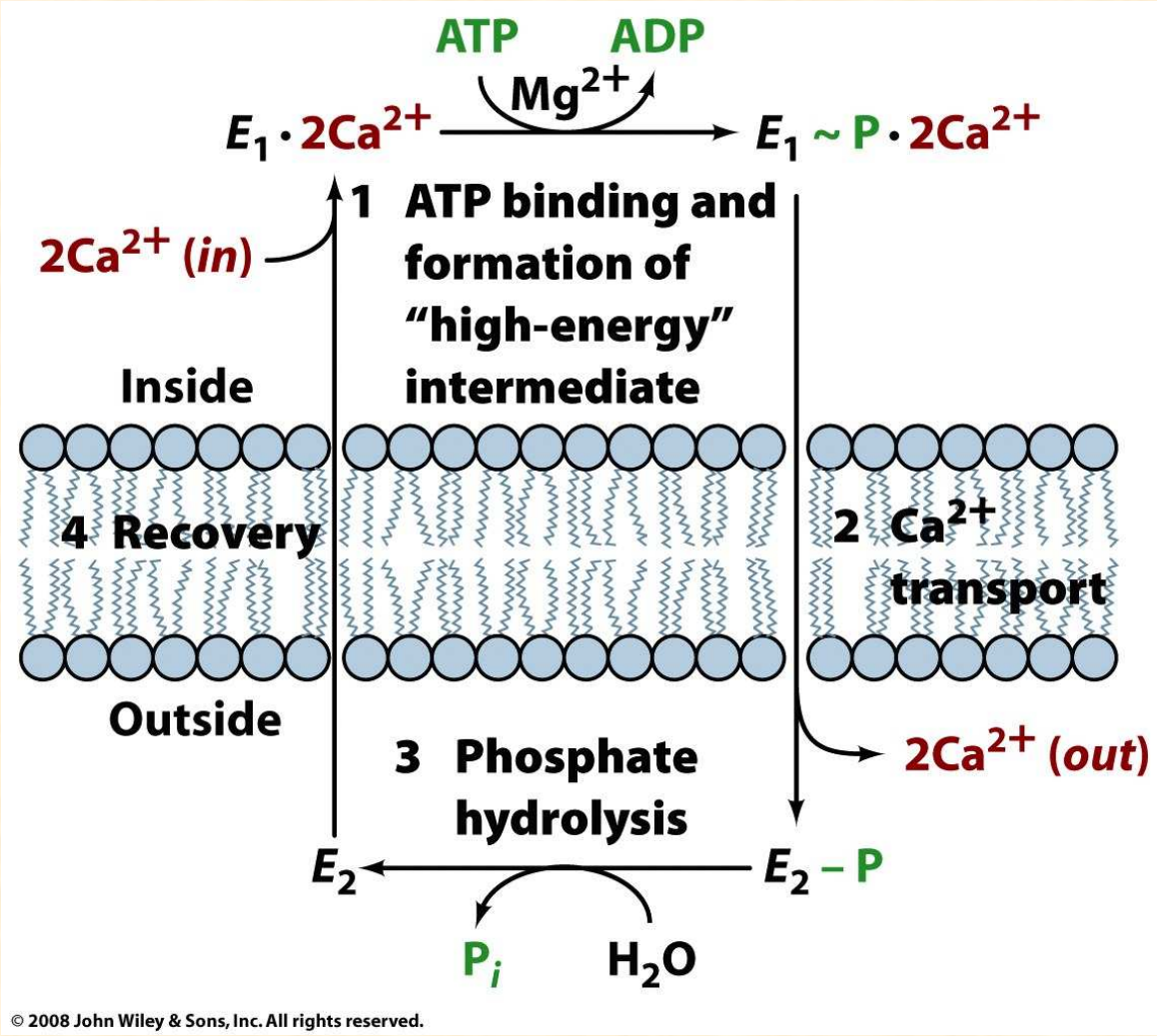
- Active Transport - Na^+- K^+- ATPase





The Transfer of Species through Membranes

- Active Transport - Ca^{2+}- ATPase



The Transfer of Species through Membranes

- Active Transport - ABC Transporter Mechanism

multidrug resistance

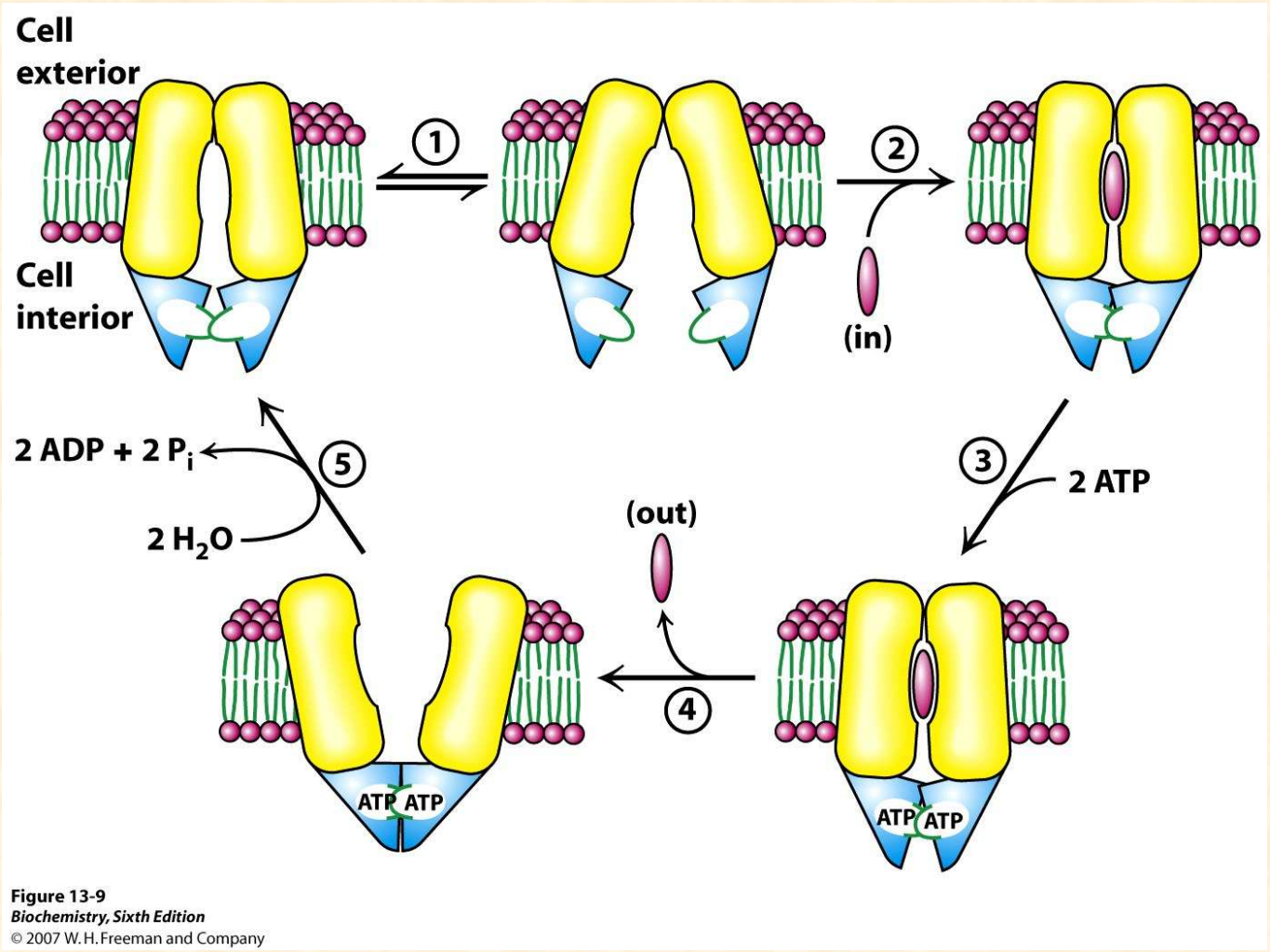
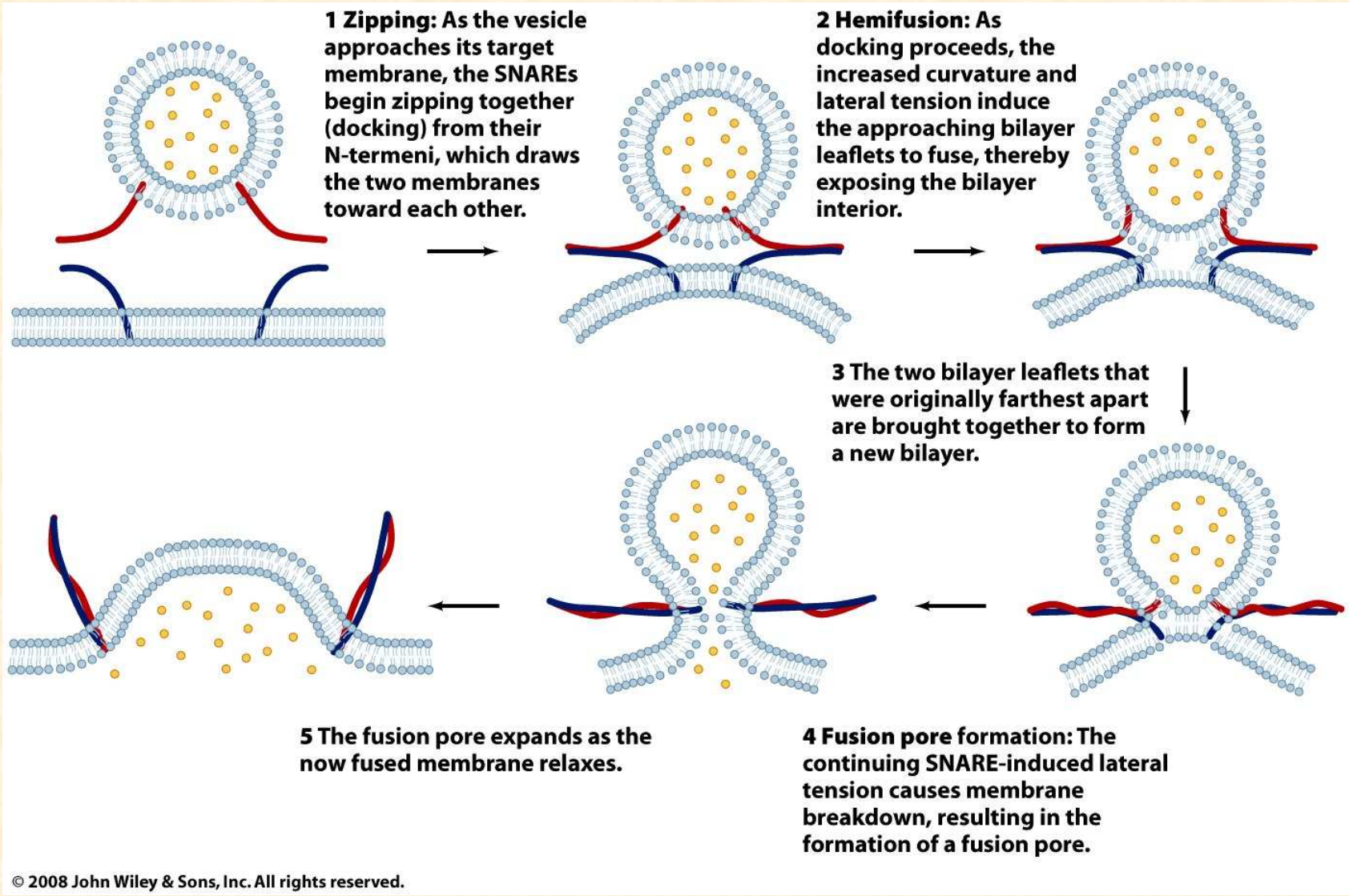


Figure 13-9
Biochemistry, Sixth Edition

The Transfer of Species through Membranes

- Active Transport - Endocytosis vs. Exocytosis



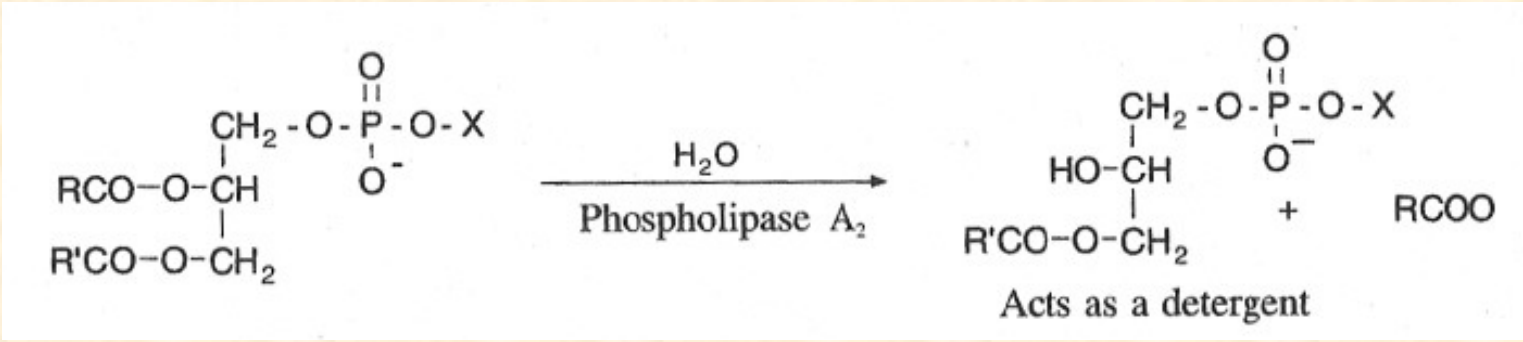
The Transfer of Species through Membranes

- Active Transport - Endocytosis vs. Exocytosis

Courtesy of John Heuser, Washington University School of Medicine, St. Louis, Missouri

Drug Action on Cell Membranes and Walls

- Action on enzymes and receptors or blocking ion channels



Disrupting the membrane/wall

- inhibiting enzymes that produce compounds to maintain the membrane

- inhibiting processes involved in formulation of the membrane/ cell wall

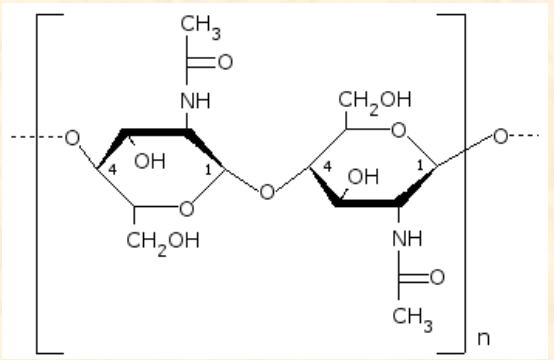
- forming channels and making the cell wall porous

- making the cell wall more porous by breaking down sections of it

Drug Action on Cell Membranes and Walls

- Antifungal agents
  - -fungal infections (*mycoses)*
    - superficial – external layer of skin/hair
      (cutaneous/subcutaneous)
    - systemic – internal tissues/organs
      (primary pathogens/opportunistic pathogens)

    - action – damage cell membrane – loss of essential cellular components



Counter action – antifungal agents
- fungistatic
- fungicidal action

Fungal microorganisms – eukaryotic cells with chitin cell wall
(targeting ergosterol biosynthesis)

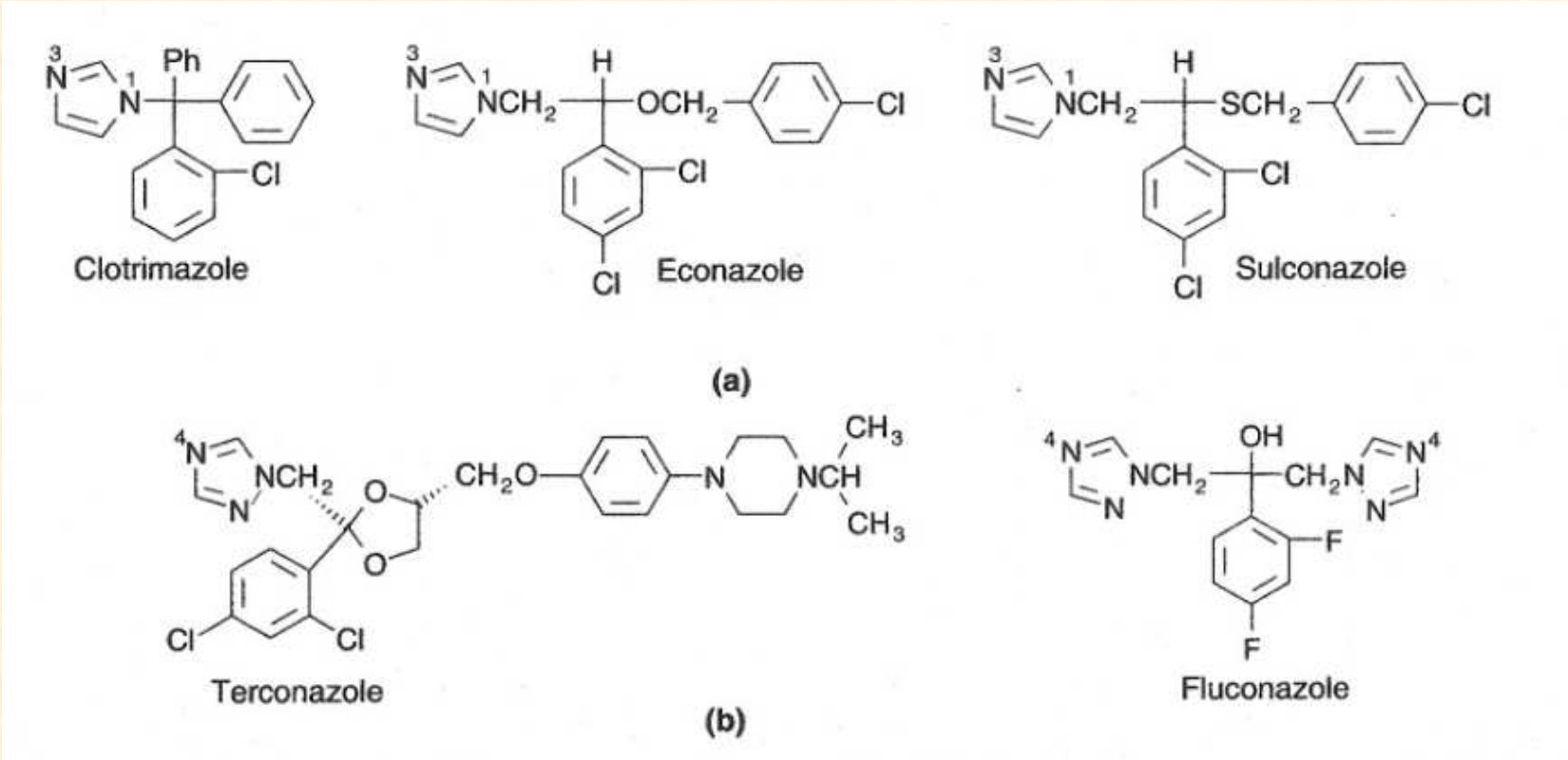
Drug Action on Cell Membranes and Walls

- Antifungal agents – Azoles (!)

Lotrimin

Spectazole

Exelderm

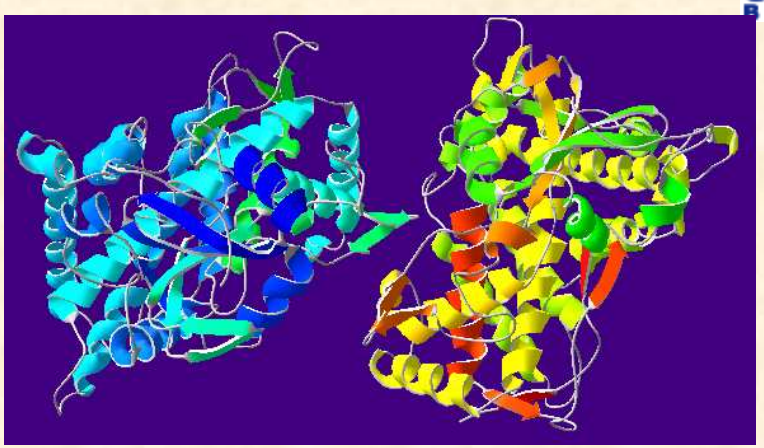


Terazole, Zazole

Diflucan

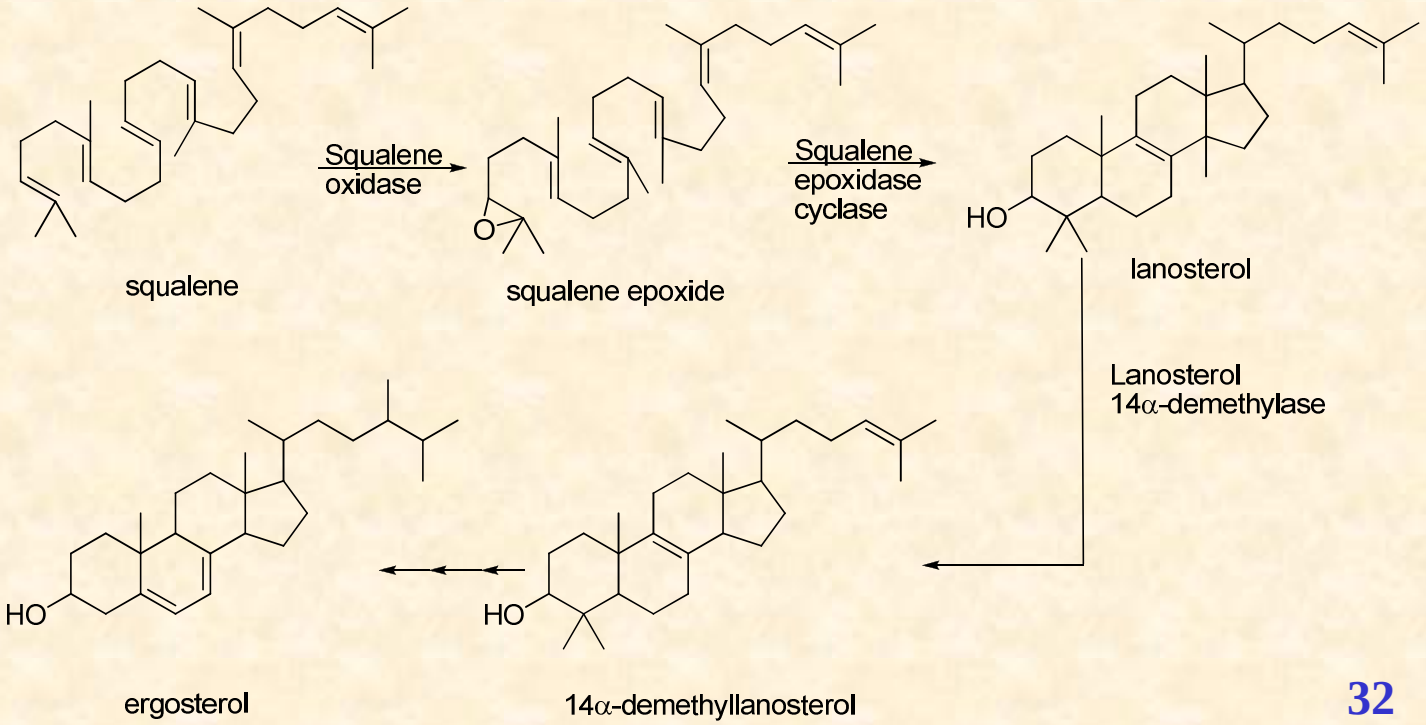
Drug Action on Cell Membranes and Walls

- Antifungal agents – Azoles



Action: inhibition of cytochrome P-450 oxidases ($P\text{-}450_{DM}$)

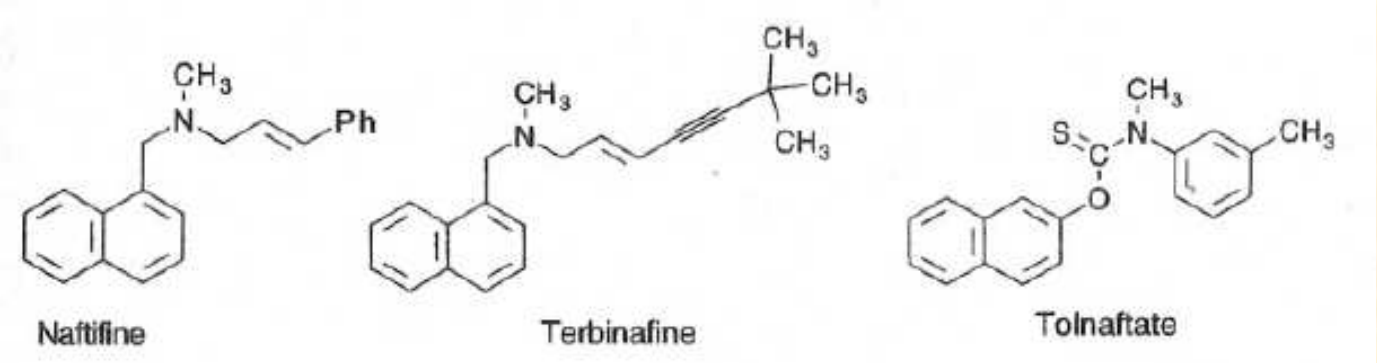
(detoxification)



Drug Action on Cell Membranes and Walls

- Antifungal agents – Allylamines and related compounds

Action: inhibition of
squalene oxidase – squalene accumulation in membrane – loss of membrane intergrity

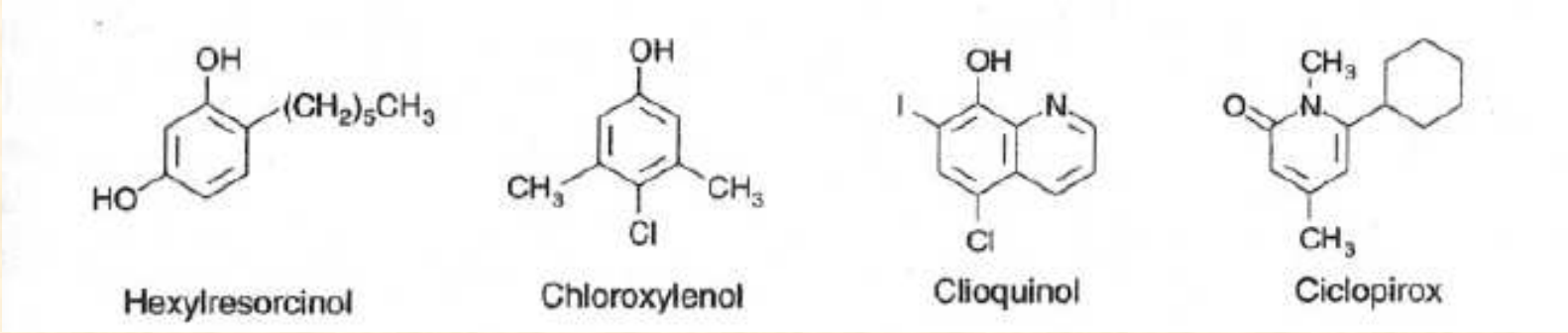


Naftin Lamisil

Drug Action on Cell Membranes and Walls

- Antifungal agents – Phenols and related compounds

Action: disrupt cell membrane



Strepsils

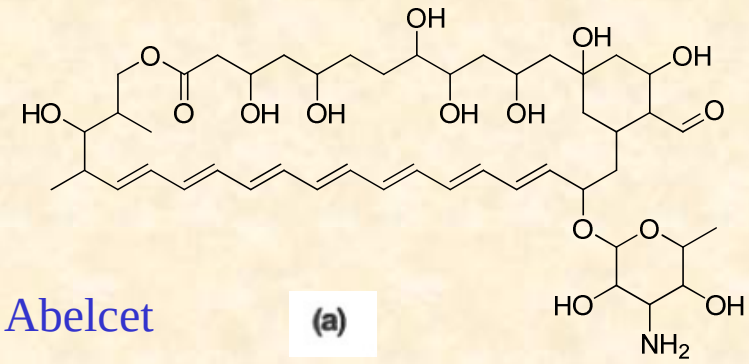
Gojo antimicrobial soap

Loprox

Drug Action on Cell Membranes and Walls

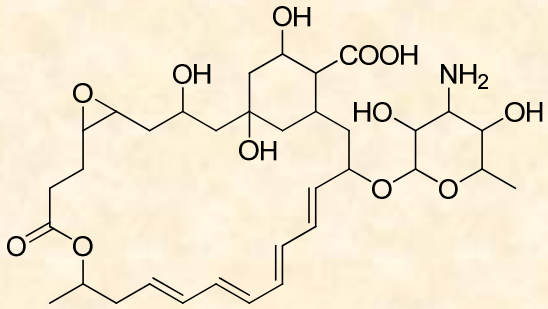
- Antibacterial antifungal agents

Action: disrupt cell membrane



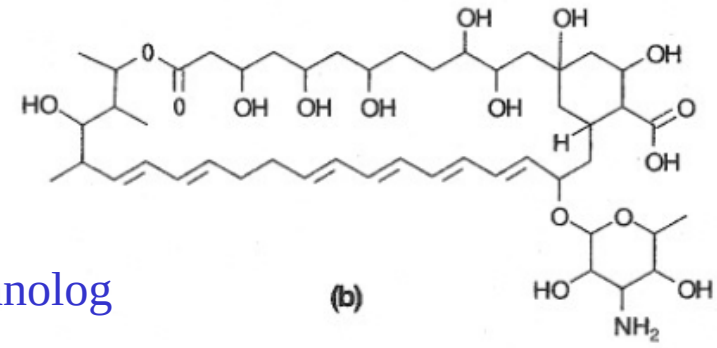
Abelcet

(a)



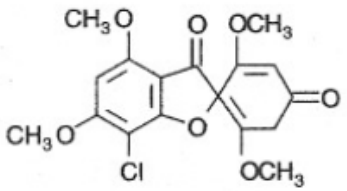
(c)

Natacyn (plus cheese additive)



Panolog

(b)



(d)

Gris-PEG (vet-med too)

Figure 7.20 (a) Amphopterin B, first isolated from Streptomyces nodosus by Gold *et al.* (b) Nystatin, first isolated from Streptomyces noursei by Hazen and Brown. (c) Natamycin, first isolated from Streptomyces natalensis by Struyk *et al.* (d) Griseofulvin,first isolated from Penicillium griseofulvium by Oxford *et al.*

Drug Action on Cell Membranes and Walls

- Antibacterial agents – Antibiotics

Action:

- Ionophoric antibiotic action

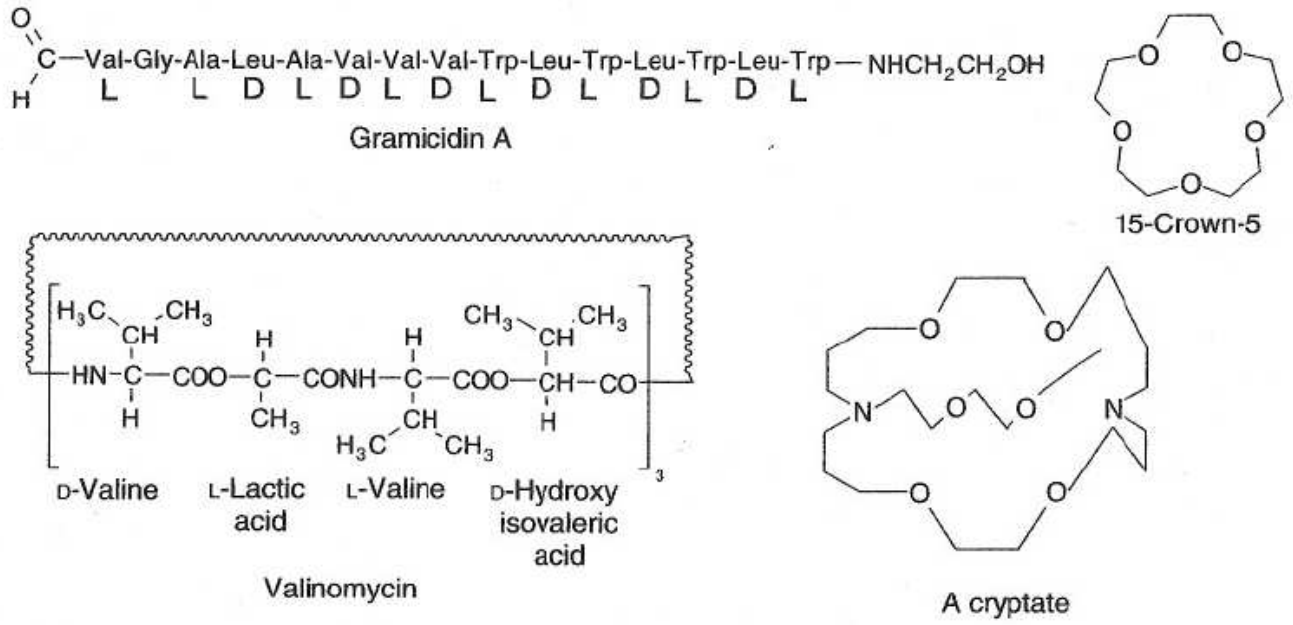


Figure 7.21 Examples of naturally occurring and synthetic ionophores

Drug Action on Cell Membranes and Walls

- Antibacterial agents – Antibiotics

Ionophoric antibiotic action usually for Gram-positive

- Channel formation – ion transport
- Carriers

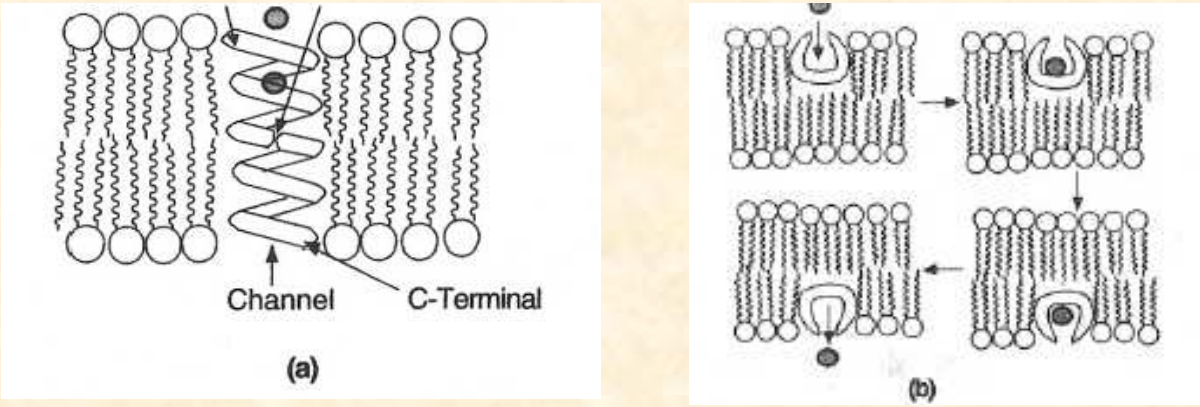


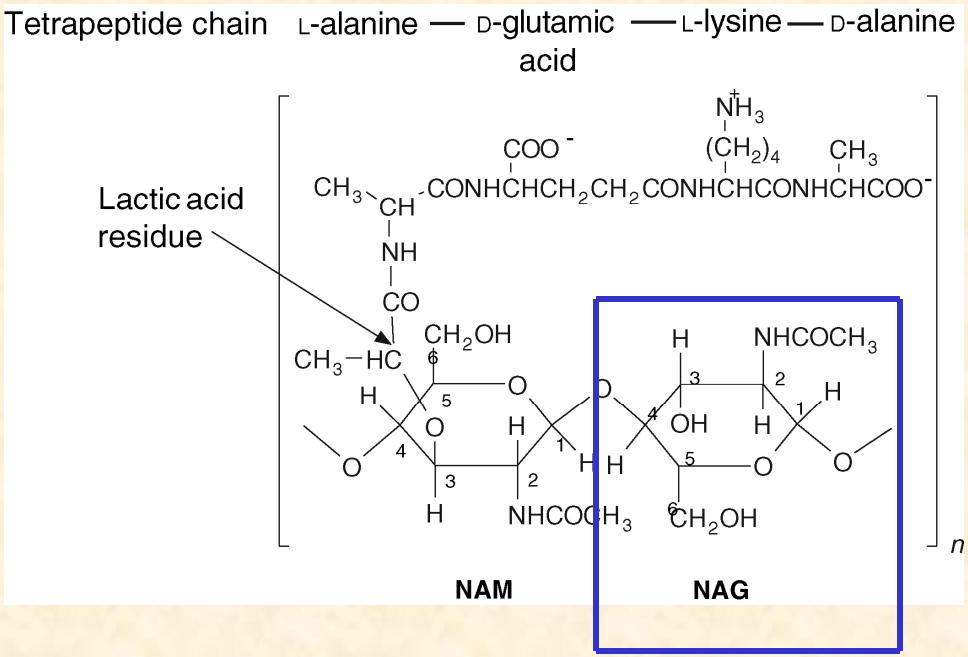
Figure 7.22 The general mode of action of ionophores in ion transport. (**a**) A channel formed by two gramicidin A molecules, N-terminal to N-terminal. (**b**) The sequence of events in the operation of a carrier ionophore such as valinomycin

Drug Action on Cell Membranes and Walls

- Antibacterial agents – Antibiotics

Cell wall synthesis inhibition multiple types (3)

1. Drugs that inhibit the formation of starting materials



Drug Action on Cell Membranes and Walls

- Antibacterial agents – Antibiotics

Cell wall synthesis inhibition

1. Drugs that inhibit the formation of staring materials

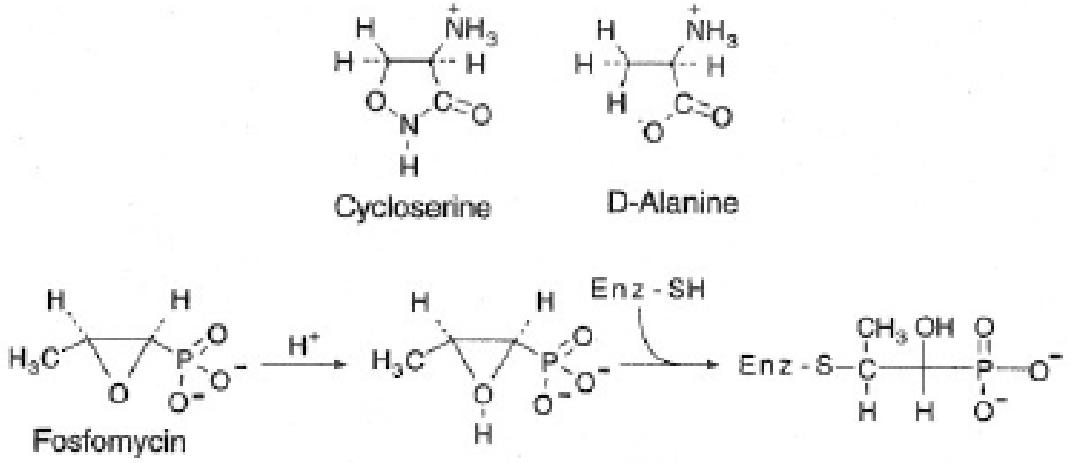


Figure 7.23 Cycloserine and fosfomucin

Drug Action on Cell Membranes and Walls

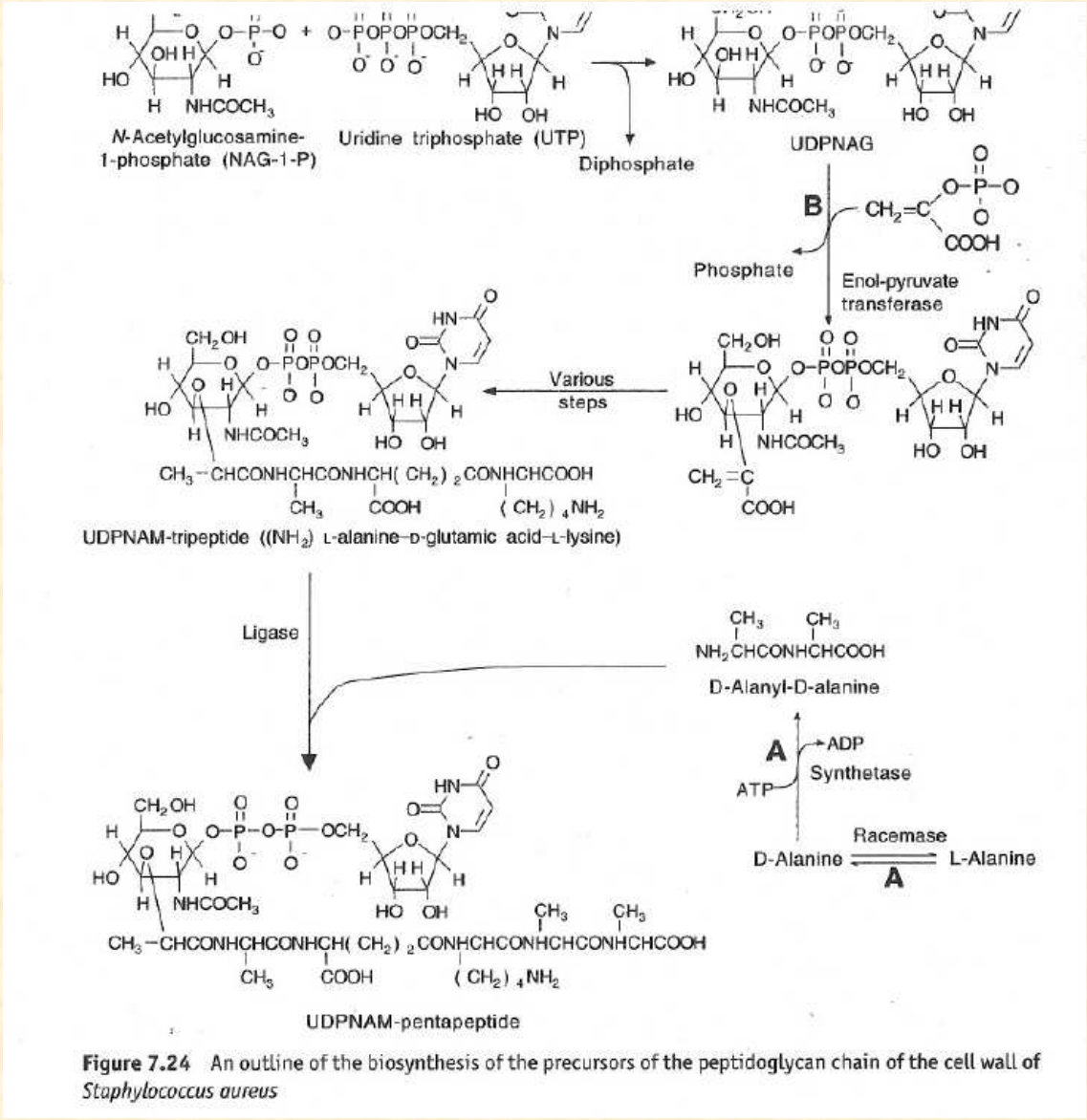


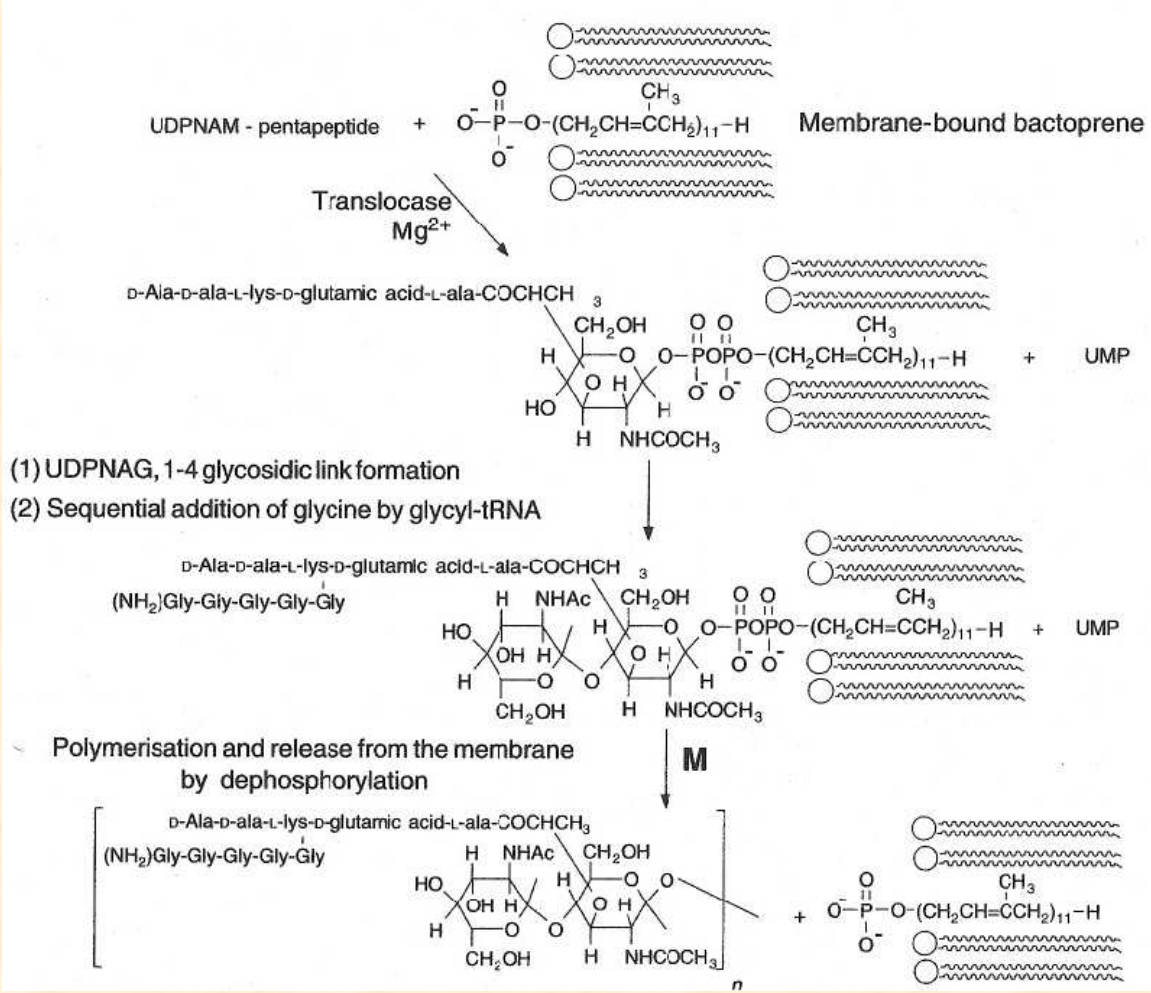
Figure 7.24 An outline of the biosynthesis of the precursors of the peptidoglycan chain of the cell wall of *Staphylococcus aureus*

Drug Action on Cell Membranes and Walls

- Antibacterial agents – Antibiotics

Cell wall synthesis inhibition –

2. Drugs that inhibit the synthesis of the peptidoglycan chain

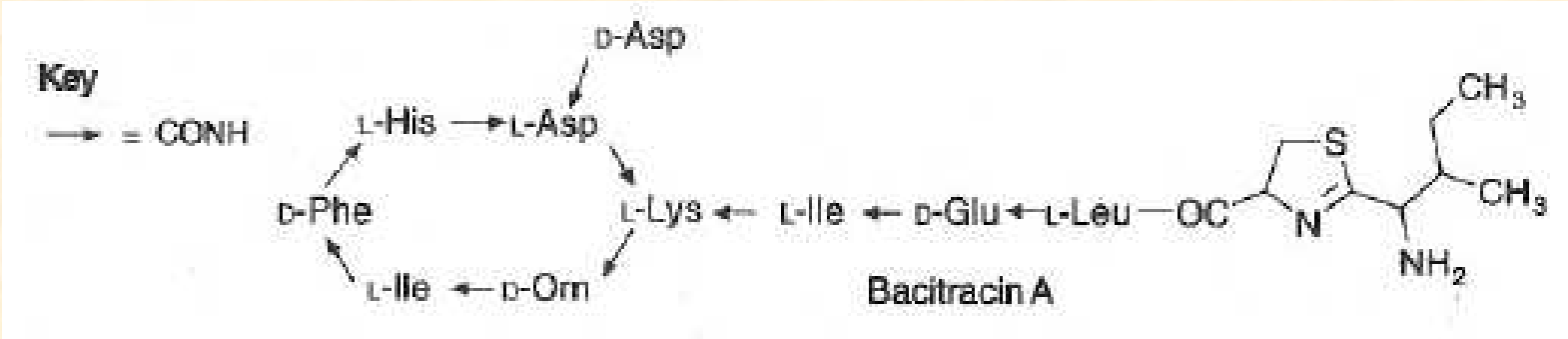


Drug Action on Cell Membranes and Walls

- Antibacterial agents – Antibiotics

Cell wall synthesis inhibition –

2. Drugs that inhibit the synthesis of the peptidoglycan chain



Drug Action on Cell Membranes and Walls

- Antibacterial agents – Antibiotics

Cell wall synthesis inhibition –

3. Drugs that inhibit the cross-linking of the peptidoglycan chain

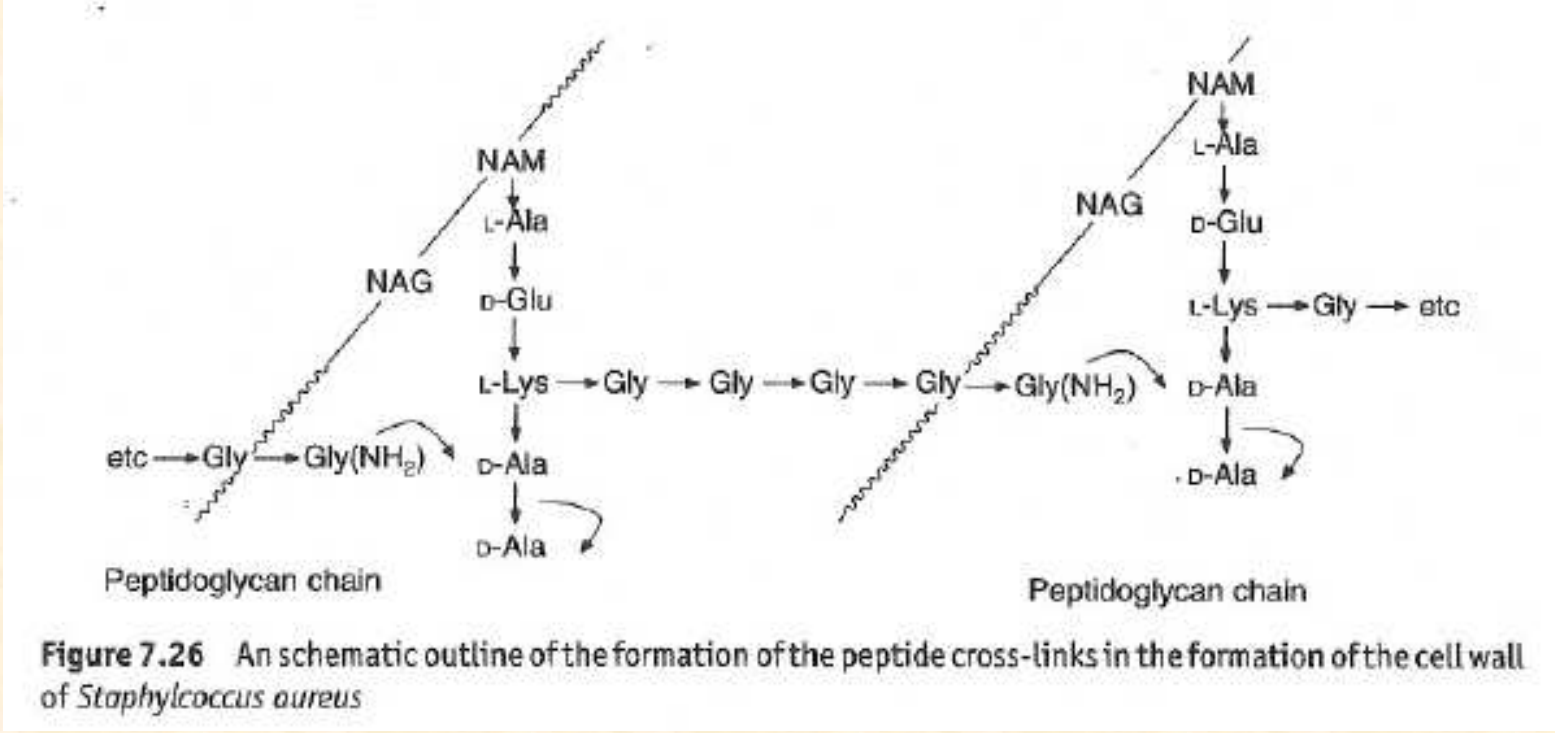


Figure 7.26 An schematic outline of the formation of the peptide cross-links in the formation of the cell wall of *Staphylcoccus aureus*

Drug Action on Cell Membranes and Walls

- Antibacterial agents – Antibiotics – Cell wall synthesis inhibition

3. Drugs that inhibit the cross-linking of the peptidoglycan chain

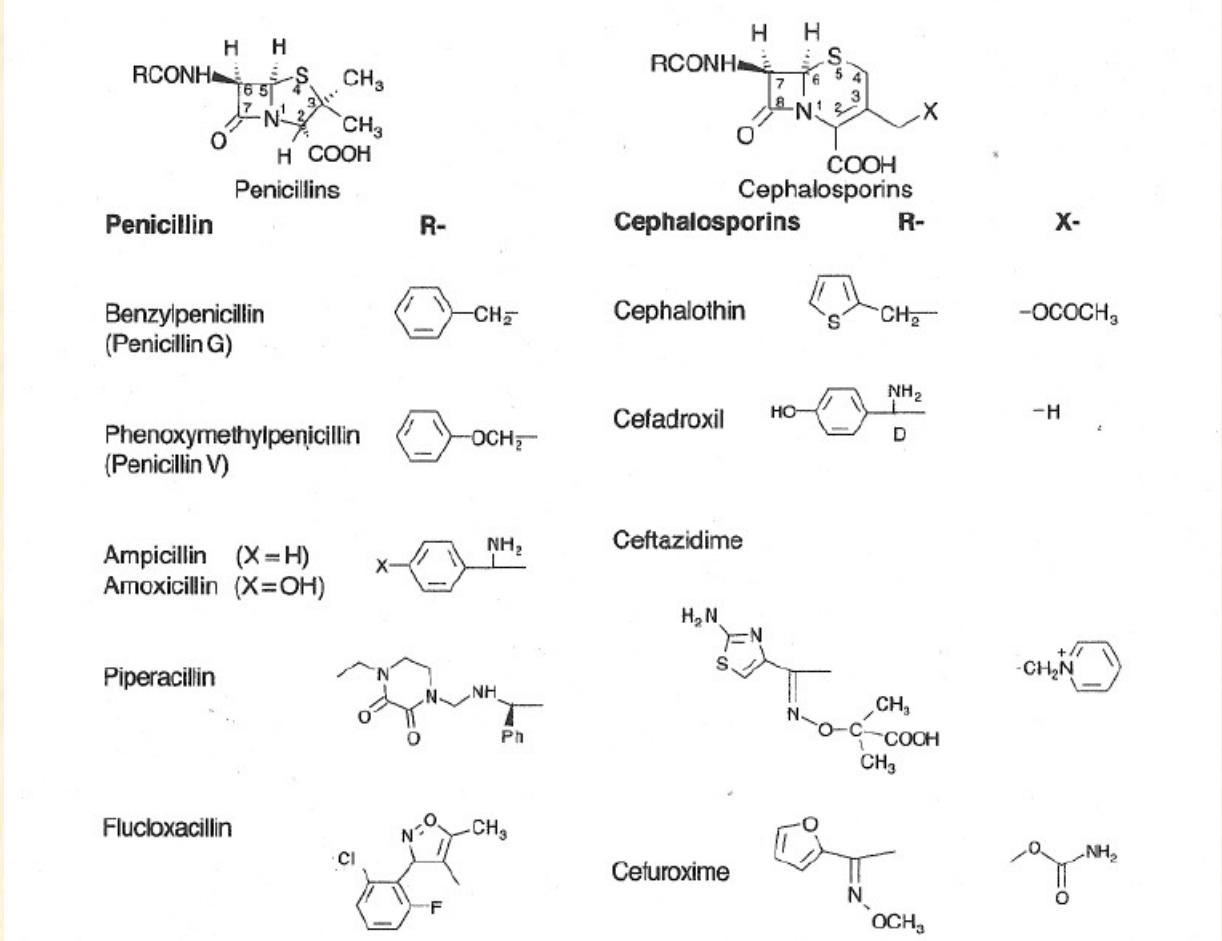


Figure 7.27 Examples of the range of penicillins and cephalosporins. The R residues of ampicillin, amoxicillin and ceftazidime have D configurations

Drug Action on Cell Membranes and Walls

- Antibacterial agents – Antibiotics – Cell wall synthesis inhibition

3. Drugs that inhibit the cross-linking of the peptidoglycan chain

β-lactame antibiotics – sensitive

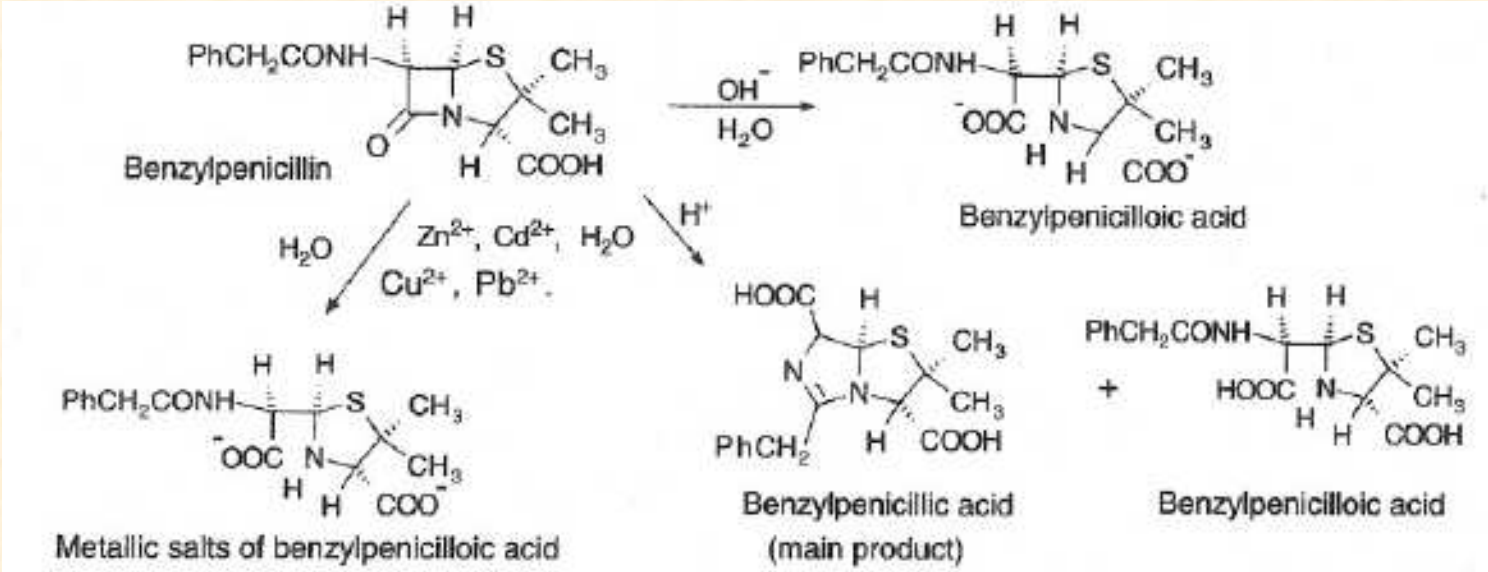


Figure 7.28 Some of the decomposition routes of the β-lactam ring of benzylpenicillin

Drug Action on Cell Membranes and Walls

- Antibacterial agents – Antibiotics – Cell wall synthesis inhibition

3. Drugs that inhibit the cross-linking of the peptidoglycan chain

β-lactame antibiotics – mode of action

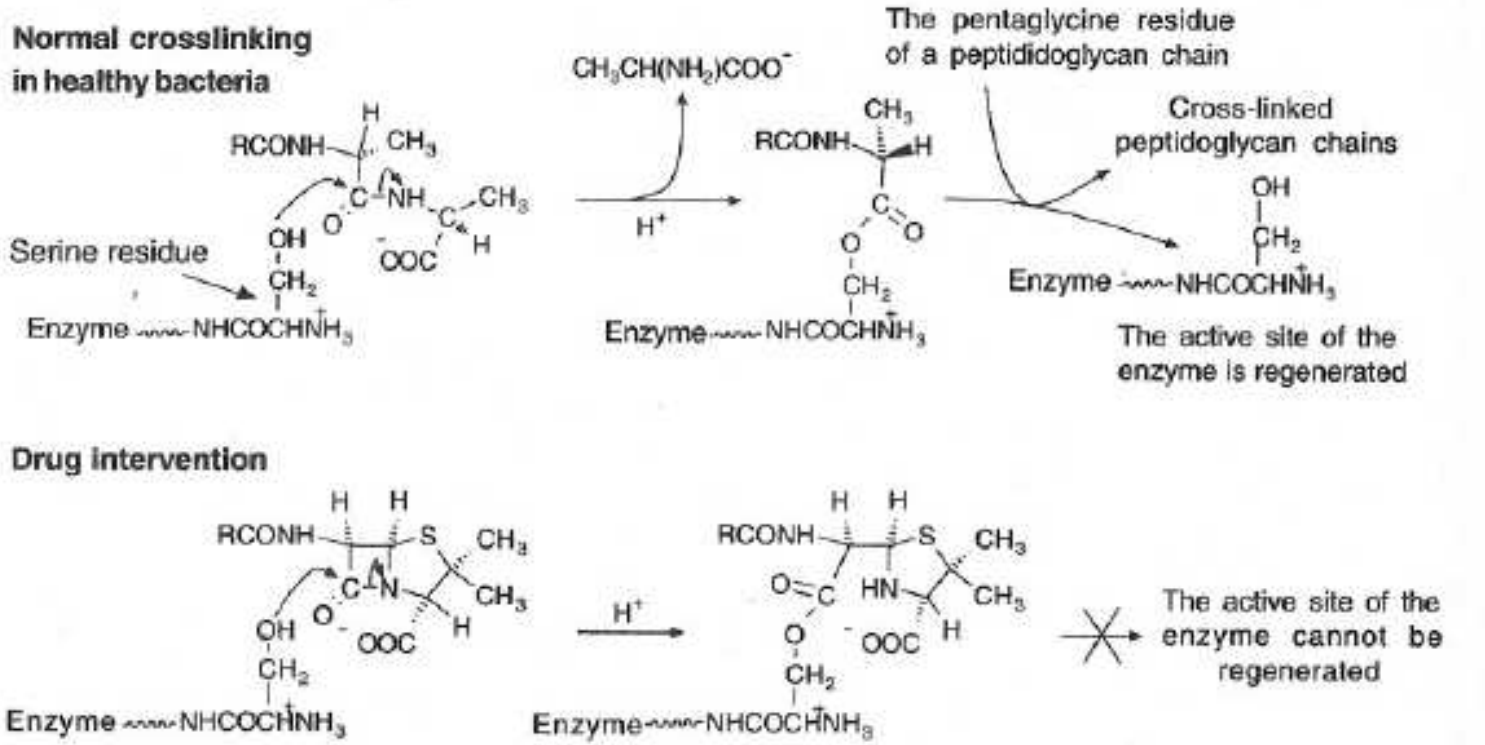


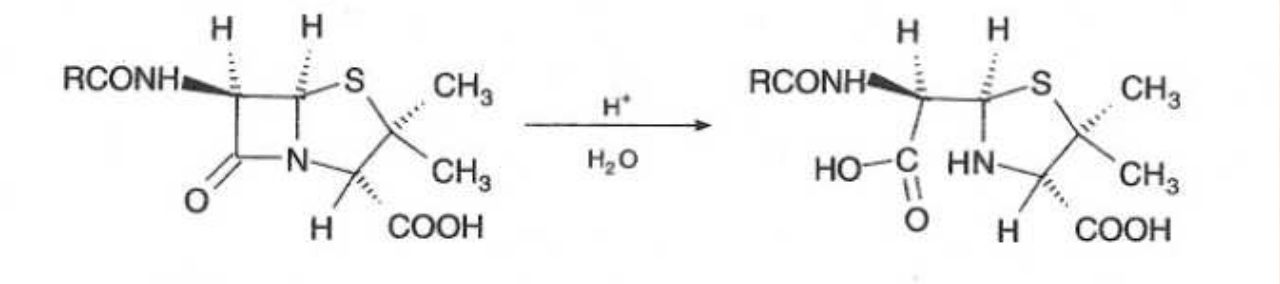
Figure 7.29 A schematic outline of the chemistry proposed for the action of penicillins

Drug Action on Cell Membranes and Walls

- Antibacterial agents – Antibiotics – Cell wall synthesis inhibition

3. Drugs that inhibit the cross-linking of the peptidoglycan chain

β-lactame antibiotics – decomposition under acidic conditions



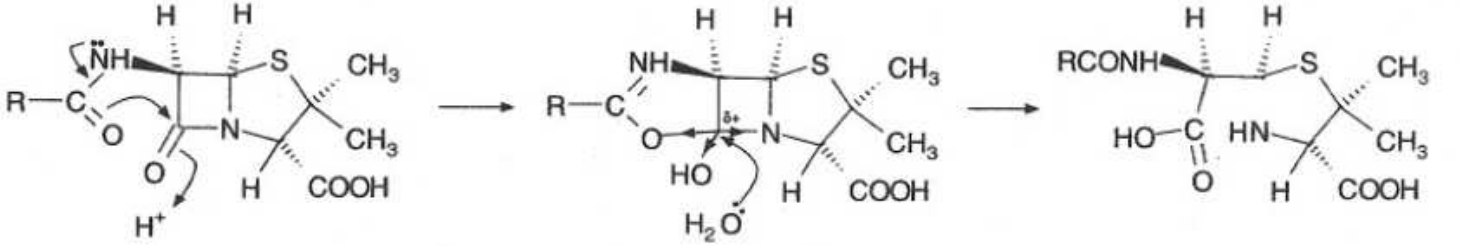


Figure 7.30 A possible mechanism for the enhancement of the reactivity of the carbonyl group of the lactam by a neighbouring group

Drug Action on Cell Membranes and Walls

- Antibacterial agents – Antibiotics – Cell wall synthesis inhibition

3. Drugs that inhibit the cross-linking of the peptidoglycan chain

β-lactame antibiotics – increase stability

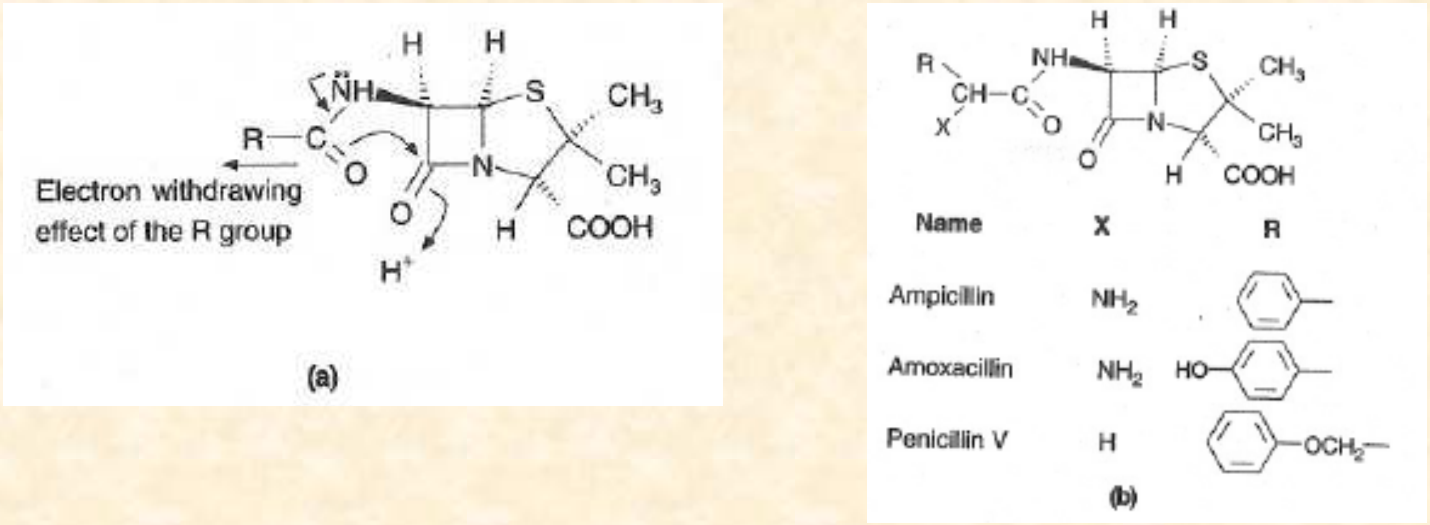


Figure 7.31 (a) It is believed that the electron withdrawing effect of the R group reduces the ability of the electrons of the carbonyl group of the amide link to influence those of the carbonyl group of the lactam. (b) Examples of penicillins in clinical use with an electron withdrawing R group

Drug Action on Cell Membranes and Walls

- Antibacterial agents – Antibiotics – Cell wall synthesis inhibition

3. Drugs that inhibit the cross-linking of the peptidoglycan chain

other β-lactame antibiotics

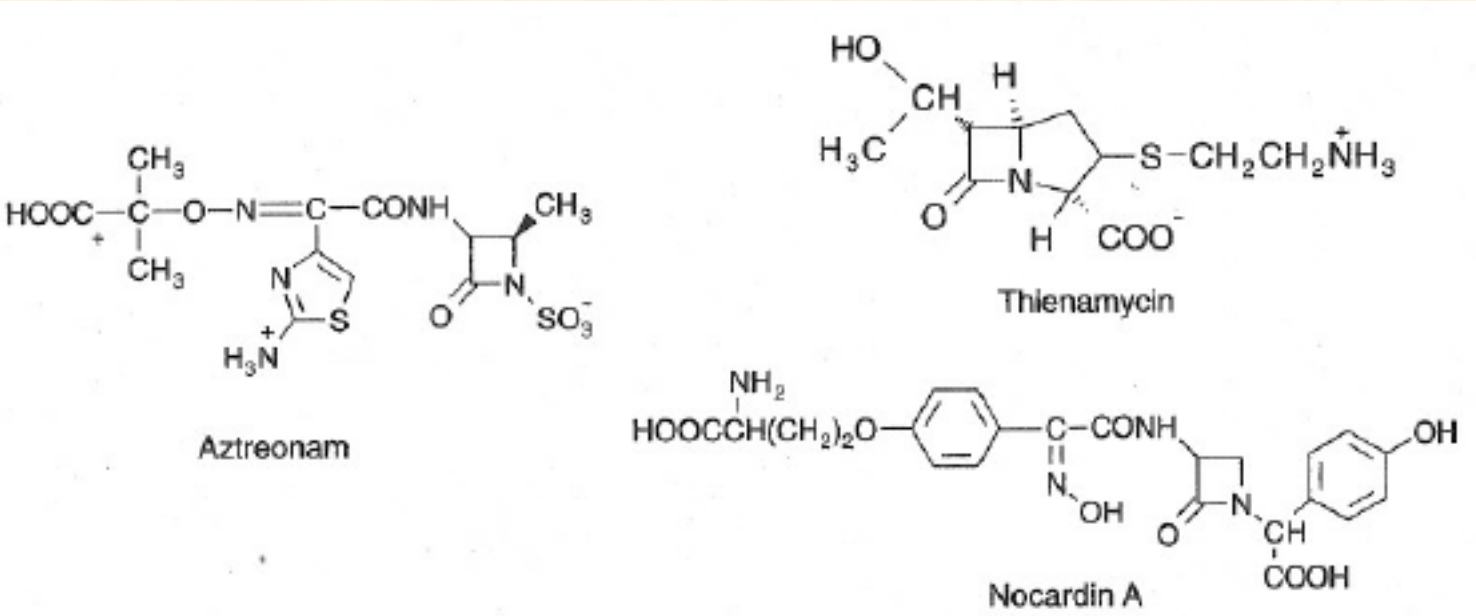


Figure 7.32 Examples of β-lactam antibiotics that do not contain a thio-ring system

Drug Action on Cell Membranes and Walls

- Antibacterial agents – Antibiotics – Cell wall synthesis inhibition

3. Drugs that inhibit the cross-linking of the peptidoglycan chain

extra additives - β-lactamase inhibitors

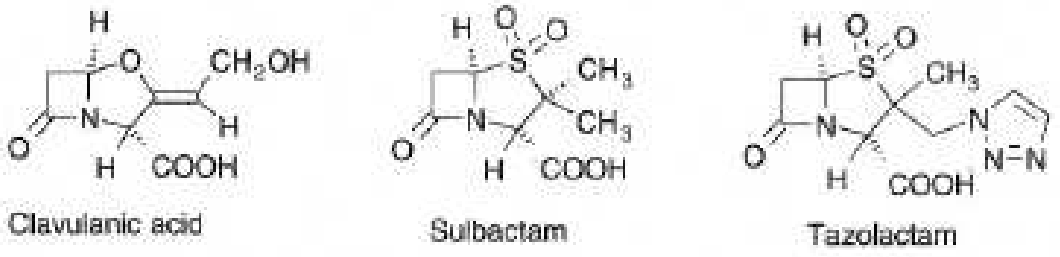


Figure 7.33 Examples of β-lactamase inhibitors used in penicillin dosage forms

Table 7.2 Examples of dosage forms containing β-lactamase inhibitors

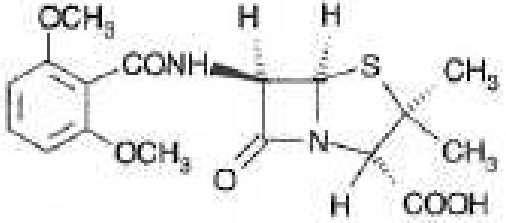
Preparation	Penicillin	β-Lactamase Inhibitor
Co-amoxiclav	Amoxicillin	Clavulanic acid
Tazocin	Piperacillin	Tazubactum
Unasyn	Ampicillin	Sulbactam
Timentin	Ticarcillin	Clavulinic acid
Augmentin	Amoxicillin	Clavulanic acid

Drug Action on Cell Membranes and Walls

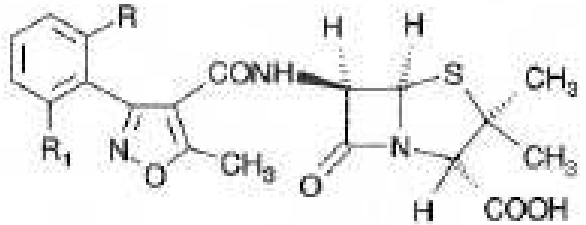
- Antibacterial agents – Antibiotics – Cell wall synthesis inhibition

3. Drugs that inhibit the cross-linking of the peptidoglycan chain

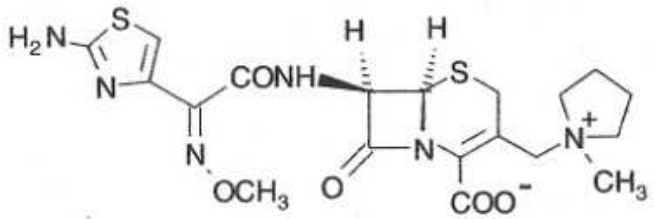
alternative approach - β-lactamase resistant drugs



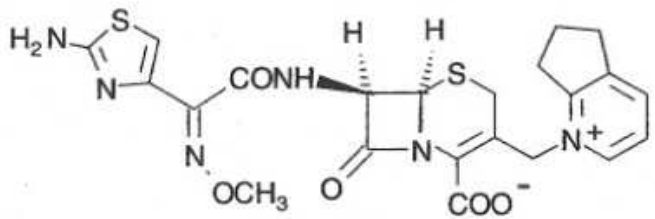
Methicillin



Cloxacillin R=H, R_1=Cl
Dicloxacillin R=Cl, R_1=Cl



Cefepime



Cefpirome

Drug Action on Cell Membranes and Walls

- Antibacterial agents – Antibiotics – Cell wall synthesis inhibition

Polypeptide antibiotics

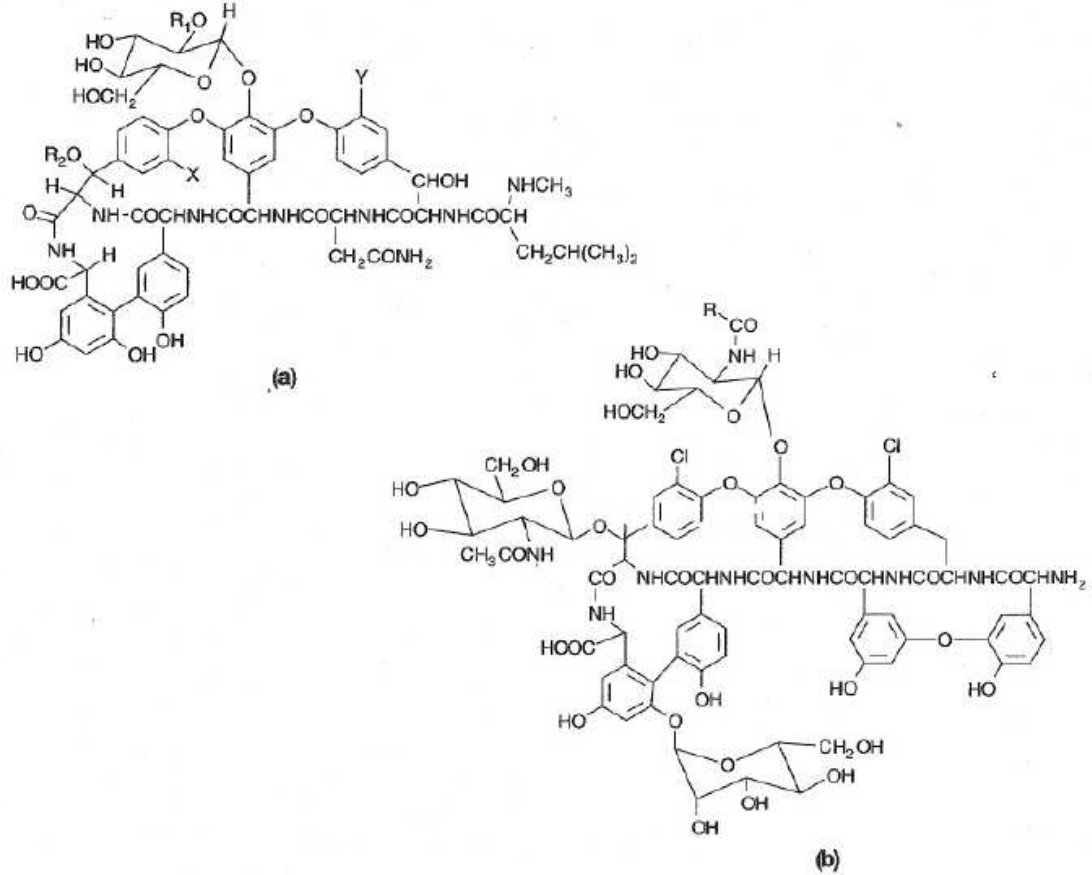
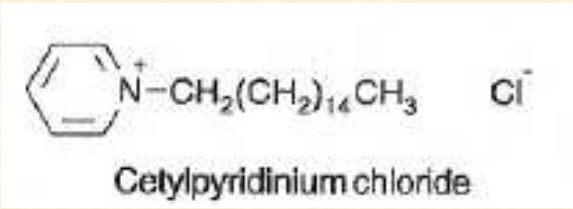
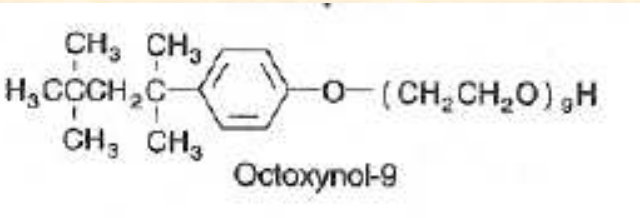


Figure 7.34 (a) Vancomycin and some related compounds. Vancomycin, X = Cl, Y = Cl, R_1 = α-vancosaminyl, R_2 = H; Decaplanin, X = H, Y = Cl, R_1 = α-rhamnosyl, R_2 = α-epivancosaminyl and Orienticin A, X = Cl, Y = H, R_1 and R_2 = α-epivancosaminyl. (b) Teicoplanin: A_{2-1}, R = $CH_3(CH_2)_4CH{=}CHCH_2CH_2$-; A_{2-2}, R = $(CH_3)_2CH(CH_2)_5CH_2$-; A_{2-3}, R = $CH_3(CH_2)_7CH_2$-; A_{2-4}, R = $CH_3CH_2CH(CH_3)(CH_2)_5CH_2$-; A_{2-5}, R = $(CH_3)_2CH(CH_2)_6CH_2$-

Surfactants



Cetylpyridinium chloride



Octoxynol-9

Drug Action on Cell Membranes and Walls

- Local anaesthetics

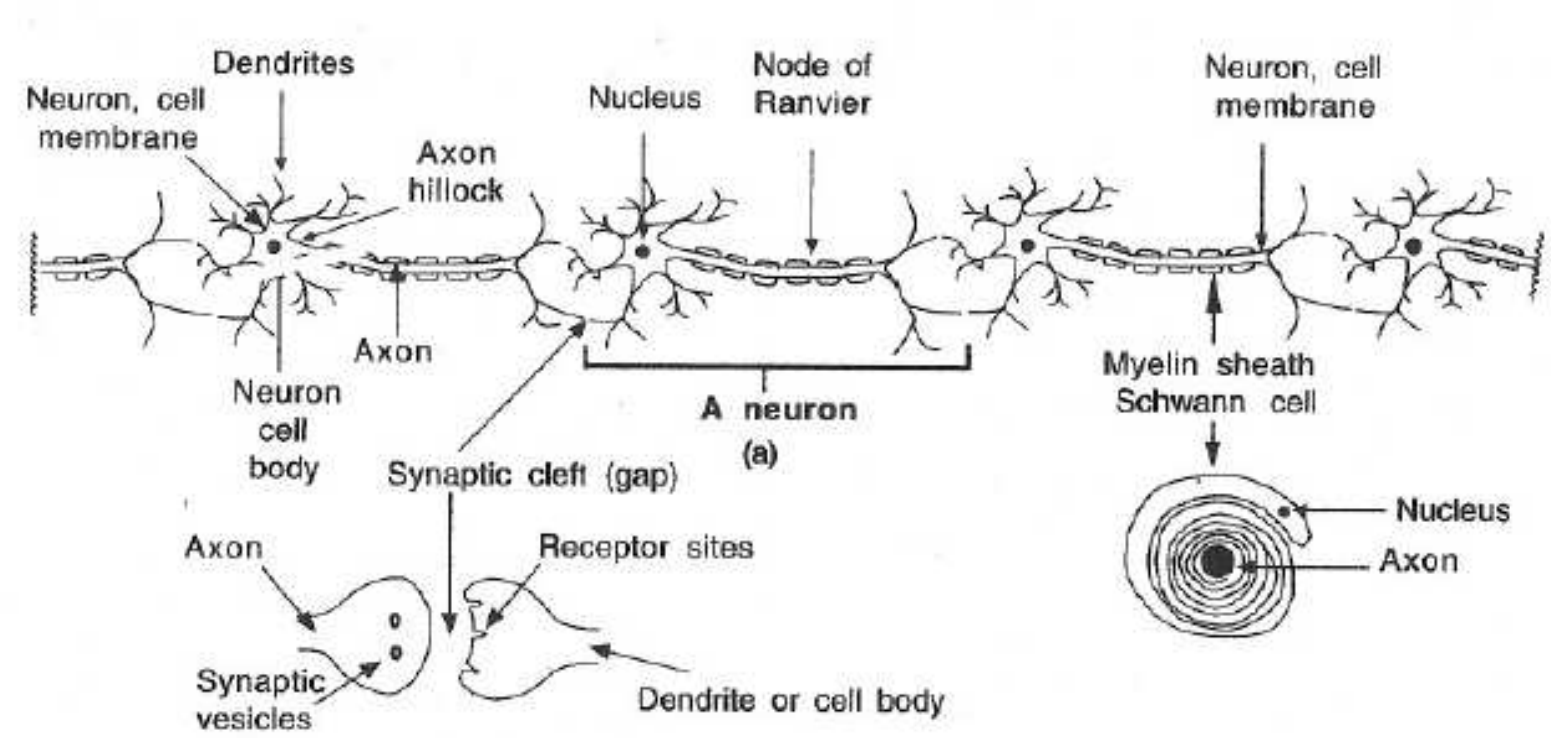


Figure 7.36 A schematic representation of a section of a nerve fibre. Nerve fibres consist of chains of cells known as neurons **(a)** where the axon of one neuron is separated from the end of either a dendrite or the cell body of a second neuron by the synaptic cleft or gap. The synaptic vesicles contain the chemical messengers (neurotransmitters) that transmit the nerve impulse by diffusing across the synaptic cleft to the receptors.

Drug Action on Cell Membranes and Walls

- Local anaesthetics

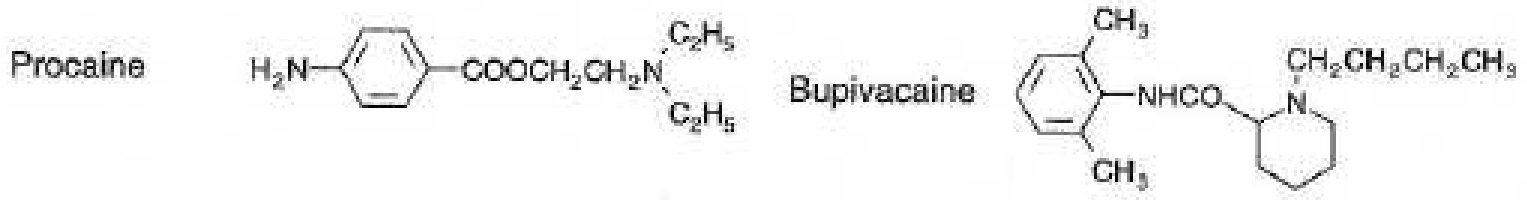


Figure 7.37 Examples of ester- and amide-based local anaesthetic agents in clinical use

mode of action: blocking the Na^+ channels

$$RN(R')_2 + H^+ \rightleftharpoons RNH(R')_2$$

- blocks external entry
- enters channel and acts as a stopper in the middle region
- binds to the (channel) proteins and distort them

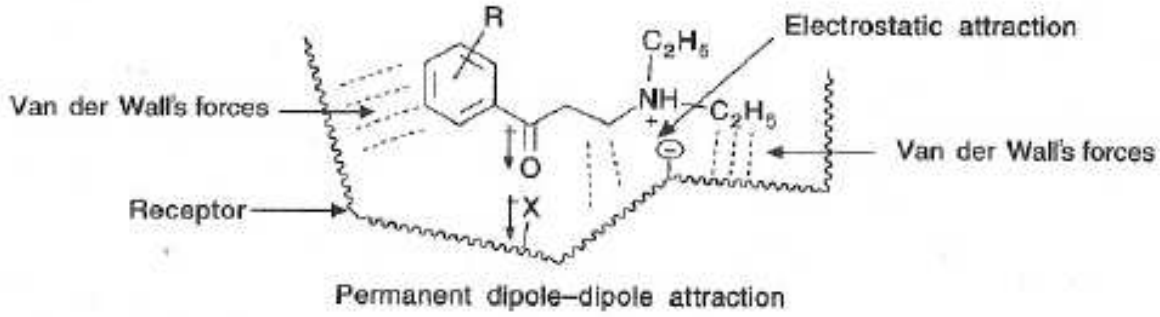


Figure 7.38 A schematic representation of the binding of ester-type local anaesthetic agents to a receptor site

Drug Action on Cell Membranes and Walls

- Local anaesthetics

mode of action:

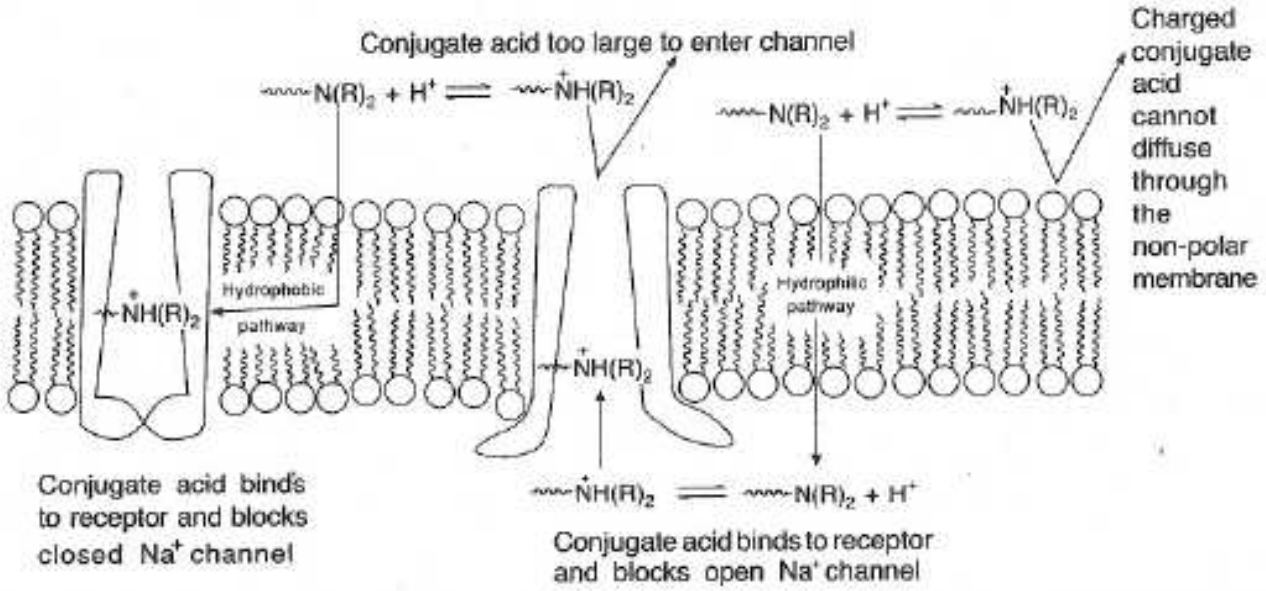


Figure 7.39 A representation of the hydrophobic and hydrophilic routes for blocking both open and closed ion Na^+ channels

SAR: