Antibiotics

Joel Goodman

STARS Minisymposium

March 6, 2006

Outline

- The spectrum of infectious agents and the global problem of human infections
- Classification of bacteria
- Intro to antibiotic classes, drug targets and resistance
- Three antibiotics in detail
  - Sulfonamides
  - Penicillin
  - Streptomycin

Statement by

Dr. David L. Heymann
Executive Director for Communicable Diseases
World Health Organization

Before the

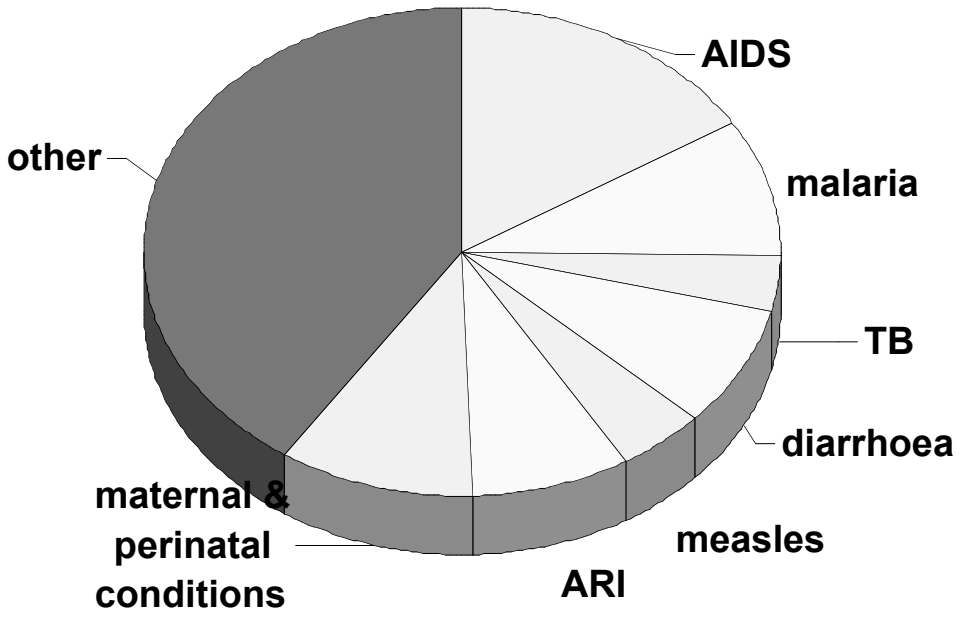
Committee on International Relations
U.S. House of Representatives

29 June 2000

"The Urgency of a Massive Effort Against Infectious Diseases"

Most deaths among young people in developing countries are caused by just a few illnesses

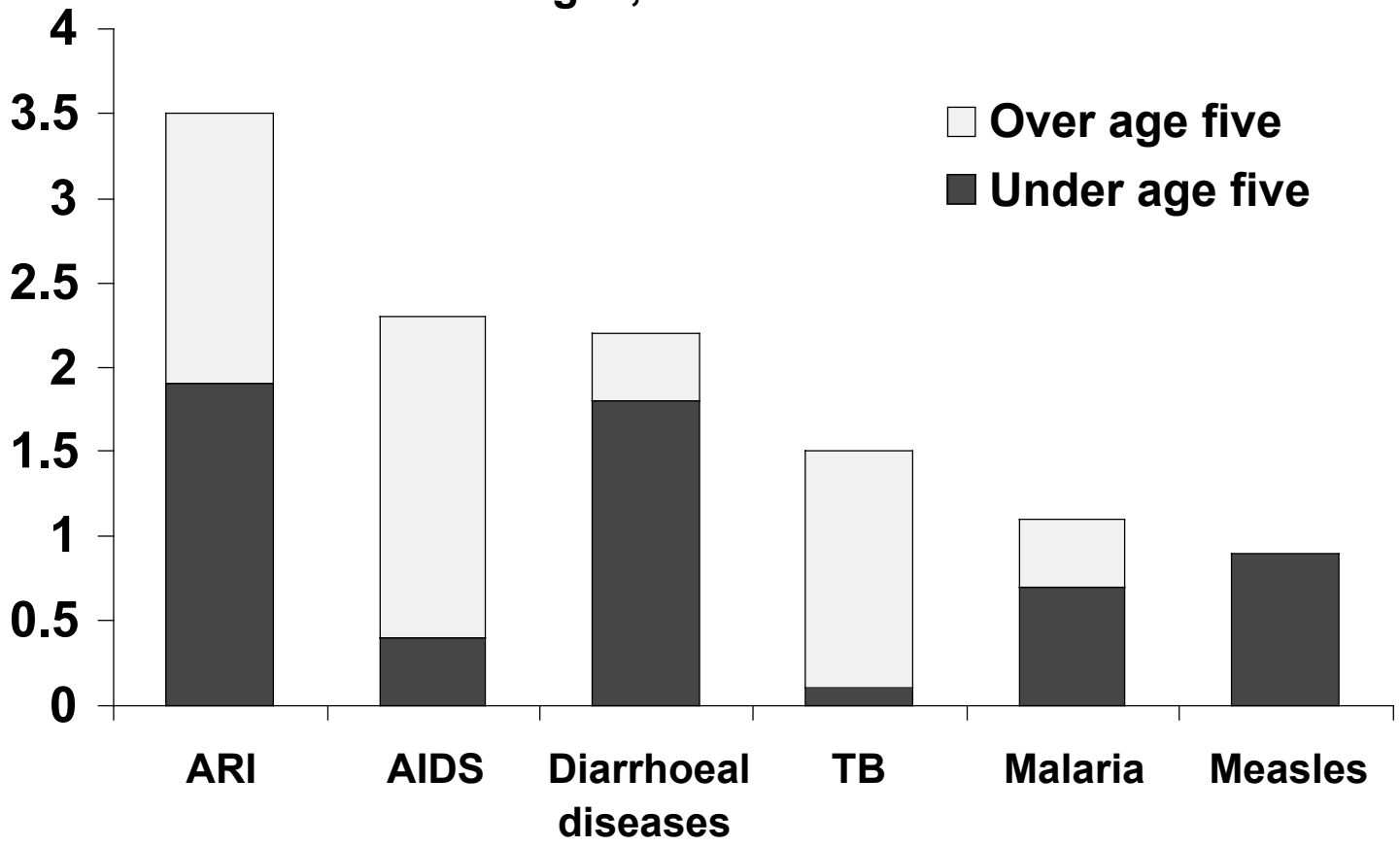
Ages 0 - 44 in South-East Asia and Africa



World Health Organization - CD

Leading Infectious Killers

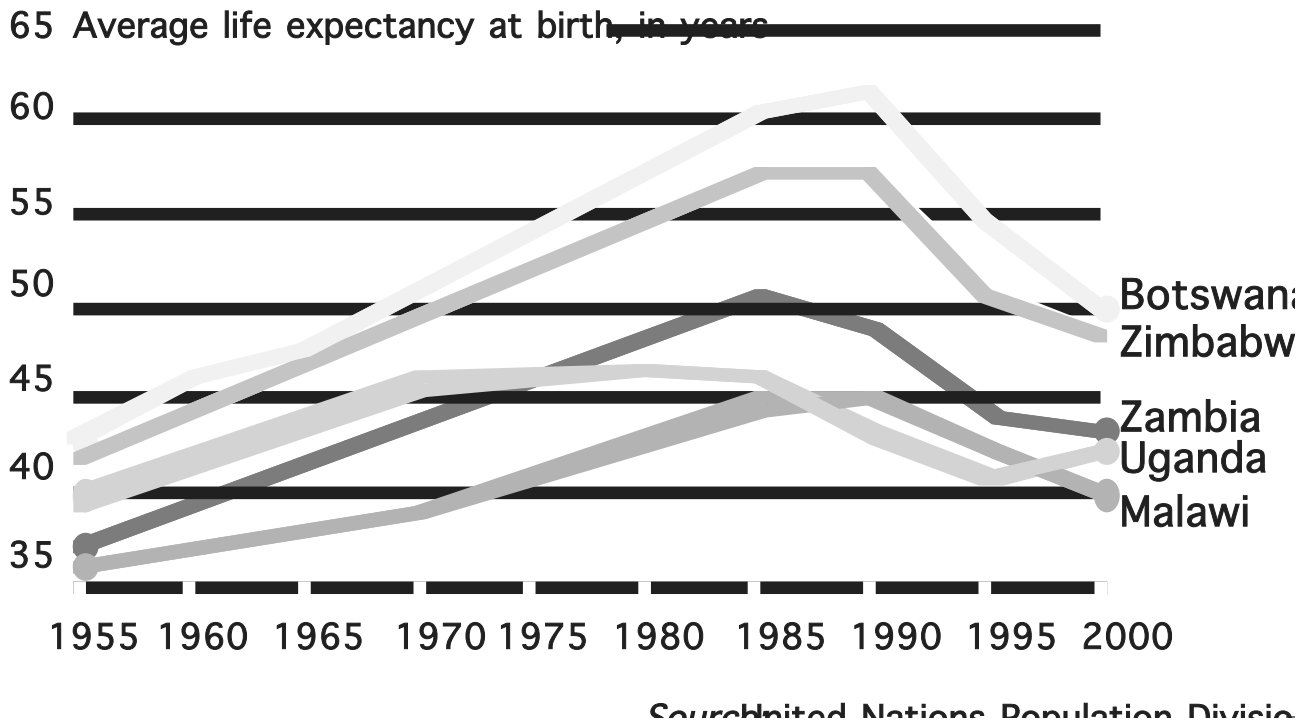
Millions of deaths, worldwide
All ages, 1998 estimate



World Health Organization - CD

Projected changes in life expectancy in African countries with high HIV preva

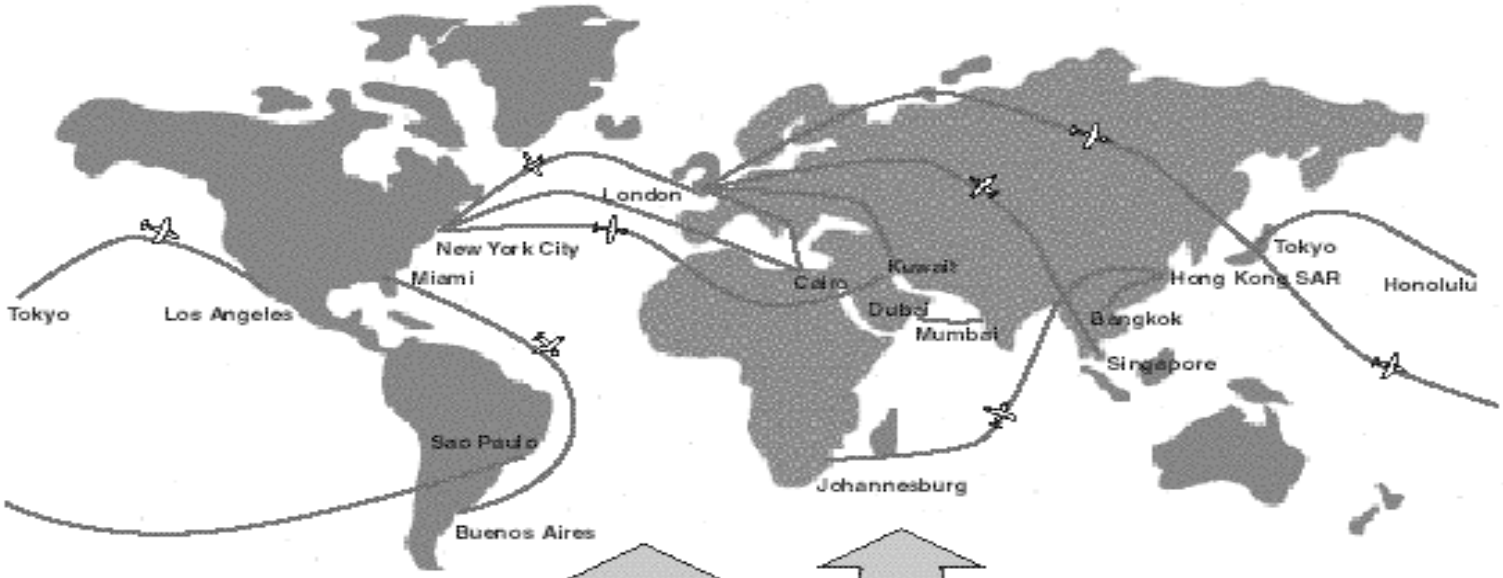
1995–2000

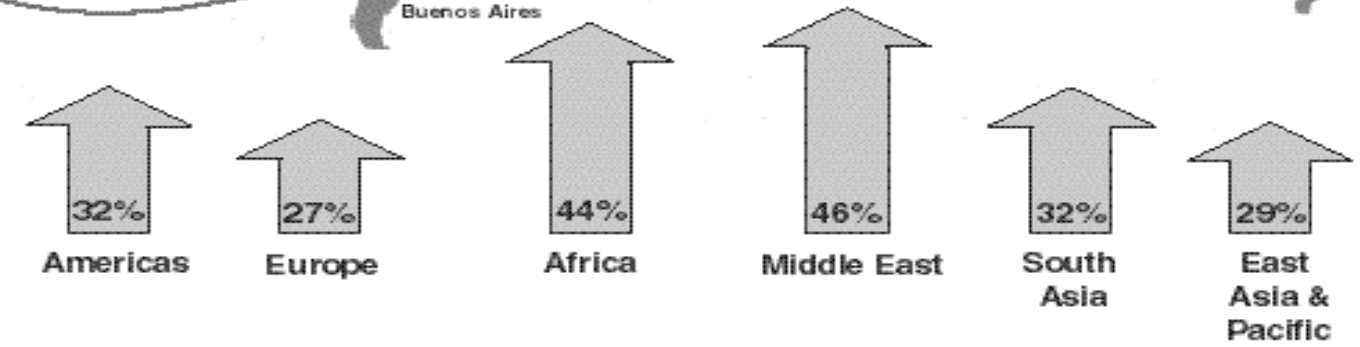


Source: United Nations Population Divisio

Frequent Flyers

Most Popular Air Routes Between Countries, 1997



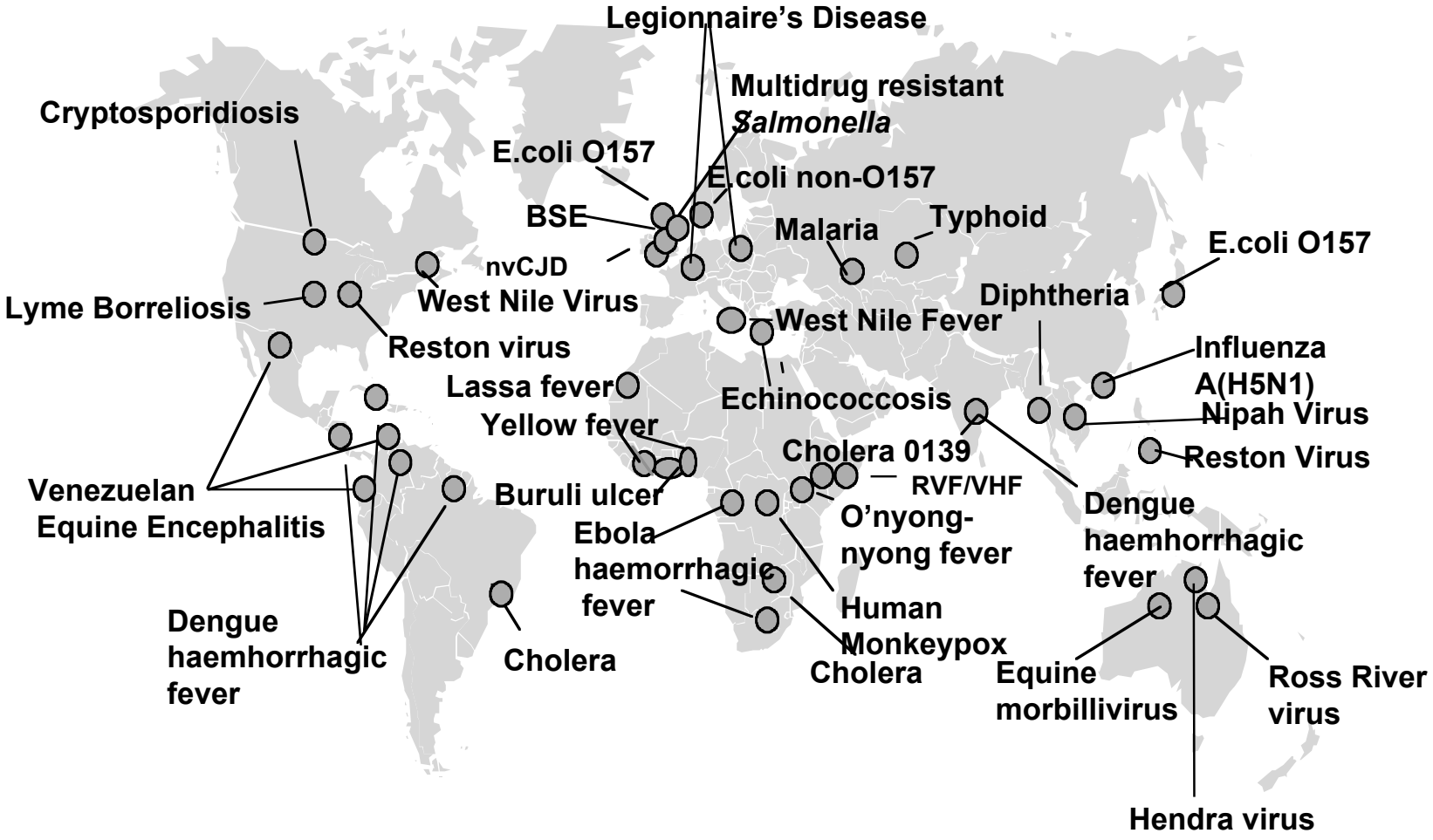


Percentage increase in international arrivals, 1993 to 1997

World Health Organization - CD

Emerging, re-emerging infectious diseases

1996 to 2000



World Health Organization - CD

Defending national borders

A strong defense must include protecting the population from microbial invaders

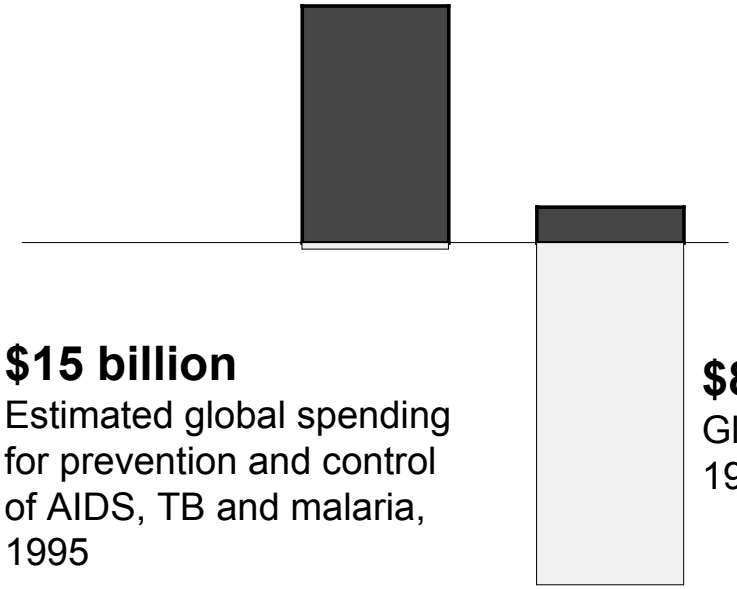
DISEASE

WAR

150 million deaths
From AIDS, TB and malaria since 1945

23 million deaths
Military and civilian from war 1945 -1993

DEATHS



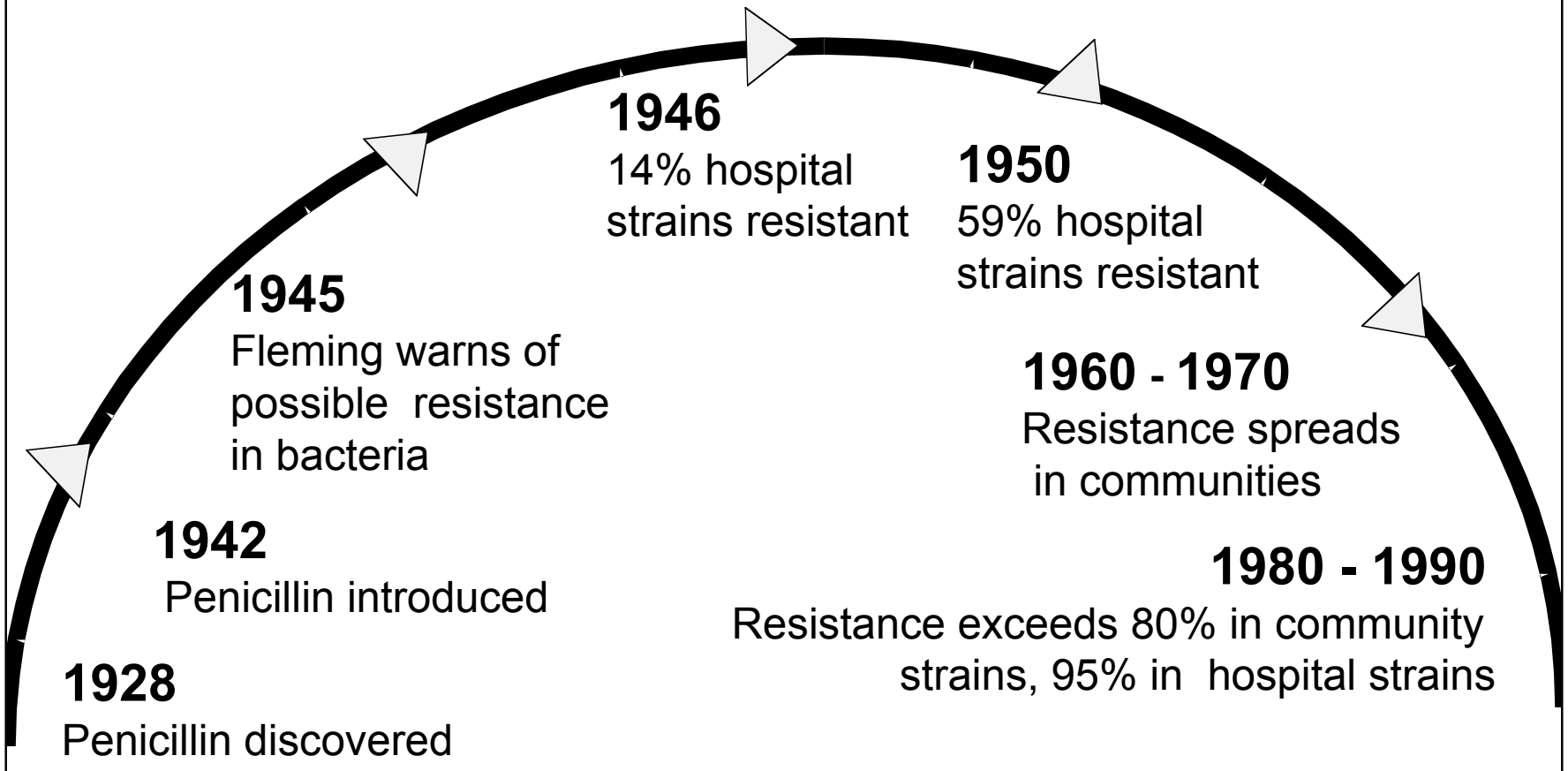
PREVENTION BUDGET

$15 billion
Estimated global spending for prevention and control of AIDS, TB and malaria, 1995

$864 billion
Global military spending, 1995

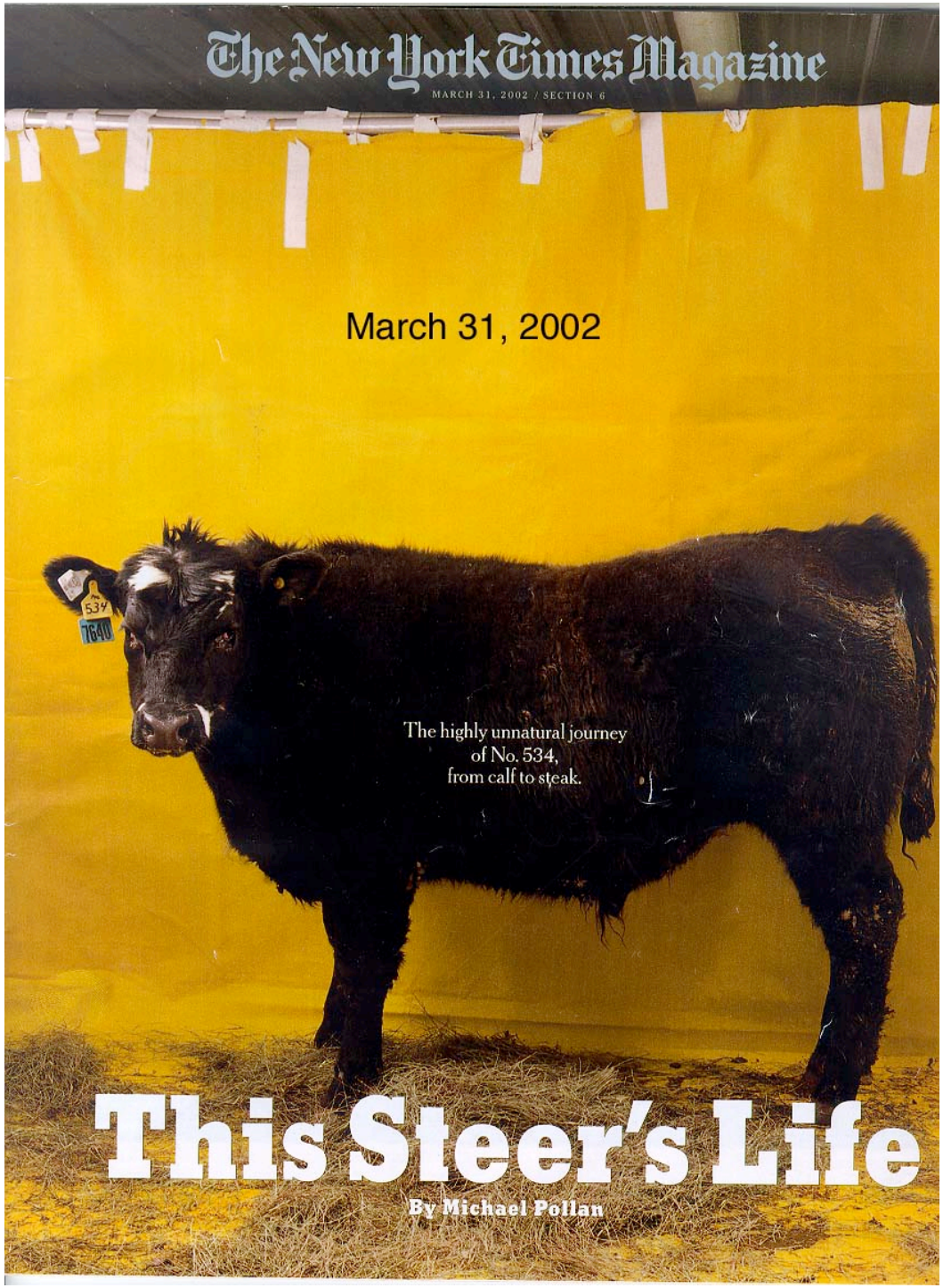
World Health Organization - CD

The Discovery and Loss of Penicillin in treating *Staphylococcus aureus*



World Health Organization - CD

"The highly unnatural journey of No. 534, from calf to steak"



Cows rarely live on feedlot diets for more than six months, which might be about as much as their digestive systems can tolerate. "I don't know how long you could feed this ration before you'd see problems," Metzen said; another vet said that a sustained feedlot diet would eventually "blow out their livers" and kill them. As the acids eat away at the rumen wall, bacteria enter the bloodstream and collect in the liver. More than 13 percent of feedlot cattle are found at slaughter to have abscessed livers.

What keeps a feedlot animal healthy — or healthy enough — are antibiotics. Rumensin inhibits gas production in the rumen, helping to prevent bloat; tylosin reduces the incidence of liver infection. Most of the antibiotics sold in America end up in animal feed — a practice that, it is now generally acknowledged, leads directly to the evolution of new antibiotic-resistant "superbugs." In the debate over the use of antibiotics in agriculture, a distinction is usually made between clinical and nonclinical uses. Public-health advocates don't object to treating sick animals with antibiotics; they just don't want to see the drugs lose their efficacy because factory farms are feeding them to healthy animals to promote growth. But the use of antibiotics in feedlot cattle confounds this distinction. Here the drugs are plainly being used to treat sick animals, yet the animals probably wouldn't be sick if not for what we feed them.

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last thir

New York Times Magazine, March 31, 2002, p51

I asked Metzen what would happen if antibiotics were banned from cattle feed. "We just couldn't feed them as hard," he said. "Or we'd have a higher death loss." (Less than 3 percent of cattle die on the feedlot.) The price of beef would rise, he said, since the whole system would have to slow down.

"Hell, if you gave them lots of grass and space," he concluded dryly, "I wouldn't have a job."

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"Tylosin is a macrolide, bacteriostatic antibiotic. It is similar in structure, mechanism of action, and spectrum as that of erythromycin" www.kuddlykorner4u.com

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last thir

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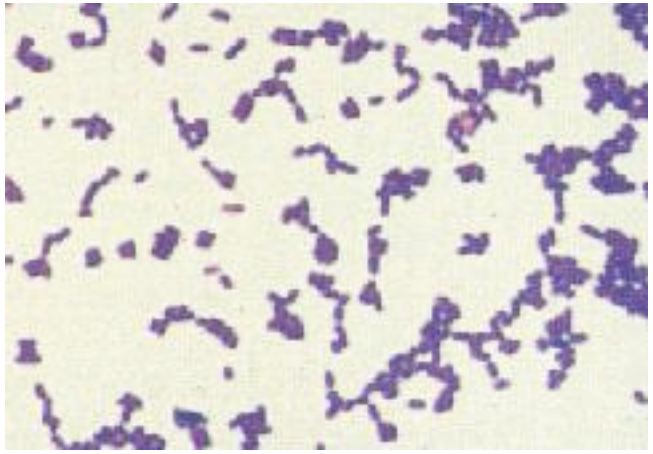
Drug Resistance *ca. 2006*

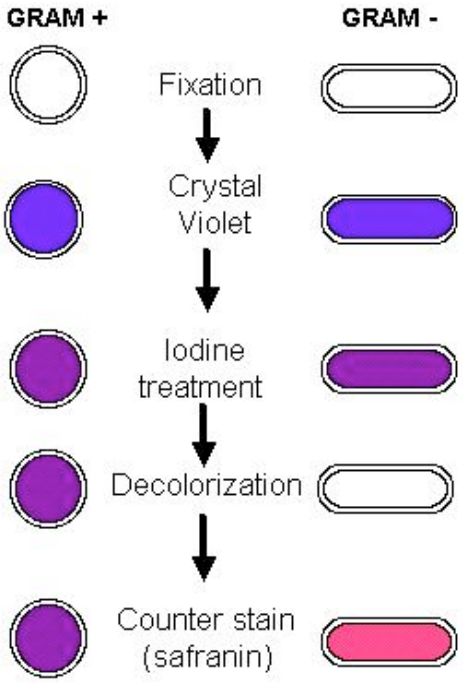
- Half the time, prescriptions for antibiotics are inappropriate. Antibiotic use promotes outgrowth of resistant organisms!
- Antibiotics in cattle feeds account for ~ 50% of use; cross-resistance occurs. Antibiotics are ubiquitous in the environment.
- Until very recently, no classes of antimicrobial drugs have been developed since 1970. Big Pharma is reluctant to get involved! Resistance has developed to ALL these classes of antibiotics.

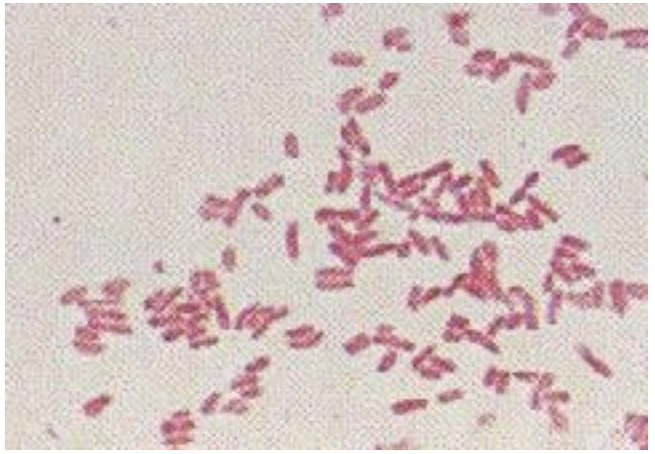
Classes of Bacteria

Classes of Bacteria

- Gram stain distinguishes two classes



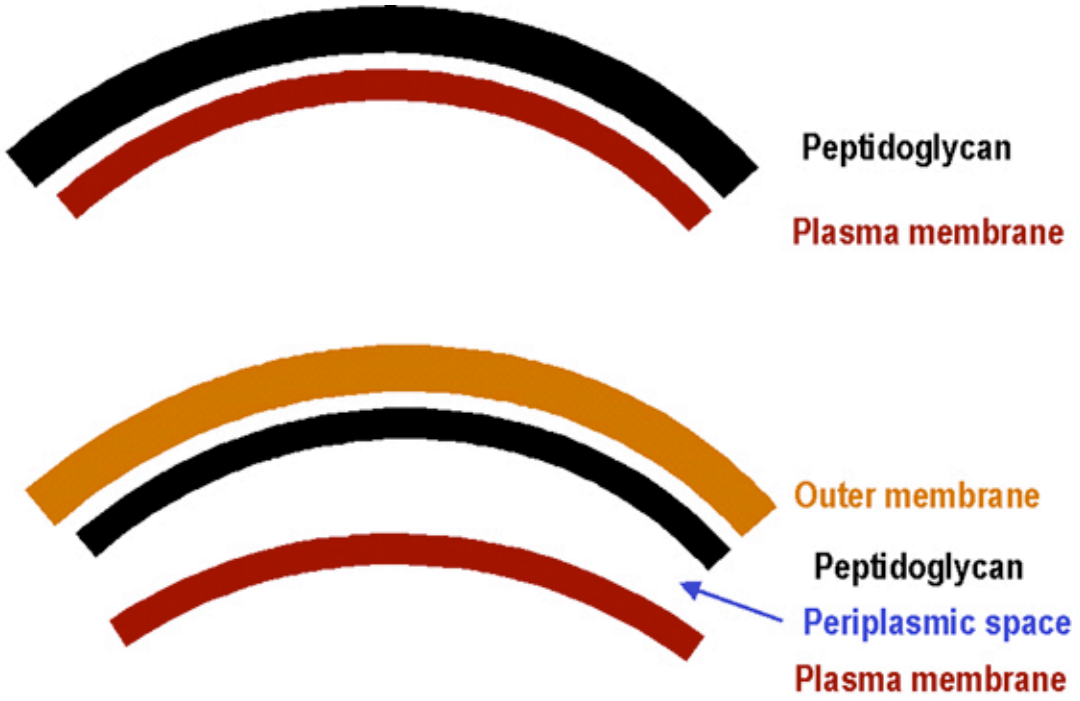




www.meddean.luc.edu/lumen/DeptWebs/microbio/med/gram/tech.htm

Gram stain stains cell wall

- Gram positive bacteria have exposed cell wall (peptidoglycan)
- Gram negative bacteria have an outer membrane that surrounds the cell wall



http://pathmicro.med.sc.edu/fox/bact-mem.jpg

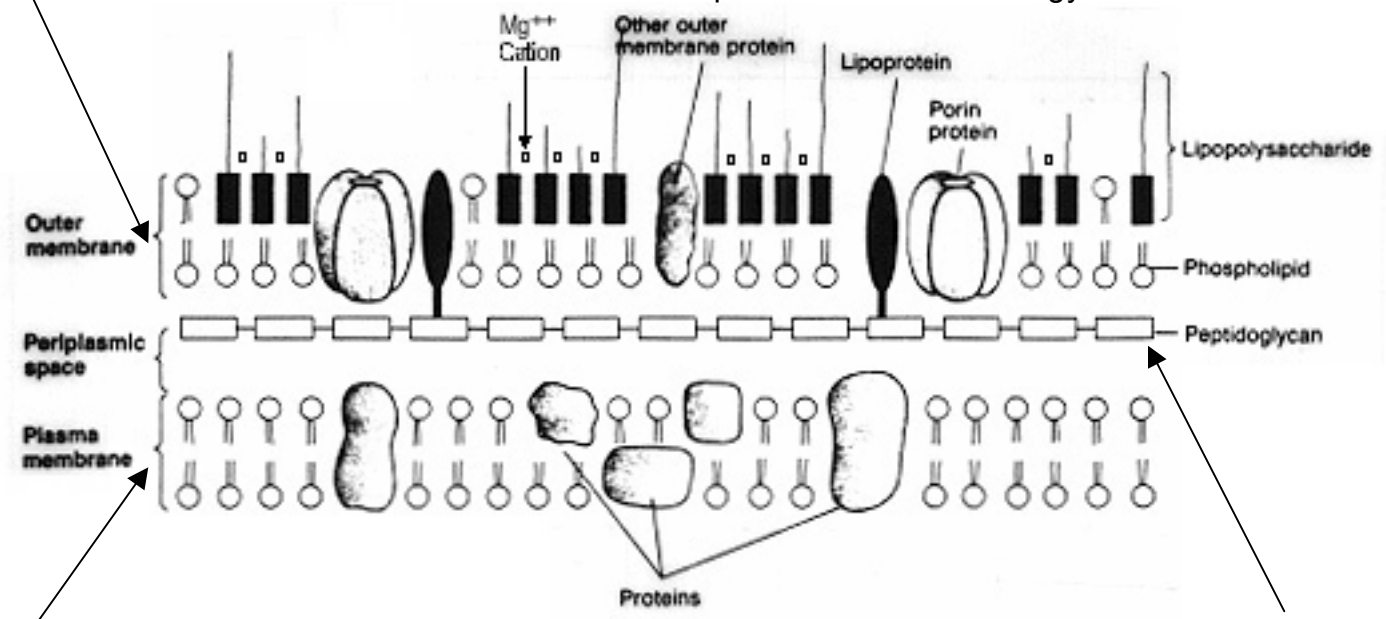
Function of envelope

Protects cells from toxic substances

Keeps important proteins concentrated in periplasm

http://textbookofbacteriology.net/structure.html

http://pathmicro.med.sc.edu/fo



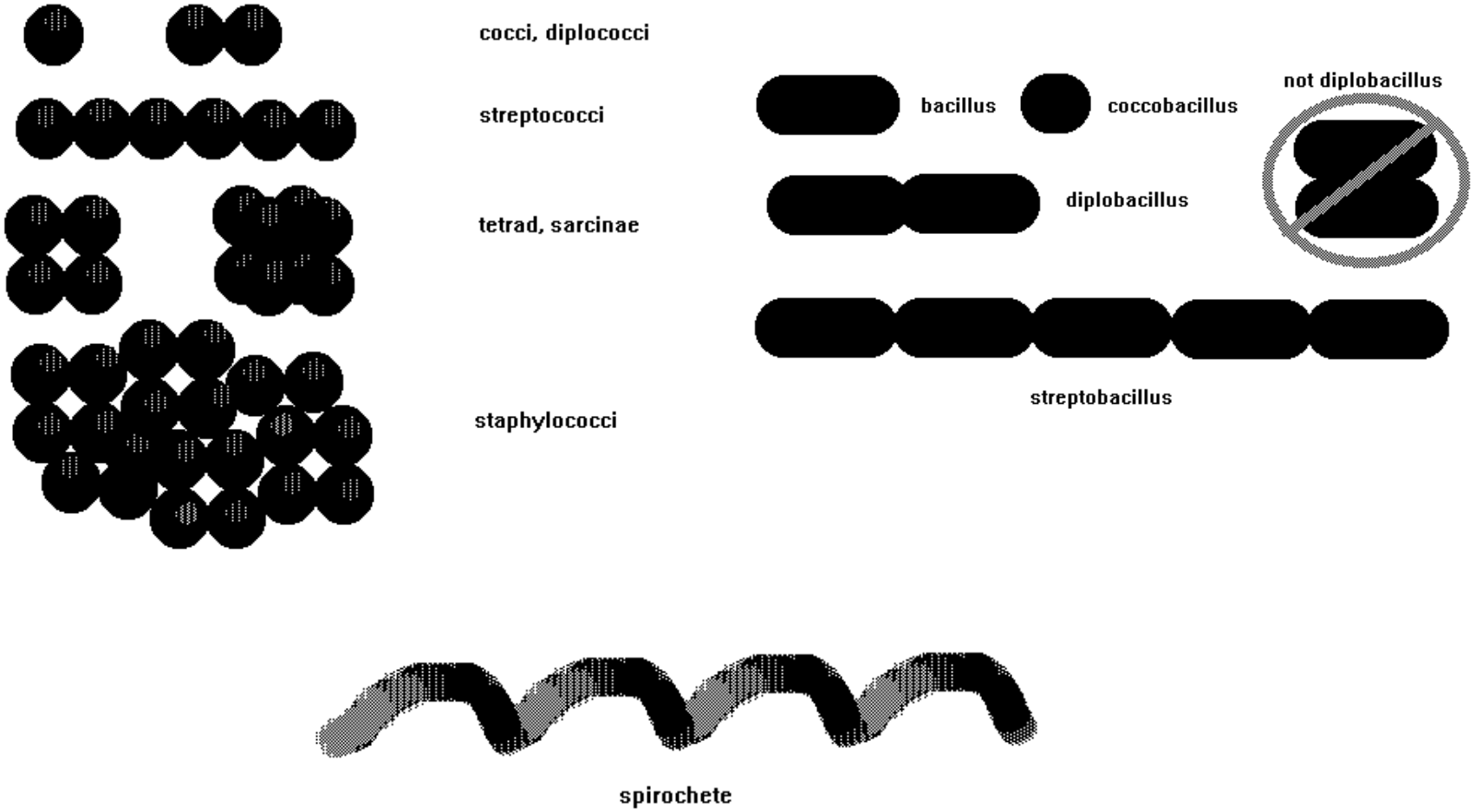
Maintains integrity of cytoplasm

Generates a proton gradient and ATP

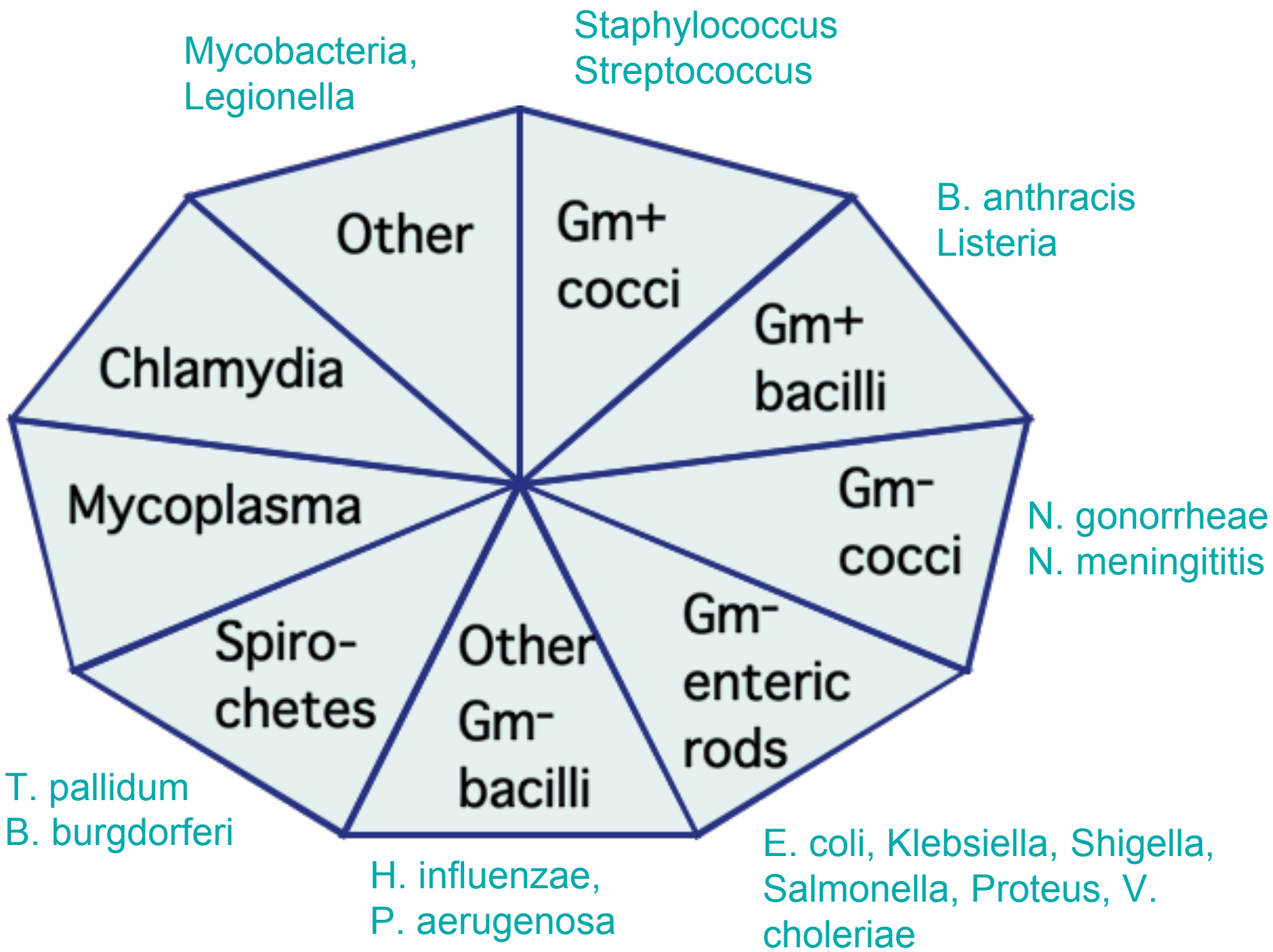
Osmoprotection

Maintains cell shape

Shapes of Bacteria



http://www.mansfield.ohio-state.edu/~sabedon/biol2010.htm


Mycobacteria,
Legionella
Staphylococcus
Streptococcus
B. anthracis
Listeria
N. gonorrheae
N. meningititis
T. pallidum
B. burgdorferi
H. influenzae,
P. aerugenosa
E. coli, Klebsiella, Shigella,
Salmonella, Proteus, V.
choleriae
Other
Gm+
cocci
Gm+
bacilli
Gm-
cocci
Gm-
enteric
rods
Other
Gm-
bacilli
Spiro-
chetes
Mycoplasma
Chlamydia

How do you treat all these bugs??

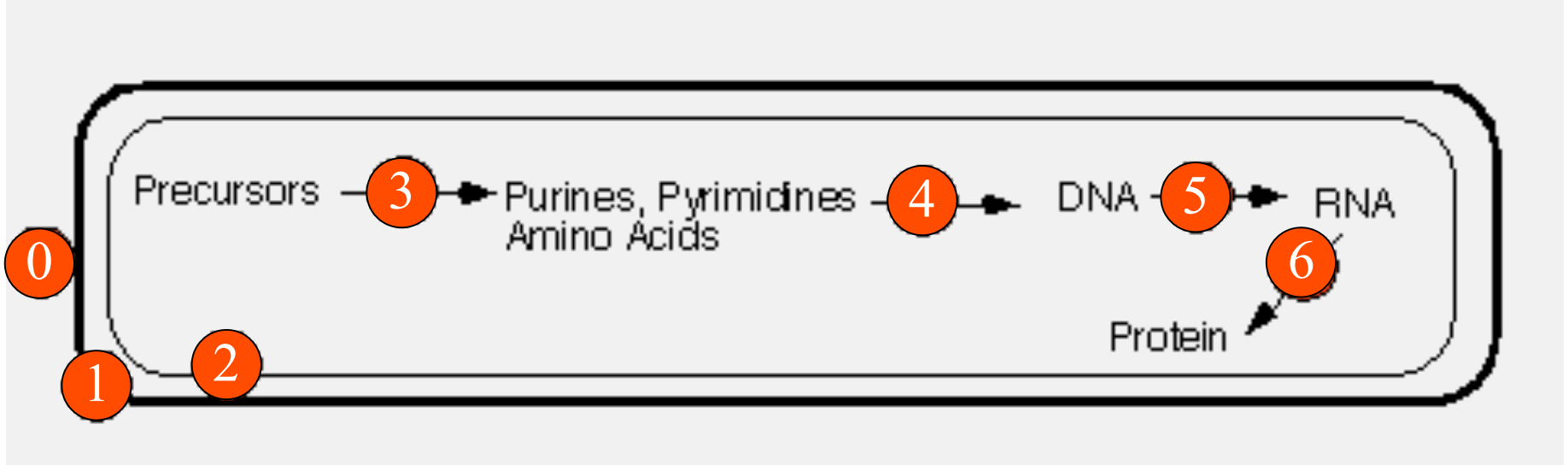
Dawn of the Antibiotic Age

- 1870s - Robert Koch - discovered the anthrax bacterium.
- 1877 - Louis Pasteur - discovered that common bacteria can prevent anthrax from growing in culture.
- 1890s - Paul Ehrlich - chemicals can be “magic bullets”. Development of Salvarsan.
- 1908 - Paul Gelmo - textile azo dyes can kill bacteria; led to sulfonamides in 1930s.
- 1928 - Alexander Fleming - discovery of penicillin. First patient cured in 1941.

Sites of Drug Action (1)

1. Cell wall: Beta-lactams (Penicillins, Cephalosporins), Glycopeptides, Bacitracin
2. Plasma membrane: Daptomycin
3. C_1 transfer: Sulfonamides, Trimethoprim (Bactrim)

Sites of Action (2)



4 DNA synthesis: Fluoroquinolones (ex. Ciprofloxacin)

5 RNA synthesis: Rifampin, fluoroquinolones

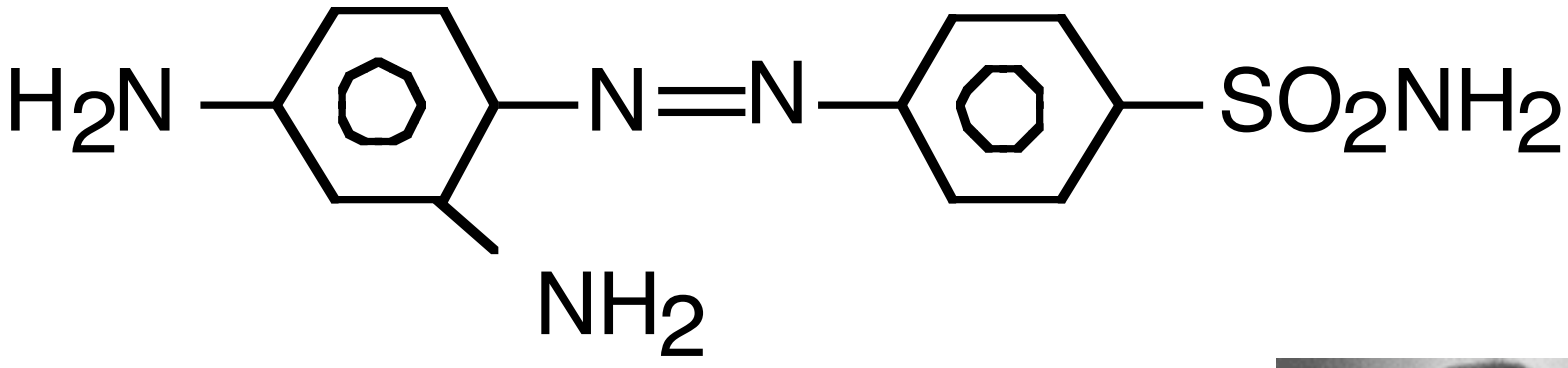
6 Translation: Aminoglycosides (ex. streptomycin), Tetracyclines, Chloramphenicol, MLSK drugs, Linezolid, Streptogramins

Sulfonamides

IG Farbenindustrie AG
~1940

http://www.us-israel.org/jsource/Holocaust/farben.html

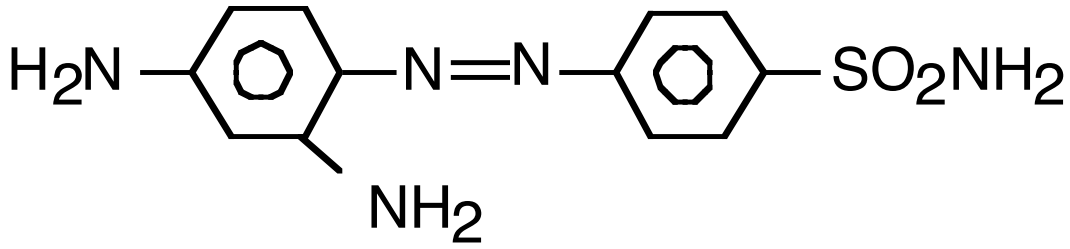
Prontosil



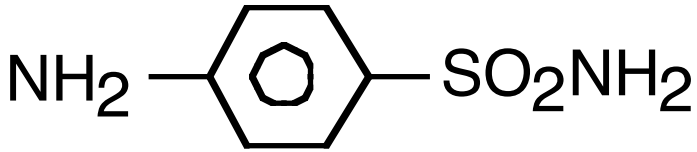
Gerhard
Domagk

Sulfanilamide, the active drug

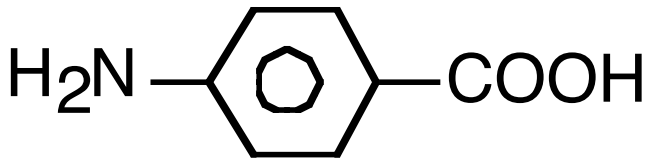
Prontosil



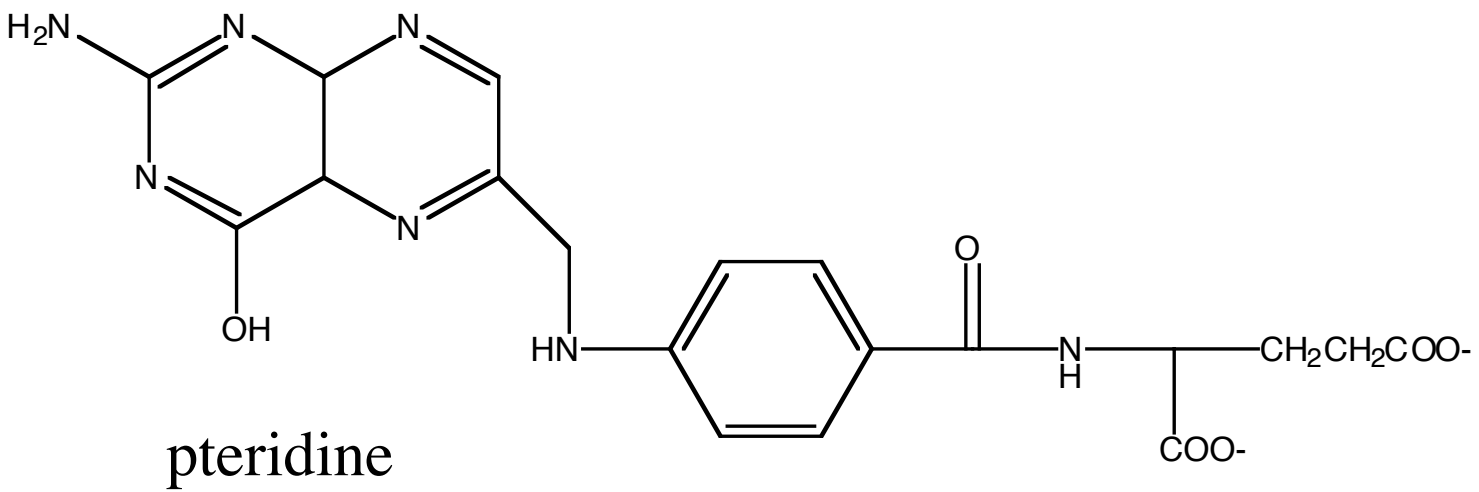
Sulfanilamide



Para-aminobenzoic acid
(*p*ABA)



Folic Acid



pteridine

p-aminobenzoic acid

glutamate

Folic acid carries methyls for. .

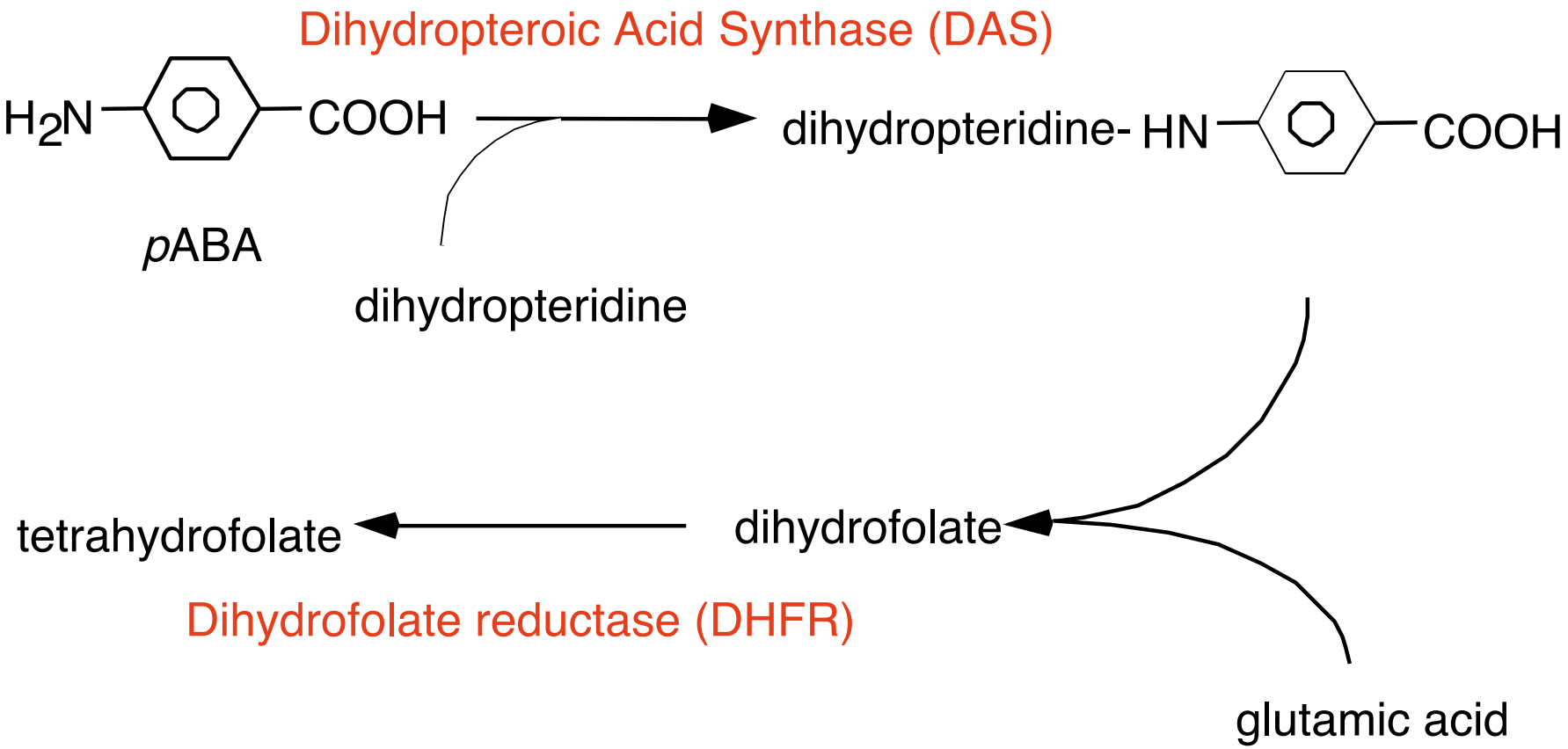
- Purine biosynthesis
  - C2 and C8 carbons are delivered by THF
- Thymidylate synthesis
  - Catalyzed by thymidylate synthetase
- Amino acid synthesis
  - Serine (from glycine)
  - Methionine (from homocysteine)

We can import folic acid.

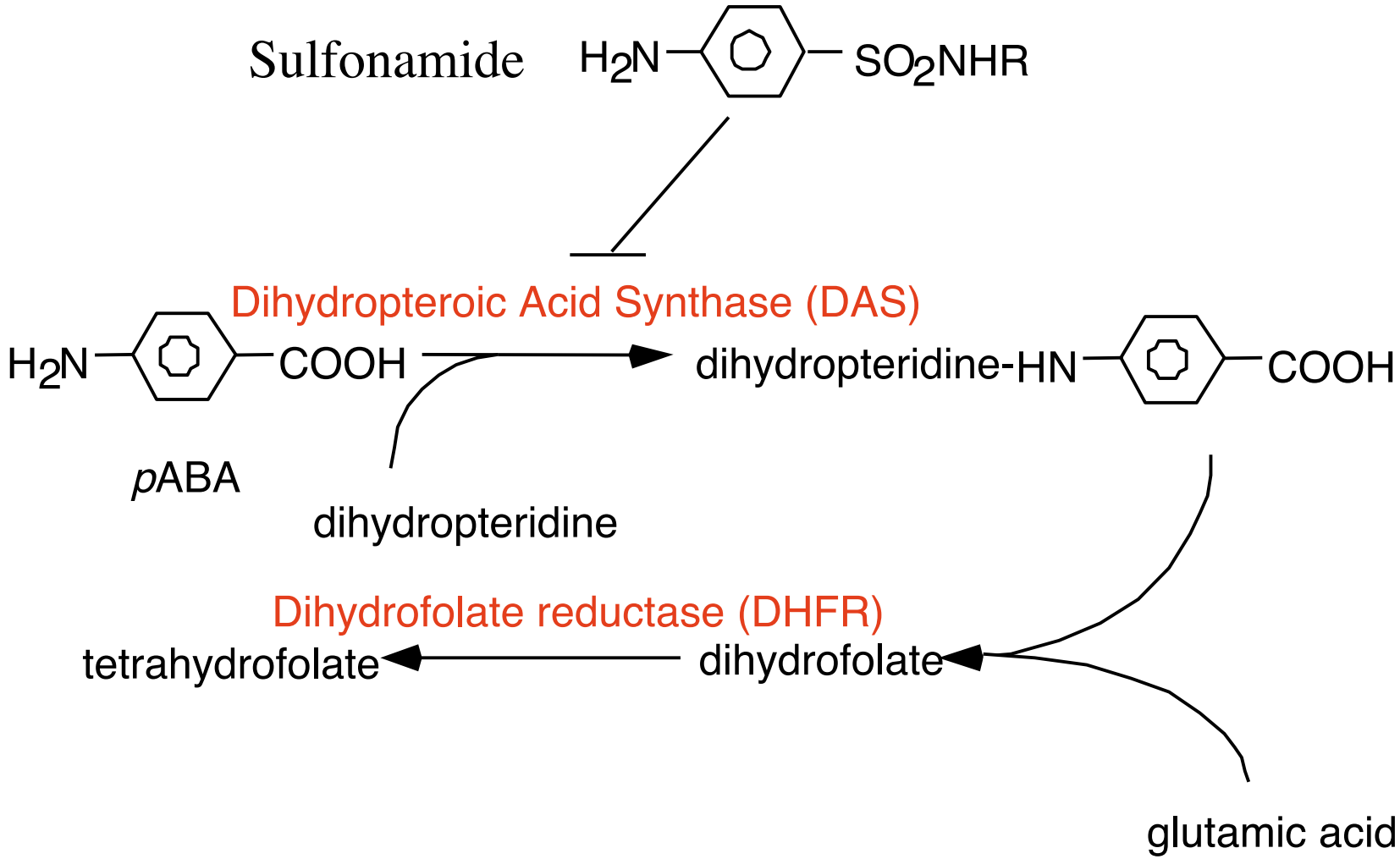
Many bacteria cannot. . .

They must synthesize it.

Folate synthesis (bacteria)



Sulfonamides are Competitive Inhibitors of DAS



Selective action of sulfa

- Mammals cannot make folic acid; they must import it. We do not possess DAS, the drug target. Instead we have a folic acid transporter.
- Bacteria cannot import folic acid (no transporter); they must synthesize it.

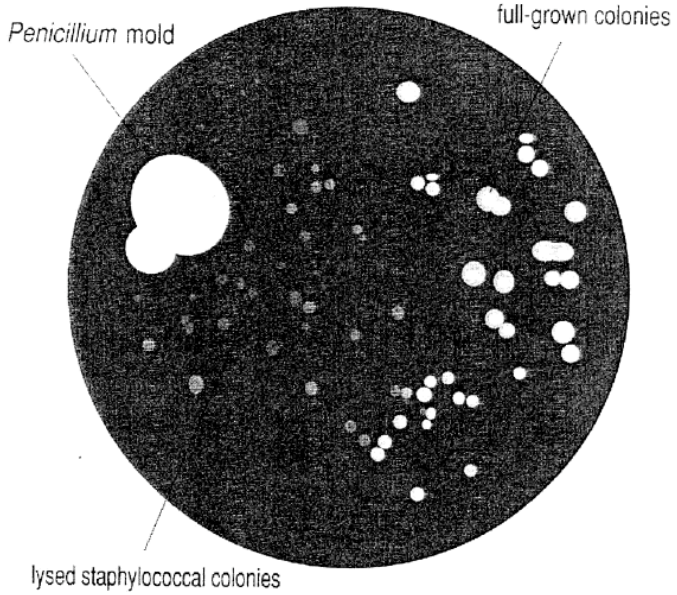
Sulfa facts

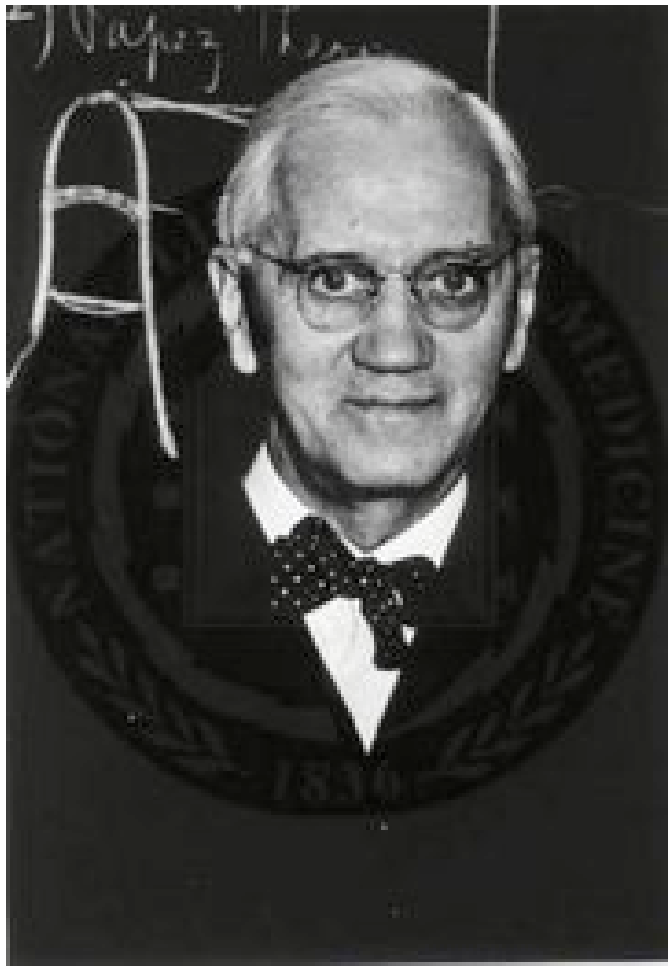
- Usually administered as a combination of sulfamethoxazole and trimethoprim (Bactrim)
- Broad spectrum, but bacteriostatic
- Usually safe, but many suffer GI distress or rashes
- Commonly used for urinary tract infections

Beta-lactams

History

- Fleming discovered penicillin (1928)





History

- Fleming discovered penicillin (1928)
- Florey, Chain and Abraham isolated it and determined structure (1940)
- First cure in human (1941)
- Critically important on the field in WWII
- Park & Strominger deduced mechanism (1965)

The Oxford Group

Ernst Chain
1906-1979

Howard Walter Florey
1898-1968

Dorothy Hodgkin
1910-1994

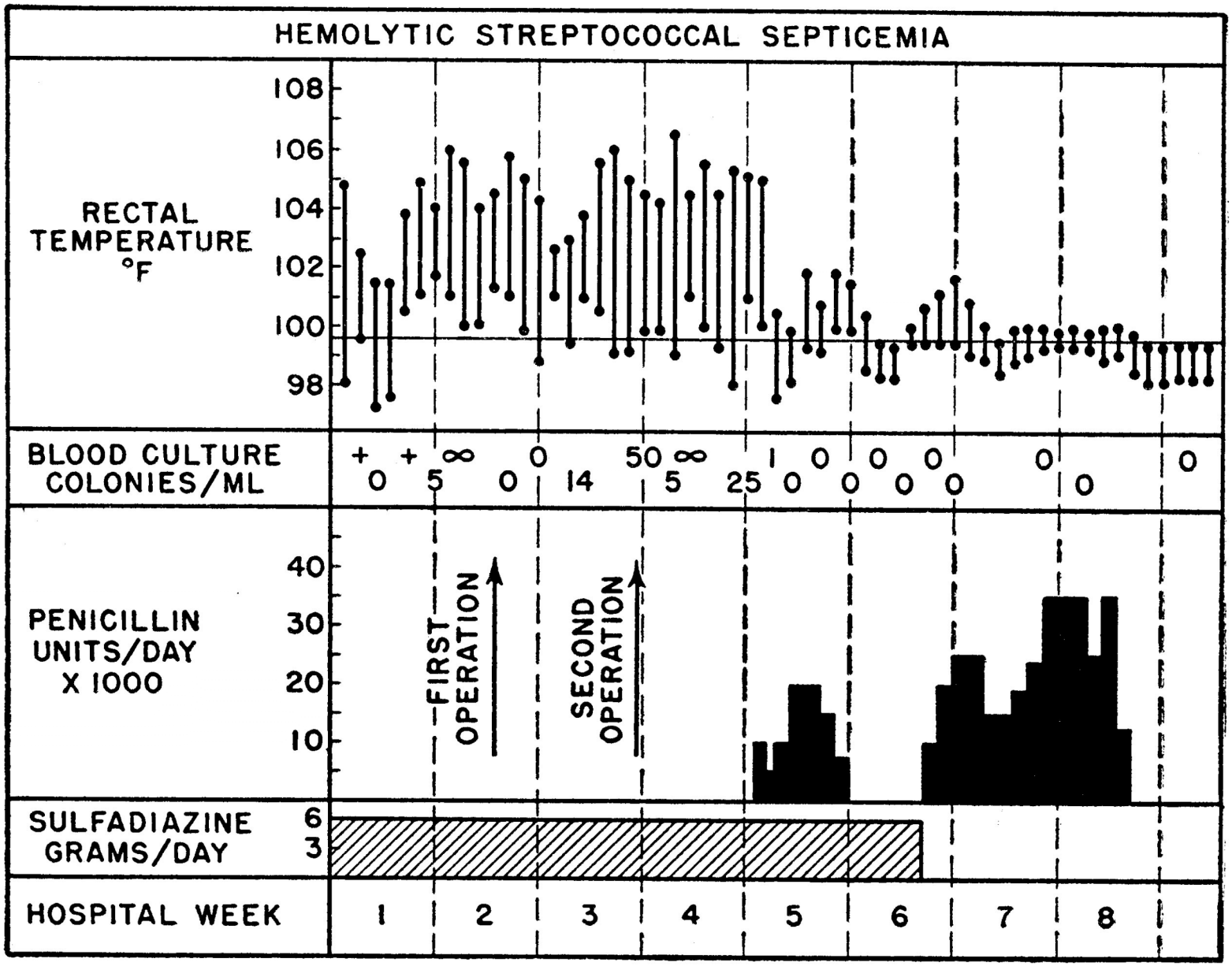
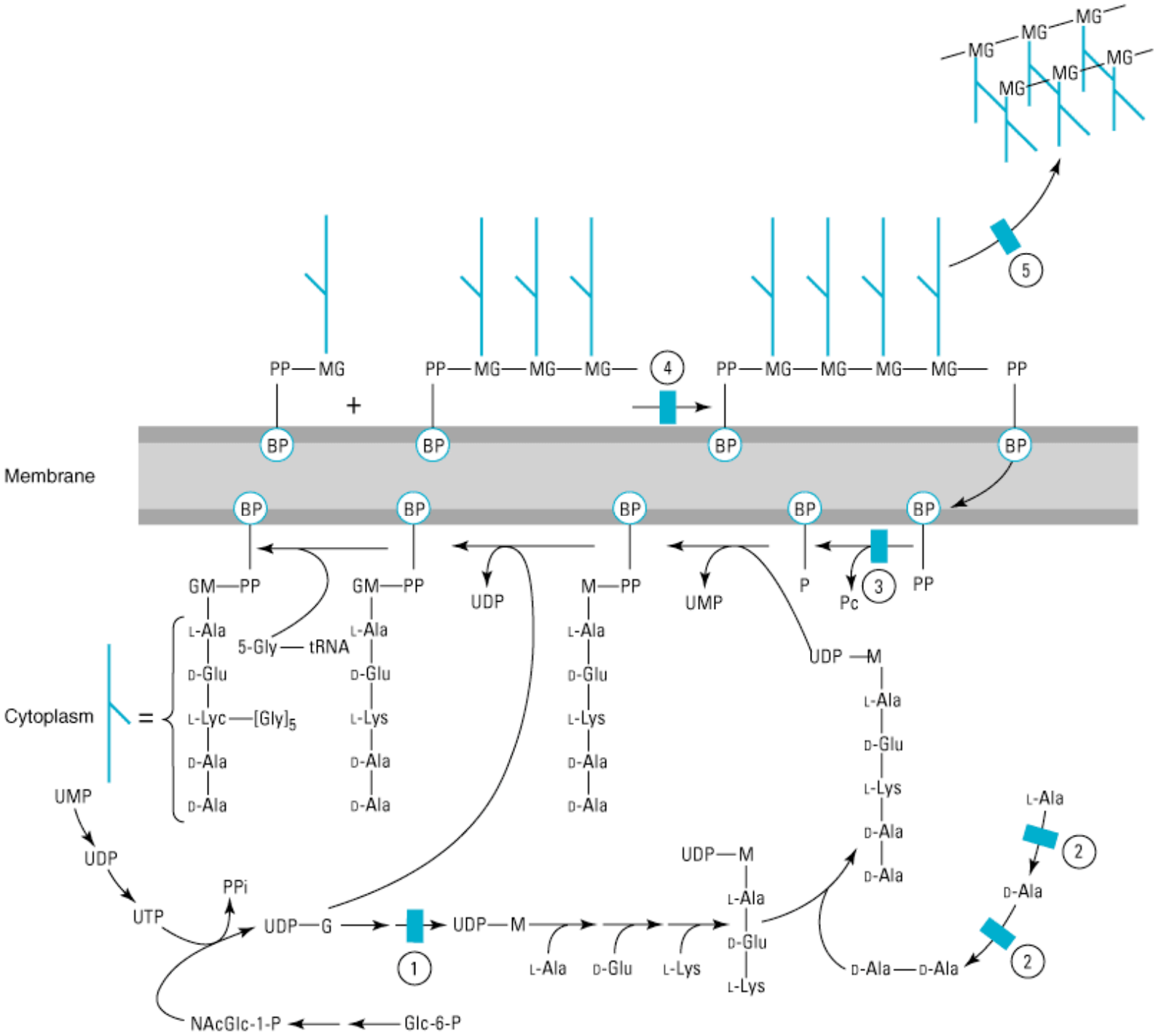


Figure 74. *First clinical trial of penicillin in the United States: penicillin therapy of β-hemolytic streptococcal septicemia.*

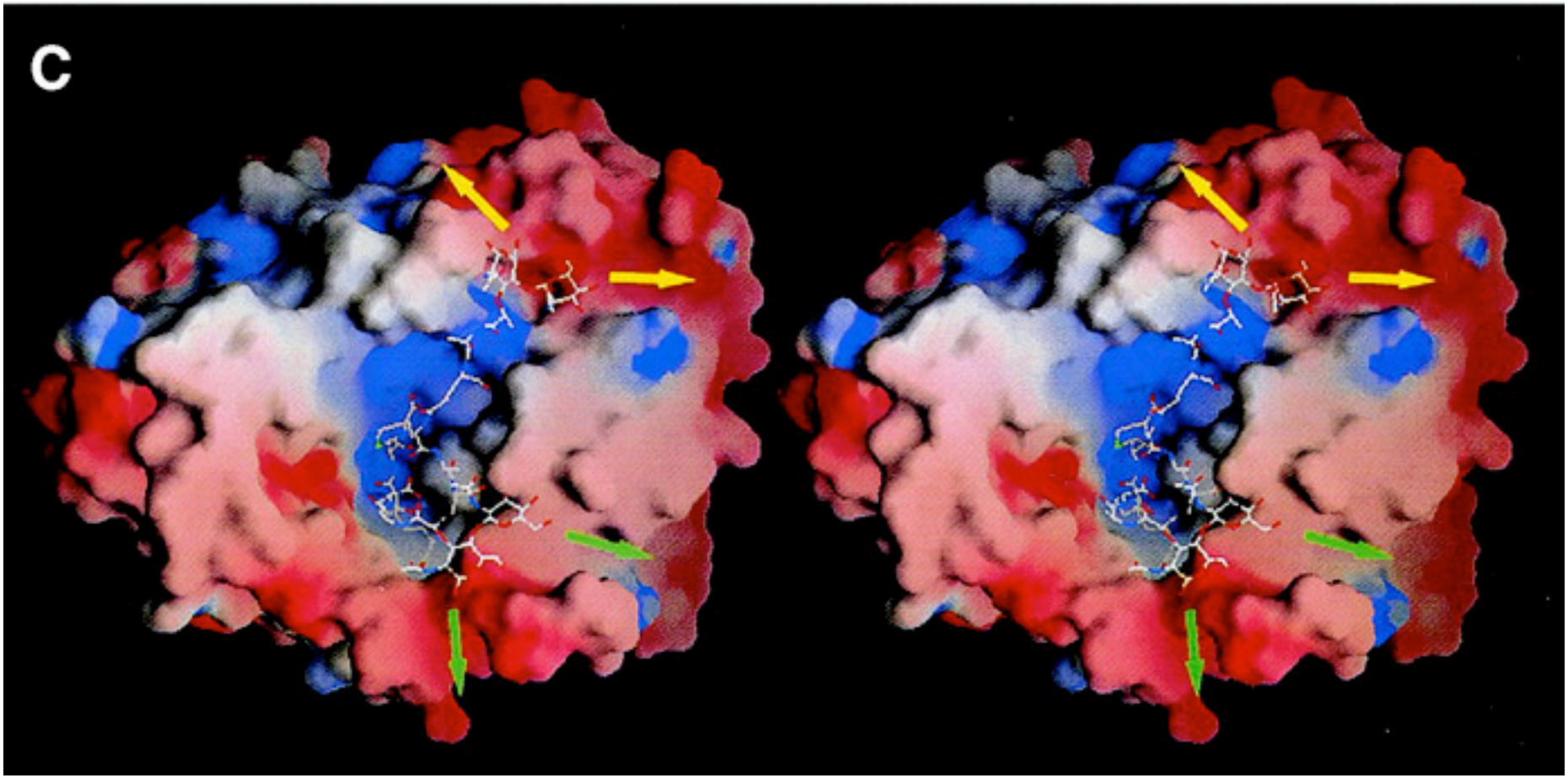
Goodman and Gilman, 2nd ed. (1955)



The biosynthesis of cell wall peptidoglycan, showing the sites of action of five antibiotics (shaded bars; 1 = fosfomycin, 2 = cycloserine, 3 = bacitracin, 4 = vancomycin, 5 = β-lactam antibiotics). Bactoprenol (BP) is the lipid membrane carrier that transports building blocks across the cytoplasmic membrane; M = N-acetylmuramic acid; Glc = glucose; NAcGlc or G = N-acetylglucosamine .

Katzung, 9th ed.

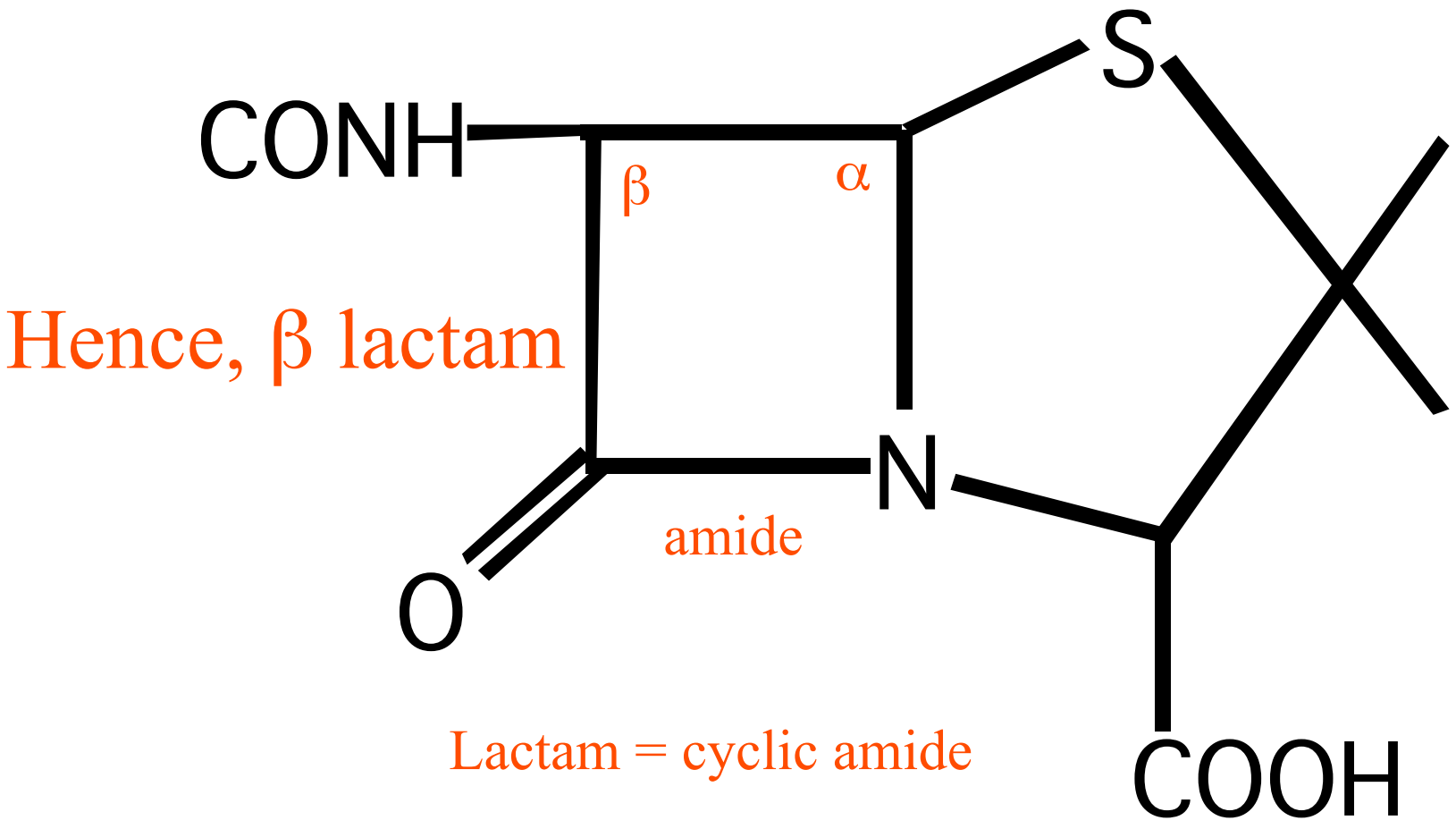
Grooves in carboxypeptidase/transpeptidase, complexed with Cephalosporin I



Green - first strand
Yellow, second strand

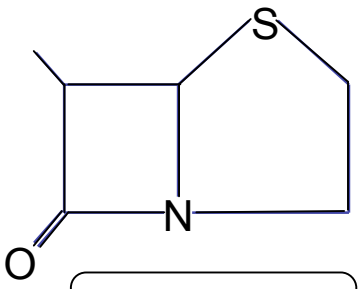
Lee et al., (2001) :PNAS
98:1427

Penicillin Structure

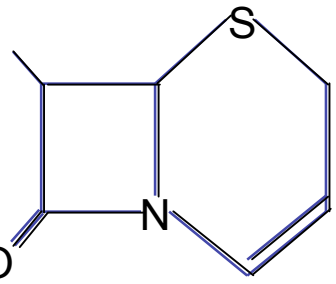


Classes of β-lactams

PenG
Ampicillin
Ticarcillin
Pipericillin



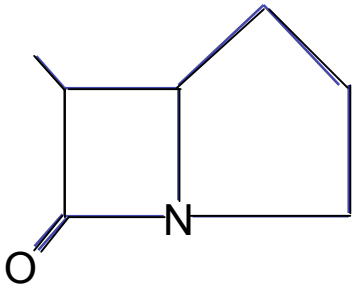
Penicillins



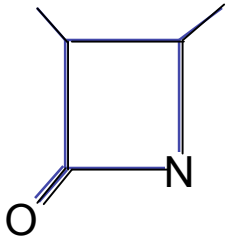
Cephalosporins

Cephalothin
Cefaclor
Ceftriaxone
Cefepime

Imipenem



Carbapenems



Monobactams

Aztreonam

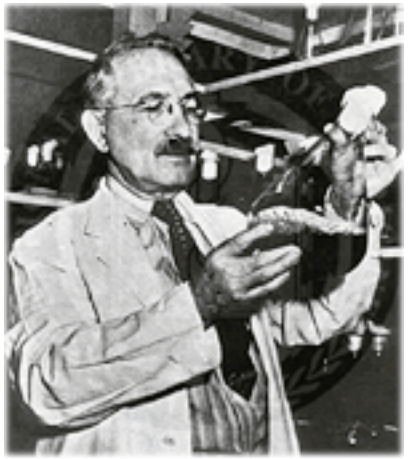
Penicillin and other beta-lactams

- Very active against gram positive organisms (MICs as low as 0.01 μg/ml)
- Inhibits crosslinking of the peptidoglycan
- Releases autolysins -> cell death
- Side effects: ALLERGY!!
- Resistance: bacteria make beta lactamases, which destroy penicillin

Ribosome Binders

- 30S binders
  - Aminoglycosides
  - Tetracyclines
- 50S binders
  - MLSK family
    - Macrolides
    - Lincosamides
    - Streptogramins
    - Ketolides
  - Chloramphenicol
- Linezolid (binds both subunits)

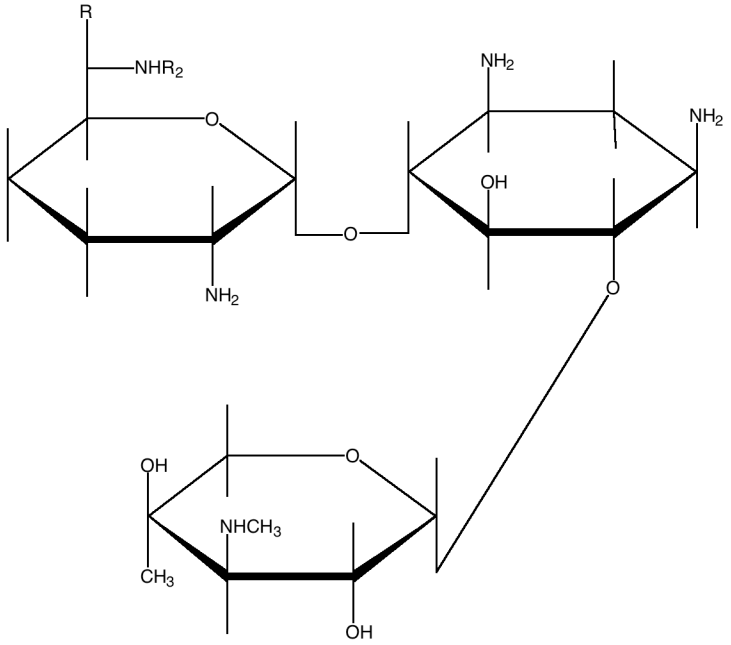
René Dubos



Selman Waksman

Aminoglycosides

Gentamycin C



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A NEW PARADIGM FOR MASSAGE BASED ON SUBTLE ENERGY AND QUANTUM SCIENCE

PART 1: SUBTLE ENERGY

Albert Schatz and Mary Brewster

Contents

Binding of streptomycin to 30S

Carter et al. (2000) Nature 407:340

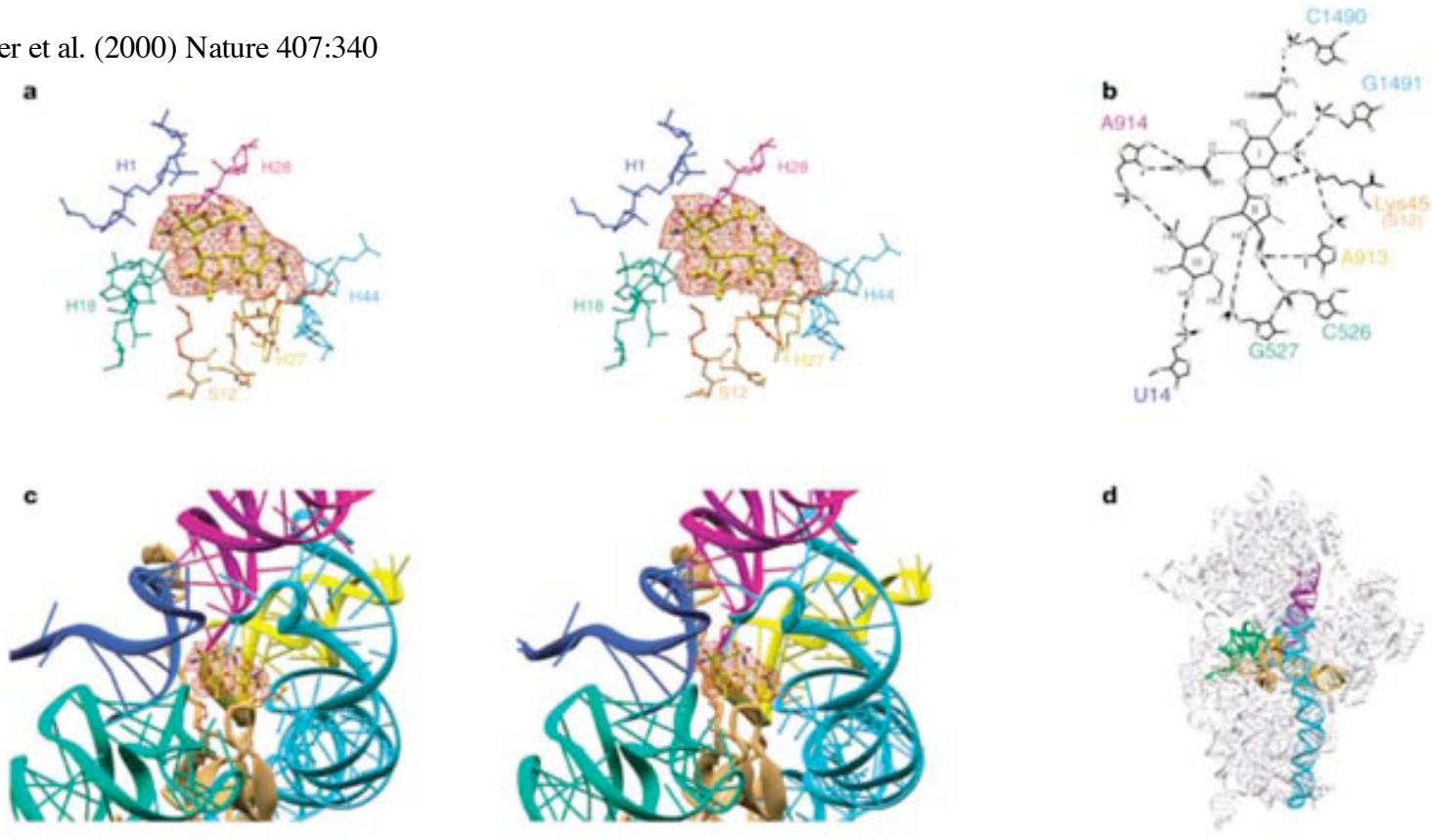

Figure 5 Interaction of streptomycin with the 30S ribosomal subunit. **a**, Difference Fourier maps showing the binding site of streptomycin. Mutations in ribosomal protein S12 that confer resistance are shown in red. **b**, Chemical structure of streptomycin, showing interactions of the various groups with specific residues of the ribosome. **c**, The streptomycin-binding site, showing its interaction with H27, the 530 loop (H18), H44 and ribosomal protein S12. **d**, A view of the 30S showing streptomycin in a space-filling model, and the surrounding RNA and protein elements

Aminoglycosides

- Used for serious gram negative infections
- Binds to ribosomes, inhibits protein synthesis and causes misreading of mRNA
- Resistance: Bugs synthesize transferases that inactivate drugs
- Toxic effects: Ototoxicity (hearing and balance loss) and nephrotoxicity

Mechanisms of resistance

- Drug inactivation
  - Penicillins, aminoglycosides
- Alteration of target sites
  - Beta-lactams, fluoroquinolones
- Decrease in accessibility
  - Tetracyclines
- Increase in competing metabolites
  - Sulfonamides