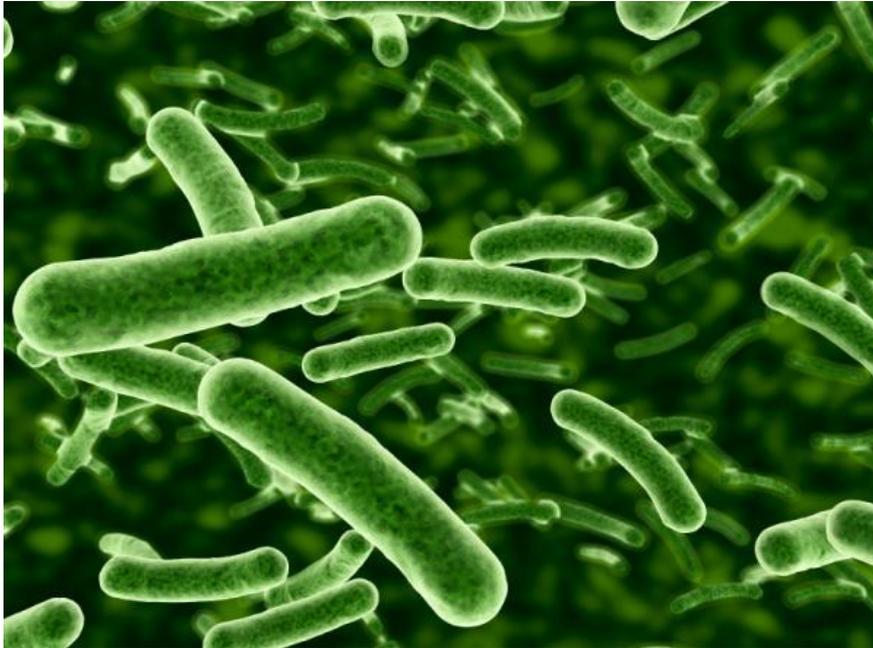
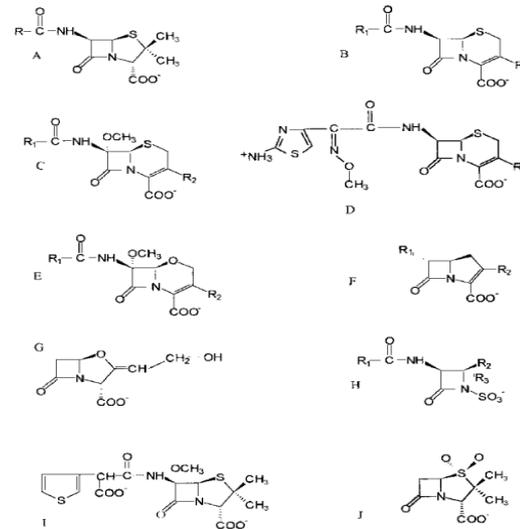


# Antibiotics and the challenges of drug discovery

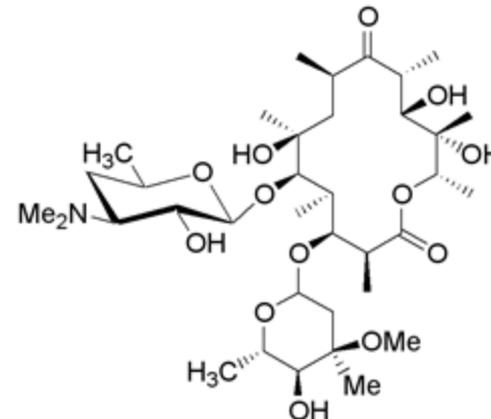


ciss.blog.olemiss.edu

**Professor Vassie Ware**  
**Bioscience in the 21<sup>st</sup> Century**  
**October 25, 2013**



[www.biochemj.org/bj/330/0581/bj3300581.htm](http://www.biochemj.org/bj/330/0581/bj3300581.htm)



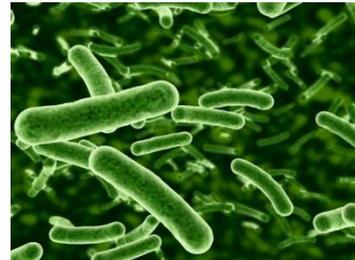
# PERSPECTIVE

- **Widespread use of antibiotics after WWII to improve global health**
- **Increasing antibiotic resistance in bacterial pathogens coupled with a lag in the development of additional antibiotics by pharmaceutical companies poses an escalating problem in the 21<sup>st</sup> century**

**20 years ago: ~13,000 deaths/year from bacterial infections.**

**Today: ~63,000 deaths/year from bacterial infections!!!**

- **Challenge to design effective new generation antibiotics**
- **Use of structure-based drug design to develop novel drugs based on high resolution structures of drug targets and their resistance mutants**



# ***General Lecture Outline***

1. Your thoughts about the value of antibiotics
2. PBS Frontline video clips: *Hunting the Nightmare Bacteria*
3. General information about antibiotics and their targets
4. Bacterial ribosomes as a target for antibiotics
5. Bacterial antibiotic resistance
6. The discovery problem
7. What response is needed globally?

**class discussion:**

**How valuable are antibiotics for human health?**

**PBS Frontline video clips: *Hunting the Nightmare Bacteria***

# Antibiotics

- **Natural or synthetic compounds that either kill (bactericidal) or inhibit growth (bacteriostatic) of bacteria (or other microorganisms)**
- **Antibiotics may be classified in several ways. Most common classification schemes are based on chemical structure of the antibiotic**

# Antibacterial agents, suitable for therapy:

## Natural –

Derived from natural sources such as fungi and soil bacteria.

Penicillin as the classic example, derived from the fungus *Penicillium*

Pharmaceutical industry produces penicillin from cultures of

*Penicillium chrysogenum* that are adapted for high yield

Others: many aminoglycosides from soil bacteria (e.g., streptomycin)

## Semi-synthetic -

Natural products that have been chemically modified to improve effectiveness of the product or to reduce side effects, etc

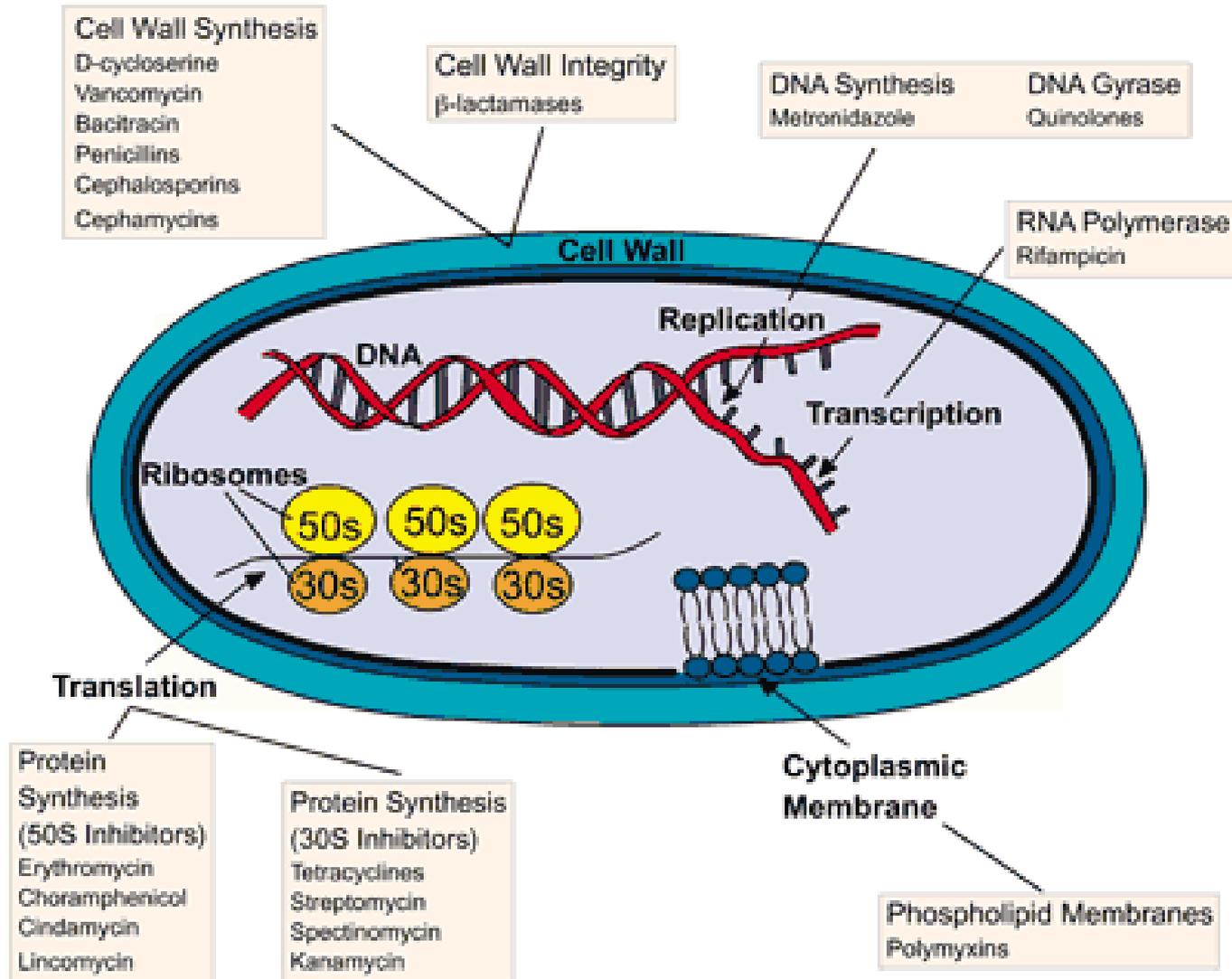
Examples include the  $\beta$ -lactams ampicillin, amoxicillin, etc, derived from fungi

## Completely synthetic –

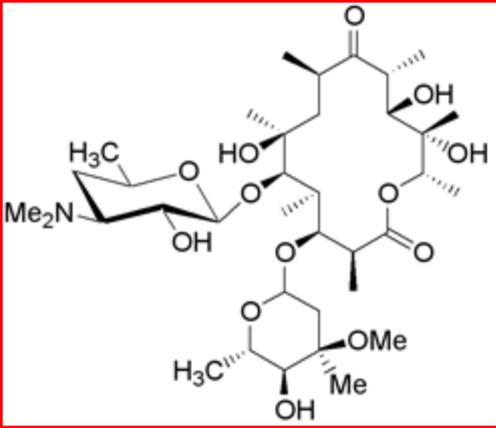
Products are synthesized completely in the laboratory

Sulfa drugs, folic acid analogs are examples

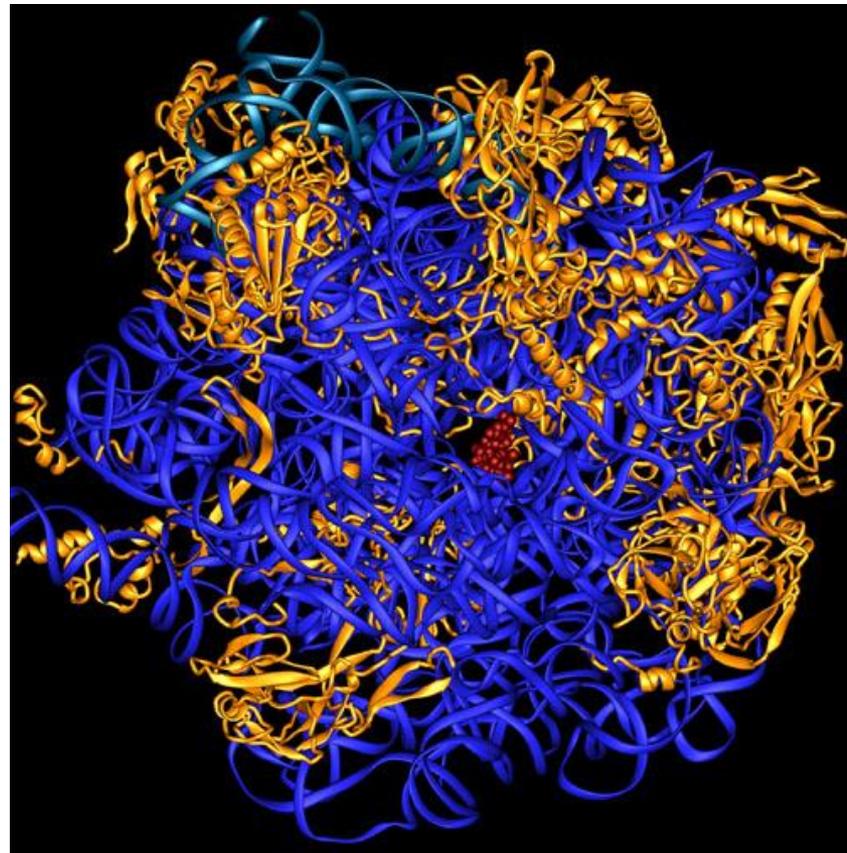
# Antibiotic Targets in Bacterial Cells







**Erythromycin – a macrolide antibiotic that blocks protein synthesis by binding to bacterial ribosomes but not to eukaryotic ribosomes**



[www.molgen.mpg.de](http://www.molgen.mpg.de)

# Resistance to Antibiotics

## Intrinsic resistance

Some bacteria are naturally more resistant to certain classes of antibiotics than others.

Examples:

- certain bacteria may lack a transport system for an antibiotic
- bacteria may lack the target of the antibiotic molecule
- the cell wall is covered with an outer membrane blocks entry of the antibiotic (as in the case for Gram negative bacteria).

## Acquired resistance

Bacteria acquire resistance to antibiotics for which they were previously susceptible through

- spontaneous gene mutation (rate of  $10^{-8}$ – $10^{-9}$ ) and fixation of mutation in the population through rapid cell division (vertical evolution)
- **horizontal gene transfer** mechanisms, such as **conjugation**, **transformation**, or **transduction**. Impact of this can be significant. For example, in 10 years' time between 1985 and 1995, the percentage of ampicillin-resistant *Shigella* (causes intestinal illness) grew from 32% to 67%!

# How do bacteria acquire resistance?

Bacteria acquire genes that encode proteins that shield or protect them from the effects of the antibiotic.

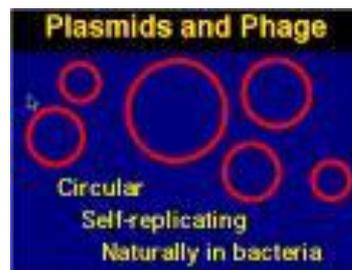
These genes may have arisen by **mutation** of existing genes  
OR  
they may have been acquired from other resistant bacteria through the **transfer of genetic information between bacteria**

Antibiotic resistance genes are often carried on **plasmids** and can be exchanged between bacteria.

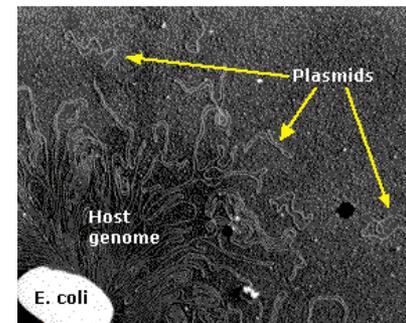


It was on a short-cut through the hospital kitchens that Albert was first approached by a member of the Antibiotic Resistance.

[www.terra-thrive.com](http://www.terra-thrive.com)

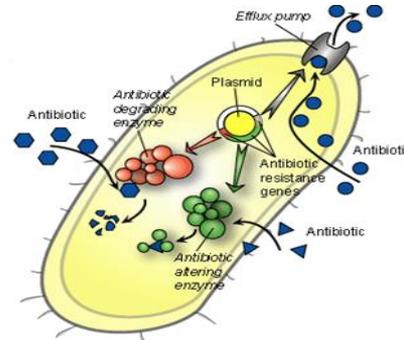


[www.life.uiuc.edu](http://www.life.uiuc.edu)



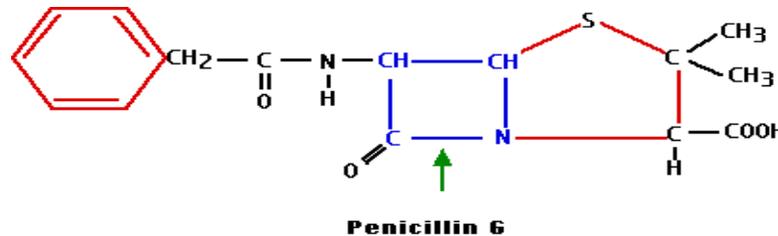
[users.rcn.com](http://users.rcn.com)

# “Clever tricks” by bacteria to inactivate antibiotics:



[http://textbookofbacteriology.net/resantimicrobial\\_3.html](http://textbookofbacteriology.net/resantimicrobial_3.html)

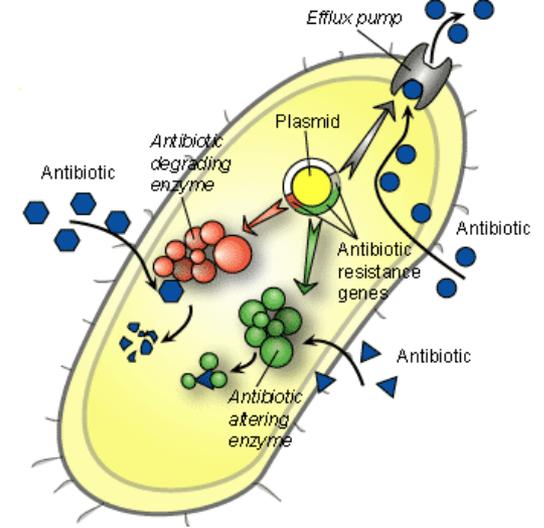
1. **Synthesis of enzymes that breakdown the antibiotic: Penicillinase (a type of  $\beta$ -lactamase, breaks the  $\beta$ -lactam ring, thereby destroying the antibiotic). Other enzyme types are also prevalent (e.g., cephalosporinases). New Delhi metallo-beta lactamase (NDM-1), an enzyme that makes bacteria resistant to a broad range of beta-lactam antibiotics (creating resistant “superbugs”)**



2. **Modification of their own enzymes that would normally be targets of the antibiotic (e.g., DNA gyrase)**

## Clever tricks, continued:

3. Synthesis of “pumps” inserted into the cell membrane to remove the antibiotic from the interior of the cell
4. Addition of chemical groups onto the target so that the antibiotic does not recognize the target. (e.g., erythromycin resistance)
5. Modification of the antibiotic so that it no longer recognizes its target (e.g., kanamycin resistance)
6. Modification of the peptidoglycan cell wall to avoid the antibiotic effect



[http://textbookofbacteriology.net/resantimicrobial\\_3.html](http://textbookofbacteriology.net/resantimicrobial_3.html)

# **The drug discovery problem (continuation of video):**

**Perspectives of industry**

**Perspectives of government**

# **SUMMARY:**

- **Bacterial antibiotic resistance is an increasingly serious global health problem**
- **Global scientific research imperatives:**
  - Development of new derivatives of antibiotics**
  - Discovery of new classes of antibiotics with novel mechanisms of action**
  - Development of new approaches to treating bacterial infections**
- **Government and industrial partnerships are essential to foster new antibiotic drug development**