Lecture #19: Antimicrobial Chemotherapy

In what year was a chemical first intentionally used to selectively kill disease-causing bacteria in a human host?

a. 1967  
b. 1542   
c. 1910   
d. 1983   
e. 1893
I. Terminology

A. Chemotherapeutic agent = Any that is used to treat a

B. Antimicrobial drug = Any chemical used to treat a

C. Antibiotics = Antimicrobial drugs

D. Selective toxicity = Antimicrobial drugs must be selectively toxic against microorganisms and

E. = the level required for treatment
    = the level at which the drug is toxic to the host

<table>
<thead>
<tr>
<th>Toxic dose</th>
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</thead>
<tbody>
<tr>
<td>Therapeutic dose</td>
</tr>
</tbody>
</table>

*The this is, the better ( )
the antimicrobial drug
II. Mechanisms of Action of Antibacterial Drugs
   A. Drugs that
      1. The β-lactam drugs
β-lactam drugs:

Generally thought to exhibit their antimicrobial activity by
of peptidoglycan*

*Although this is the most commonly proposed mechanism of action, the mechanism of the penicillins is still being debated. It has recently been proposed that they stimulate bacterial holins that form holes in the plasma membrane.

b. Affective only when cells are actively synthesizing their cell walls, when cells are
c. The peptidoglycan layer of Gram-negative cells is by the outer membrane. Because of this, Gram-negative cells tend to be innately to β-lactam antibiotics.

Gram-negative cells are also more likely to produce enzymes called that can

d. Other than allergic reactions, β-lactam antibiotics tend to have
### Types of β-lactam antibiotics:

<table>
<thead>
<tr>
<th>Antibiotic type</th>
<th>Source</th>
<th>Effective against</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broad-spectrum Penicillins</td>
<td><em>Penicillium chrysogenum</em> Partially</td>
<td>bacteria Some</td>
<td>Penicillin G Penicillin V</td>
</tr>
<tr>
<td>Extended-spectrum Penicillins</td>
<td>Partially synthetic</td>
<td>bacteria</td>
<td>Ticarcillin Piperacillin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Some (e.g. <em>Pseudomonas</em>)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Acremonium</em> (More recent derivatives are partially synthetic)</td>
<td>Some G+ More recent derivatives are effective against</td>
<td>Cefepime</td>
</tr>
</tbody>
</table>
2. Vancomycin
   a. **Vancomycin:**

   Binds to the and stops synthesis of peptidoglycan.

   b. of Gram-negative bacteria so these organisms are innately resistant.
   c. Often good for treating Gram-positive infections if the β-lactam antibiotics are (e.g. antibiotic-resistant *Staphylococcus aureus*).
   d. Administered
3. Bacitracin
   a. Inhibits cell wall synthesis by interfering with the
      of peptidoglycan precursors across the
cytoplasmic membrane.
   b. Used only in
### B. Drugs that inhibit

#### Antibiotics that inhibit protein synthesis:

<table>
<thead>
<tr>
<th>Antibiotic type</th>
<th>Mechanism of action</th>
<th>Effective against</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>Bind to 30S ribosomal subunit causing it to</td>
<td>Mainly bacteria that (e.g. <em>Proteus</em>, <em>Escherichia</em>, and <em>Klebsiella</em>)</td>
<td>Gentamicin</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Reversibly bind to the and stop protein synthesis</td>
<td>Certain (rickettsias and chlamydiae)</td>
<td>Tetracycline Doxycycline</td>
</tr>
<tr>
<td></td>
<td>Reversibly bind to the and stop protein synthesis</td>
<td>A variety of bacteria, mainly , but also those that cause &quot;walking pneumonia&quot;</td>
<td></td>
</tr>
</tbody>
</table>


C. Drugs that inhibit nucleic acid synthesis

The quinolones are effective against a variety of Gram-positive and Gram-negative organisms (\textit{E. coli}, \textit{Klebsiella pneumoniae}, \textit{Neisseria}, \textit{Pseudomonas}, \textit{S. aureus}, \textit{M. tuberculosis}).\textbf{\textit{Vancomycin}} is an example.

D. Drugs that interfere with cell membrane integrity

\textbf{Polymyxin B} binds to the membrane of Gram-negative cells and Cellular components and eventually the cell dies. Because this drug can also damage eukaryotic cells, it is used only as an active ingredient in
In general, which type of cell is easier to kill/inhibit with antibiotics?
   a. Gram-negative cells
   b. Gram-positive cells

Why??
Because of the rise in antibiotic resistance, many efforts are under way to develop new drugs (e.g. Zyvox (linezolid) - in a new class of drugs that inhibit protein synthesis and is active against MRSA). Some efforts are focused on combination therapy in which the antibiotic is administered with a beta-lactamase inhibitor or a efflux pump inhibitor. 

What other efforts are under way??

Efforts are also underway to develop new antifungal and antiviral drugs. Why is this more difficult??