CHAPTER 3
CHEMISTRY OF ANTIBIOTICS WITH SPECIAL REFERENCE TO TETRACYCLINES, PENICILLINS AND CEPHALOSPORINS
Pasteur and Joubert were the first investigators to recognize the clinical potential of microbial products. In 1877 they observed and speculated on the fact that life destroys life among the lower species. It is more so in higher animals and in plants. They also came to an astonishing conclusion that this might hold great promise for therapeutics.

The modern era of antimicrobial therapy started with the clinical use of sulphanilamide in 1936. The golden age of antibiotics began with the production of penicillin in 1941. The result of their wide spread use has been the emergence of antibiotic resistant pathogens, which in turn has resulted in an ever-increasing need for new drugs.

The word antibiotic was first used by Vuillemen in 1889, derived from anti-bios meaning against life. Antibiotic refers to a metabolic product of one microorganism that in very small amounts is detrimental or inhibitory to other microorganisms. They can be defined as those chemical substances of microbial origin which in small amounts exert antimicrobial activity.

Hundreds of antibiotics have been identified and many have been developed to a stage where they are of value in therapy of disease. Antibiotics differ markedly in physical, chemical and pharmacological properties, antibacterial spectra, and mechanism of action. Knowledge of molecular mechanisms of bacterial, fungal and
viral replication has greatly facilitated rational development of compounds that can interfere with the life cycle of organisms.

Infectious diseases have always been the scourge of human kind for ages. The treatment of infectious diseases was revolutionized with the discovery of antibiotics. The treatment of disease with a chemical substance is known as chemotherapy. The chemical substance is called as chemotherapeutic agent. Today they may be synthesized in laboratories or synthesized from raw materials obtained from natural sources.

Paul Ehrlich made the first systematic and deliberate invention of a compound that has potent microbicidal properties, low toxicity and good chemical stability. He discovered an arsenical compound known as Salvarsan for the treatment of syphilis, for which he was awarded Nobel Prize in the year 1908. In 1929 Sir Alexander Fleming noticed that an agar plate inoculated with Staphylococeus aureus had contaminated with a mold that showed interesting properties. That was isolated and studied to become a source of wonder drug 'penicillin'.

Since then chemists are synthesizing hundreds of molecules that are potent, having no side effects and causing no development of microbial resistance.

1929 – Discovery of the existence of penicillin

1945 – Discovery of the fungus Cephalosporium acremonium

1947 – Discovery of chloramphenicol

1948 – Discovery of the first tetracycline-chlortetracycline
1949 – Isolation of neomycin

1950s – Beta-lactam nucleus of penicillin identified

1957 – Kanamycin

1960s – Extended spectrum penicillin; first generation cephalosporins, amino glycosides

1962 – Nalidixic acid

1970s – Broad spectrum penicillin and 2nd generation cephalosporins

1980s – Third generation cephalosporins and quinolones

This trend has continued up to the present time and has occurred primarily because of advances in technologies which have led to the more efficient identification and development of newer compounds.

**Classification of antibacterial agents**

1. **Based on the type of action**

1. **Bactericidal agents**

   Bactericidal action refers to killing of the bacteria.

   Ex:  
   * Beta-lactams
   * Quinolones and
   * Aminoglycosides

2. **Bacteriostatic agents**

   Bacteriostatic action refers to suppressing the growth of bacteria.
Ex: * Macrolides (except at high doses)*
    * Tetracyclines
    * Chloramphenicol and
    * Sulfonamides

II. Based on the spectrum of activity

On the basis of the spectrum of activity antibiotics are classified as narrow spectrum, extended spectrum, and broad spectrum antibiotics.

1. **Narrow spectrum antibiotics**

   Active mainly against either gram positive or gram negative organism only.

<table>
<thead>
<tr>
<th>Gram positive organisms</th>
<th>Gram negative organisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>Streptomycin</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Gentamicin</td>
</tr>
<tr>
<td>Bacitracin</td>
<td>Cycloserine</td>
</tr>
</tbody>
</table>

2. **Extended spectrum antibiotics**

   Active against gram-positive and significant number of gram-negative organisms.

   | Ampicillin               | Cephalosporins          |
3. **Broad spectrum antibiotics**

Active against a wide variety of microbial species.

<table>
<thead>
<tr>
<th>Fluoroquinolones</th>
<th>Tetracyclines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloramphenicol</td>
<td></td>
</tr>
</tbody>
</table>

### III. Based on the mechanism of action

There are four principle mechanisms of antibiotic action.

![Antibiotic Mechanisms Diagram](image)

**Figure 3.1**

1. **Disruption of the cell wall**

   Beta-lactam antibiotics bind to the enzymes that cross-link peptidoglycans in the bacterial cell wall. This disrupts the cell wall and kills the cell by bursting it. Human cells have no cell wall and therefore unaffected. Glycopeptides also act at the cell wall in the same way.
2. **Alteration of the cell membrane**

Antibiotics such as polymixins bind to the bacterial cell membrane and increase its permeability. This disrupts the ionic balance of the cell and the bacteria dies.

3. **Interference in the protein synthesis**

Macrolides, tetracyclines and aminoglycosides all exert their antibacterial action by interfering with bacterial protein synthesis.

4. **Interfering with bacterial DNA**

Quinolones inhibit the replication of bacterial DNA. Because replication is essential to the functioning of the cell, this effect is bactericidal. Refampicin and metronidazole also interfere in the bacterial DNA.

There are several other types of antibiotics that work through an effect on DNA. Trimethoprim and sulphonamides, for e.g., inhibit the synthesis of folic acid, an essential building block for DNA.
IV. Based on the group to which they belong

| 1. Beta – lactams  
  e.g., penicillins 
  cephalosporins | 4. Tetracyclines  
  e.g., Oxytetracycline  
  Doxycycline |
|------------------|------------------|
| 2. Macrolides  
  e.g., erythromycin  
  azithromycin  
  clarithromycin | 5. Aminoglycosides  
  e.g., gentamycin  
  steptomycin |
| 3. Quinolones  
  e.g., Ciprofloxacin  
  Sparfloxacin | 6. Glycopeptides  
  e.g., Vancomycin |

Among these antibiotics, tetracyclines, penicillins and cephalosporins are well known. These are commonly administered due to their wide spectrum of activity and they find use in the treatment of large number of infections. Their low price makes them readily available to common man.

Chemistry of tetracyclines

The tetracyclines form a group of antibiotics, which are originally derived from certain *Streptomyces Spp.* The tetracyclines are obtained from the fermentation procedures from *Streptomyces* species or by chemical transformation of the natural products. The chemical identities of tetracyclines are established by degradation studies and confirmed by the synthesis of three members of the group, tetracycline\(^{143,144}\), 6-demethyl-6-deoxytetracycline\(^{145}\) and anhydrochlorotetracycline\(^{146}\) in their (±) forms. All of them are having a common tetracycline system corresponding to naphthacene. They are having similar properties.
Unlike aminoglycosides they find use as bacteriostatic at the concentrations which are usually achieved in the body. They act similarly to the aminoglycosides by getting interfered with protein synthesis in susceptible organisms. All tetracyclines exhibit a broad spectrum of activity, which include gram-positive and gram-negative bacteria, rickettsias. Tetracycline has a low order of toxicity in laboratory animals.\textsuperscript{147}

Tetracyclines are yellow in colour. They are having bitter taste. They are having slight solubility in water but their hydrochlorides are much soluble in water. They are amphoteric, forming crystalline salts with many strong acids and bases. In solution tetracyclines retain its activity for three weeks or more.

Tetracyclines readily form stable chelate complexes with the many metal ions e.g., calcium, magnesium, iron. The strong binding property of tetracyclines with metal ions caused Albert\textsuperscript{148} to suggest that their antibacterial properties are due to their ability to remove essential metal ions as chelate compounds.

Chlortetracycline was the first tetracycline, which was discovered in 1948. Its discovery was followed by the oxytetracycline and tetracycline. Tetracycline, chlortetracycline, oxytetracycline refer to all natural products that are being isolated from \textit{Streptomyces Spp}. They are kept in tightly closed containers which are light resistant.
Tetracyclines find use effectively in the treatment of cholera, amoebic dysentery. Tetracyclines find use topically for treating chlamydial infections of the eye. For the treatment of systematic infections they are generally administered by mouth. For the treatment of severe acute infections, they may be administered either by slow intravenous infusion or by intramuscular injection. It is essential to substitute parenteral therapy by oral administration as soon as practicable. Tetracycline base finds use in oral suspensions. As tetracyclines are going to affect the teeth of the children, they should be used as and when they are absolutely essential.

Chemistry of penicillins

The penicillins form a group of antibiotics that get produced in whole or in part by growing the mould Penicillium in suitable culture media. They are strong monobasic acids with a pH value of 2.8. They are soluble in water and in many other solvents. The penicillins refer to the derivatives of 6-amino penicillanic acid. Their structure is having a fused thiazolidine ring and a β-lactam ring. They readily
yield salts and esters. The general term ‘penicillin’ is used for these salts and esters and the acids themselves.

6-Aminopenicillanic acid

The term 'penicillin' is now generically used for describing the entire group of natural and semisynthetic penicillins. Penicillins are still the most widely used antibiotics. They are usually well tolerated due to the hypersensitivity reactions. They are bactericidal due to their inhibitory action on the synthesis of the bacterial cell wall.

The so called 'natural' penicillins are produced by the addition of different side-chain precursors to fermentation of the mould *Penicillium chrysogenum*. Among these first two pencillins were benzyl penicillin and phenoxymethly penicillin, which were produced by the growth of *P. notatum* or related organisms. These are still variously used.

Benzylpenicillin (C₆H₅-CH₂CONH) is having phenylacetamido side-chain at 6th position. Benzylpencillin is regarded as the parent compound of the penicillins. It is active against gram positive bacteria and *Neisseria Spp.* It gets inactivated by penicilllinase producing bacteria. It is not stable to gastric acid. Therefore, it is usually injected. Since then number of side-chain precursors are introduced at 6th
position to produce various penicillins like benzathin penicillin, benethamine penicillin, phenoxy methyl penicillin.

If side-chain precursor is not added to the fermentation medium at 6 position, 6-amino penicillinic acid itself is produced. Initially it was isolated from cultures of *P. chrysogenum* grown in a medium free from side-chain precursors.

Many penicillins can be synthesized from 6-amino penicillanic acid by carrying out the substitution at the 6-amino position. The aim is to improve the instability of benzyl penicillin to gastric acid. The other objectives are widening of antimicrobial spectrum and to reduce its rapid rate of renal excretion.

Among the semisynthetic penicillins fluxacillin, phenethicillin, cloxaciline, ampicillin, amoxycillin and carbenicillin are important. In therapy penicillin is used in the form of its potassium, sodium and calcium salts.

**Chemistry of cephalosporins**

Microbes and humans share an age-old relationship. The more man tries to conquer the microbe the more the microbe outwits him. Multi-drug resistance is now the scourge of mankind.

It is against this background that cephalosporins enter the picture. They are most commonly prescribed antibiotics in hospitals.

Cephalosporins refer to the semisynthetic antibiotics. They are derived from cephalosporin C, a natural antibiotic which gets produced by mould *Cephalosporium acremonium*. Cephalosporin contain the 7-amino cephalosporanic acid nucleus. This is closely related to the penicillin nucleus 6-amino penicillanic acid.
It is having a betalactam ring which gets fused with a 6-membered dihydrothiazine ring and is having an acetoxymethyl group at position 3. The parent saturated bicyclic skeleton is known as cepham. Hence 7-aminocephalosporanic acid is named as (7R)-7-amino-3-acetoxymethyl-3-cepham-4-carboxylic acid. Chemical modification of positions 3 and 7 gives rise to a series of antibiotics which are having different characteristics.

Cephalothin was the first cephalosporin to become available which is able to retain the 3-acetoxymethyl group of parent compound cephalosporin C.
Cephalosporins are bactericidal. Similar to penicillins they act by inhibiting synthesis of the bacterial cell wall. They have been found to be active against wide range of gram positive and gram negative bacteria.

Cephalosporins are widely used in the treatment of infections of respiratory and urinary tracts and other infections because of susceptible organisms including those which get caused by penicillin-resistant Staphylococci.