CHEMOTHERAPY

Definition :→ Use of chemical agents in treatment of infectious diseases, so as to destroy the offending organisms. and these agents shouldn't have any effect over host tissue.

History of chemotherapy :→

- The evidence of succesful chemotherapy is from Ancient peru, where Indians used bark from the cinchona tree to treat Malaria.
- Other substances were used in Ancient china.
- Modern chemotherapy begins with Paul Ehrlich in Germany, who discovered effective agents to treat Syphillis.

Evolution of chemotherapy :→

The Evolution of chemotherapy can be classified into three distinct periods

1. Pre Ehrlich Era (before 1891)
2. Era of Paul Ehrlich
3. After Paul Ehrlich era

Pre Ehrlich Era before 1891 it was considered as Pre Ehrlich era.

Many scientists didn't know about any names of chemical agents and the discovery was based on trial and error basis.

Eg: Cinchona bark – Malaria
Mercurials – Syphillis

2. Era of Paul Ehrlich (1854 - 1915)

Paul Ehrlich reasoned that chemical substances might be produced that could unite and kill the parasitic agents without harming the host tissue. These were considered as "Magic Bullets"

He also postulated that the cell membrane contained specific chemical groups or Receptors, which combined with essential materials like Oxygen and caused their uptake inside the cells.

In 1891, Methylene blue, a dye which stained and killed many bacterial cells was found to be effective against Malaria. He also discovered many Arsenicals (Arsephenamine) which was effective against Syphilis.

In 1909, he was awarded with a Nobel prize and was named as "Father of Modern Chemotherapy"

- **Heptophore** - any group / receptor present on cell membrane which binds to endogenous substances and gives way to the entry inside the cell.

- **Toxophore** - a substance which enhances / enables to produce its specific action / pharmacological action.

* Chemotherapeutic Index = $\frac{LD50}{ED50}$.

* Toxic effect → Any drug ℰ has more affinity towards host cell, then it is called as Organotropic / toxic effect

* Curative effect → Any drug ℰ has more affinity towards parasite, then it is called as Parasitotropic / curative effect

After paul Ehrlich Era

1> Sir Alexander Flemming in 1928 → Penicillin

Staphylococcus studies org in plate was killed by fungal attack. The fungus was cultivated and extracted. The extracted supernatent layer was poured on a culture which killed the organism.

Fungus → Penicillia notatum

↓

Penicillin → ⊗ no. of Gram +ve organism.

2> In 1938, Domangk and Mietsch worked on Azodyes and landed with a compound called as Prontosil - effective against Streptococcus bacteria.

* Nitti, fuller, Bovet - examined Prontosil and explained that the presence of Sulphonamide side chain is responsible for the activity against bacteria.

Sulphonamide → Sulfanilamide (active)

* In 1908 Gelmo synthesized Sulphonamides.

* 1877, Pasteur found some common bacteria at a particular dilution prevent the growth of Anthrax bacili in urine.

* 1899, Emerrich found some substances from Pseudomonas aurigenosa killed many cocci. Eg:- Diptheria, cholera, Typhoid, plague.

3→ In 1941. Abraham, Chain and Florey worked on Penicillins and found to be very potent and antiinfective during II world war. and these were awarded Nobel prize in 1945.

4→ In 1944, Walksman, Bugie and Schatch gave definition to Antibiotic → As "chemical substance produced by microorganism having the property of inhibiting growth of or destroying other m.o. in high dilution".

* discovered Streptomycin from Streptomyces griseus.

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Broad spectrum antibiotic, even kill mycobacteria

5→ Later Sulphonamides, Quinolones were discovered and the efficacy of all the above were by

(a) host defence (b) Source of infection (c) tissue damaged
(d) Margin of Safety (e) Susceptability or Resistence.

Bacteriostatic → ē inhibits M.O. growth

Bactericidal → ē destroy / kill the M.O.

Based upon the above the agents were classified depending upon site of action. Mainly include.

1. Cell wall
2. Cytoplasmic membrane
3. Ribosomes and interfere ē protein synthesis
4. on RNA interfere ē translation of genetic information

General Principles of Chemotherapy

These are necessary for a rational chemotherapeutic regimen for an individual patient.

These mainly include.

(a) Selection of Antimicrobial agent
   - (1) Host related factors
     - Age of the patient
     - Pregnancy & Neonatal period
     - Immunocompetency status
     - Severity of infection
   - (2) Pathogen related factors
   - (3) Drug related factors

(b) Antimicrobial combinations

(c) Antimicrobial Prophylaxis

(d) Microbial Drug Resistance

(e) Dangers / Risks in Antimicrobial therapy.

(f) Misuse of Antimicrobial Agents.

Pathogen related factors

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→ Evaluation of probable microbial etiology and expected clinical course of the infection

→ Identification of the causative microorganism and its sensitivity to Antimicrobial drugs.

→ Possibility of drug resistance.

Drug related

→ Nature of the drug

→ Risk of drug toxicity

→ The cost of therapy

→ Pharmacokinetic properties of the drug

→ Probability of drug compliance by the patient.

Antimicrobial Combinations

* To achieve an additive or Synergistic effect against a single organism.
* In mixed infections ∑ bacteria sensitive to different drugs.

Eg:- Synergistic effect → Gentamicin + Carbenicillin. against Pseudomonas infection.

Eg:- Penicillin | Metronidazole combined ē an aminoglycoside. in peritonitis

* To delay the development of or to overcome the drug resistance. Eg:- In TB.
* To decrease the adverse reactions.
* When etiological diagnosis is difficult, the infection is severe and the body defence is poor.
  Eg:- Malnourished patients, Immunosuppressant patients etc.
* For reducing the chances of Super infection
  Eg:- In AIDS Tetracycline + Antifungal. ↓ prevent Superinfection due to fungi Monilia
* Drug Antagonism

Antimicrobial Prophylaxis

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given as a cover to prevent colonization by various organisms in the internal and external environment.

Microbial Drug Resistance

Bacterial resistance → Natural
Eg:- E coli produces penicillinase.
∴ Penicillin doesn't work.

→ Acquired

developed by ↑ conc^{n} of Antimicrobial drug.

can develop due to genetic mutation — alteration in the structure of DNA.

genetic exchange — acquisition of extrachromosomal DNA from other bacteria.

resistance of low level.

↓
clinical drug resistance.

Dangers / Risks in Chemotherapy

- Development of allergic and Anaphylactic reactions
- Selective toxicity
- Development of Super infection
- " of Multiple drug resistant.
- Deficiency of certain vitamins
- Fetal damage.
- A False sense of security in the patient as well as physician leading to neglect in the exact diagnosis.

* Three classes of reactions.

I → Utilisation of glucose or some alternative Carbon source like ATP and TCA cycle, which are used as precursors in the next class of reactions.

II → Utilisation of precursors and energy to make the necessary small molecules like Amino a, Nucleotides, phospholipids, amino sugars, Carbohydrates and growth factors.

III → Assembly of small molecules into Macromolecules like protein, RNA, DNA, polysaccharides and peptidoglycan.

Targets. (I) not a very good target

(II) better targets than class (I) since some pathways involved in class (II) doesn't exist in parasitic cells ∴ any such difference in pathway represents a potential target.

Eg: folate, pyrimidine and purine analogues.

(III) good targets for selective toxicity bcoz every cell has to make its own macromol. & cannot be picked up from the environment.

Eg: peptidoglycan syn., protein syn., Nucleic a syn.

* Formed structures like cell membrane, DNA, intracellular organelles like Microtubules/filaments, Vacuoles, muscle fibres etc can also act as targets.

Classification of Antibiotics

1. Drugs Affecting cell wall :→ Penicillins, Cephalosporins, Cycloserine, Vancomycin, Bacitracin
2. Drugs inhibit cytoplasmic membrane :→ Polymyxin & polyene antibiotics, Detergents
3. Drugs interfering with Protein Synthesis :→ Aminoglycosides, Macrolides, Tetracyclines, Chloramphenicol
4. Antimetabolite Antibiotics :→ Sulphonamides, Sulfones, paraamino salicylic acid
5. Drugs interfering with mRNA transcription & translation :→ Ethambutol, Rifampicin, Metronidazole
6. Drugs which inhibit Enzymes responsible for DNA Synthesis in Virus :→ Acyclovir, Antiprotease