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RESEARCH ARTICLE

ANTIBIOTIC DRUG DISCOVERY AFFORDING POSSIBILITIES IN EXPLORING CHEMOTHERAPIES

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ABSTRACT

The remarkable and spectacular breakthroughs accomplished by Pasteur, Koch, Jenner, and a host of others more or less paved the way towards several miraculous discoveries in curing fatal and dreadful human ailments thereby minimizing their immense sufferings. Between 1935 and 1944 the field of microbiology, and by implication medicine as a whole, underwent dramatic advancement. The discovery of the extraordinary antibacterial properties of sulphonamides, penicillin, and streptomycin triggered a frantic hunt for more antimicrobial drugs that was to yield an abundant harvest in a very short space of time. Many meaningful and wonderful researches also led to the discovery of a good number of causative agents of diseases and altogether newer techniques for diagnosis, which ultimately rendered the diagnosis of these ailments rather rapid and precise. By the early 1960s more than 50 antibacterial agents were available to the prescribing physician and, largely by a process of chemical modification of existing compounds, that number has more than tripled today. Antimicrobial Agents and Chemotherapy is a major forum exclusively devoted to antimicrobial, antiviral, antiparasitic, and anticancer agents and chemotherapy. It is also a key source for microbiologists, pharmaceutical researchers, biochemists, pharmacologists, clinicians, and other specialists in infectious diseases. Progress in the development of novel antibacterial agents has been great, but the development of effective, nontoxic antifungal and antiviral agents has been slow. Proper selection of new antibiotics will be a major force in slowing the development of antimicrobial resistance. Proper hygiene practices will reduce plasmid transfer and the establishment of multiple drug-resistant bacteria in the hospital and will delay the appearance of such species in the community. We have now become so used to the ready availability of these relatively safe and highly effective 'miracle drugs' that it is now hard to grasp how they transformed the treatment of infection.

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INTRODUCTION

Infectious diseases caused by bacterial pathogens represent a serious public health concern. Killing microorganisms or suppressing their multiplication or growth by the use of chemicals called "Antimicrobial Chemotherapy". The modern era of chemotherapy began with the work of the German physician Paul Ehrlich(1854-1915). Antimicrobial agents such as anti-bacterial drugs are often indicated for chemotherapy of bacterial infections in clinical medicine [1]. Chemotherapy is the drug treatment for the diseases caused by bacteria and the other pathologic microorganisms, parasites, and tumour cells. The objective of chemotherapy is to study and to apply the drugs that have highly selective toxicity to the pathogenic microorganisms in host body and have no or less toxicity to the host, so as to prevent and cure infective diseases caused by pathogens.

The objective of chemotherapy is to study and to apply the drugs that have highly *selective toxicity* to the pathogenic microorganisms and have no or less toxicity to the host. Paul Ehrlich began the modern age of chemotherapy.

History of Antimicrobial Agents

The remarkable and spectacular breakthroughs accomplished by Pasteur, Koch, Jenner, and a host of others more or less paved the way towards several miraculous discoveries in curing fatal and dreadful human ailments thereby minimizing their immense sufferings. Antimicrobial chemotherapy made remarkable advances, resulting in the overly optimistic view that infectious diseases would be conquered in the near future. Antimicrobial chemotherapy has conferred huge benefits on human health. A variety of microorganisms were elucidated to cause infectious diseases in the latter half of the 19th century. Thereafter, antimicrobial chemotherapy made remarkable advances during the 20th century, resulting in the overly

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optimistic view that infectious diseases would be conquered in the near future[2]. Antimicrobial drugs have revolutionized human and veterinary medicine through the provision of effective and inexpensive means of treating, and in some circumstances preventing, bacterial infectious disease.

Classification of antimicrobial drugs by susceptible organisms

- Antibacterial drugs (narrow and broad spectrum).
Examples: Penicillin G, erythromycin, cephalosporins, sulfonamides
- Antiviral drugs (examples: acyclovir, amantadine)
- Antifungal drugs (examples: amphotericin, ketoconazole)

Classification by the mechanism of action

Antimicrobial agents affect susceptible organisms in various ways, and bacteria sometimes protect themselves from these destructive effects by a variety of means [3]. The major mechanisms of action of antimicrobial agents, with examples of each type, are as follows: 1) inhibition of cell wall synthesis: penicillins, cephalosporins and cephamycins, vancomycin, bacitracin, cycloserine; 2) impairment of cell membrane function: polymyxin B, colistin, tyrocidin, amphotericin, nystatin; 3) inhibition of protein synthesis: tetracyclines, aminoglycosides, spectinomycin, chloramphenicol, macrolides, lincosamides; 4) inhibition of DNA synthesis and replication: novobiocin, quinolones, griseofulvin; 5) inhibition of DNA-dependent RNA polymerase: rifamycins; 6) inhibition of folic acid and consequently DNA synthesis: sulfonamides, trimethoprim [4].

1. Drugs that inhibit bacterial wall synthesis or activate enzymes that disrupt the cell wall.
2. Drugs that increase cell membrane permeability (causing leakage of intracellular material)
3. Drugs that cause lethal inhibition of bacterial protein synthesis.
4. Drugs that cause nonlethal inhibition of protein synthesis (bacteriostatics).
5. Drugs that inhibit bacterial synthesis of nucleic acids
6. Antimetabolites (disruption of specific biochemical reactions-->decrease in the synthesis of essential cell constituents).
7. Inhibitors of viral enzymes.

Reasons For Failure Of Antibacterial Therapy

Possible reasons for failure of antibacterial therapy include the following: 1) The diagnosis was incorrect, eg, viral and not bacterial infection. 2) The organisms were not susceptible to the action of the antibiotic that was selected, or they were in static phase and therefore refractory ("persisters"). 3) Although originally susceptible, the bacteria developed resistance. 4) The antibiotic(s) was insufficient for multiple pathogens. 5) A combination of incompatible antibiotics was administered. 6) Superinfection by a resistant opportunistic pathogen occurred. 7) Reinfection by the original or by other pathogenic bacteria occurred. 8) Drainage was inadequate in surgical infections, or

a foreign body was present. 9) Perfusion and penetration to the site of infection were impaired because of inflammation, cellular debris, tissue destruction, abscessation, etc. 10) The organism is intracellular in location and able to avoid detrimental effects by phagocytic cells.

11) Defense mechanisms (specific and nonspecific) of the animal were compromised by disease, malnutrition, or concurrent therapy. 12) Detrimental changes, such as hypoxia, acidosis, or accumulation of tissue debris, developed in infected tissue, which reduced the effectiveness of the antibiotic or sulfonamide. 13) An inappropriate route of administration was selected or an incorrect dosage regimen was followed because the pharmacokinetic characteristics of the antimicrobial drug were not appreciated. 14) Expired or substandard products were used. 15) The selected agent had to be withdrawn because of adverse effects. 16) Interaction of the selected antimicrobial agent(s) with other concurrently administered drugs occurred, which diminished the antimicrobial effect or altered the pharmacokinetics of the agent(s). 17) The prescribed dosage regimen was not reliably followed (lack of owner compliance). 18) Supportive therapy was inadequate. 19) Nutritional deficits were not corrected. 20) Nursing care was substandard, and the stress associated with the disease process was not reduced. 21) Predisposing management factors were not corrected[5].

Emergence of Resistant Bacteria

Antimicrobial resistance is the ability of a microorganism to survive and multiply in the presence of an antimicrobial agent that would normally inhibit or kill this species of microorganism. The emergence of many antibiotic-resistant strains of once-sensitive bacteria is a major theme of current research and scientific literature, and is regularly publicized. Widespread use of antibiotics promotes the spread of antibiotic resistance [6]. Bacterial susceptibility to antibacterial agents is achieved by determining the minimum inhibitory concentration that inhibits the growth of bacteria. Antibiotic resistance first became challenging shortly after Penicillin gained extensive use in the 1940s [7].

There are various factors that contribute to the occurrence of resistance such as; incorrect use of antibiotics, patient related factors, prescriber's prescriptions, use of monotherapy, hospitals, veterinary prescriptions, commercial promotion, over the counter sale of antibiotics, under use of microbiological testing and globalization. Incorrect use of antibiotics such as too short a time, at too low a dose, at inadequate potency or for the wrong diagnosis always enhances the likelihood of bacterial resistance to these drugs.

Mechanisms of Resistance

1. Alteration of Targets – usually affects ribosomes
2. Alteration of Membrane Permeability- Change in the receptor that binds the drug
3. Development of Enzymes – b-lactamase
4. Efflux pumps – Membrane proteins many Gram negatives that pump out drug
5. Alteration of Metabolic Pathway – Development of

alternate pathway

Limiting Resistance

- Constant exposure to high levels of antibiotic
- Use of multiple antibiotics
- Restricted use of antibiotics

New approaches

Increase drug resistance requires new approaches for developing effective antimicrobials

- Prevent iron –scavenging capabilities
- Inhibit genetic controls (riboswitches)
- Probiotics and prebiotics
- Combination therapy
- Phage therapy

Antiviral chemotherapy

Thus antiviral chemotherapy is an exciting frontier with opportunities for making major contributions to improved health from the control of acute, persistent, and latent viral infections that are highly prevalent [8]. The following are the prominent features of Antiviral chemotherapy;

- Difficult as viruses intracellular infective agents and utilise many of host metabolic pathways
- Number of therapeutic agents increasing
- inhibition of viral replication
- modulation of host immune responses

Antifungal chemotherapy

The availability of antifungal drugs with different molecular weights has opened new avenues for exploring combination therapies of two or even three agents [9]. The features of this therapy are

- Tend to be opportunistic infections
- local
- systemic
- Mechanisms of action
- disruption of fungal cell membrane
- inhibition of mitosis
- inhibition of DNA synthesis

Combination Therapy

Treatment with antimicrobial combinations may be necessary in certain cases. The administration of 2 or more agents may be beneficial in the following situations: 1) to treat mixed bacterial infections in which the organisms are not susceptible to a common agent, 2) to achieve synergistic antimicrobial activity against particularly resistant strains (eg, *Pseudomonas aeruginosa*), 3) to overcome bacterial tolerance, 4) to prevent the emergence of drug resistance, 5) to minimize toxicity, or 6) to prevent inactivation of an antibiotic by enzymes produced by other bacteria that are present [10].

Effects of Combinations of Drugs

- **Synergism** occurs when the effect of two drugs together is greater than the effect of either alone
- Streptomycin and penicillin
- **Antagonism** occurs when the effect of two drugs together is less than the effect of either alone
- Tetracycline stops cells from growing, therefore interferes with penicillin, which requires cells to grow

Safety evaluation of antimicrobial agents

When assessing safety of antimicrobial agents, whether or not changes in laboratory values were adverse events, are classified into two groups: a shift from a normal to an abnormal value or an aggravation from the abnormal value before administration. When laboratory values are within the range of abnormal changes, accompanying any adverse symptoms or findings, or possibly resulting in them, or requiring additional tests or treatment, they should be handled as adverse events, and the causal relationship with the investigational drug should be assessed [11] [12].

Future of Chemotherapeutic Agents

Chemotherapy agents are found to use in the treatment of non-cancer conditions like transplant rejections and autoimmune diseases such as rheumatoid arthritis and multiple sclerosis. These agents are classified according to their composite structure, similarity to other compounds, derivation, and mechanism of intracellular action, and can be classified

- **Antimicrobial peptides-** produced naturally, cationic peptides
- **Nubiotics:** antisense strands of DNA that targets the DNA of the pathogen that produces pathogenic proteins blocking synthesis
- **Phage therapy:** virus that are selective in their infective activity
- **siRNA:** Complementary RNA that binds mRNA to inhibit translation of pathogenic proteins
- **probiotics:** Developing antibiotics is not profitable

CONCLUSION

The field of antibiotic drug discovery and the monitoring of new antibiotic resistance elements have yet to fully exploit the power of the genome revolution. In summary, it is clear that the use of antimicrobial agents resulted in the selection of resistant bacteria. Since the advent of new mighty drugs is highly difficult, the proper use of currently available antimicrobial agents as well as efforts to minimize the spread of resistant bacteria through appropriate infection control would be quite important, and may represent a first step in solving the issue of resistant microorganisms.

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