INTRODUCTION

Life, whether that belongs to vegetable or animal kingdom, is extremely complex; the complexity being greater in the more advanced forms of animals. Human body, being endowed with complicated organs, each performing its own functions, is full of varied types of organic compounds some of which e.g., the hormones, the proteins, the enzymes and other metabolites being highly active components.

Then, there are microbes which exist in countless numbers in air, water, food, plants, birds, higher animals (including human beings) and earth. This unavoidable association of the invisible microbes of diverse types has a great impact on all visible forms of life including plants and animals. While many of these invisible associates are good for the development and well being of plants and animals, others, by virtue of their metabolic processes, upset their metabolic functions and cause abnormalities we call infectious diseases. Besides these, through the impact of food or abnormal functioning of various organs or by natural slow changes in the metabolisms of plants and animals, diseases of various types are caused.
Even though human beings, naturally must have tried to fight the various ailments from the very beginning, fairly advanced type of treatments developed in due course giving rise to two good systems viz. the Ayurvedic and the Tibbi systems. Both systems developed around the use of herbs and minerals. These systems, however, had their limitations and a new chapter in this field was opened by Paul Ehrlich (1) who synthesised several valuable arsenicals and demonstrated the use of trypan red (I) ($R = H$ in one unit and $SO_3Na$ in the second unit) as a remedy against African trypanosome infections. Continuation of research led to the development and marketing by Baeyer Dye Works in 1920 of the synthetic drug suramin (antrypol)($\tau$,3) (II).

\[
\begin{align*}
\text{I} & \quad \text{II} \\
\begin{array}{c}
\text{Na}_2\text{O}_5\text{S} \quad \text{N}=\text{N} \quad \text{N}=\text{N} \\
\text{SO}_3\text{Na} \quad \text{SO}_3\text{Na} \\
\text{NH}_2 \quad \text{NH}_2 \\
\text{R} \quad \text{CO}
\end{array}
\end{align*}
\]

Ehrlich coined the word 'chemotherapy' with special reference to the use of chemicals in the treatment of infectious diseases even though it literally means, medicinal treatment with the aid of chemicals or drugs (4).

Since limitations have been placed on the word 'chemotherapy' by Ehrlich's definition of the term, the
headings 'Drug Chemistry' and 'Medicinal Chemistry' are being used to cover the whole field of treatment of diseases by means of chemicals. The initiative for the modern development, however, rests with Paul Ehrlich. Since then innumerable natural products and synthetic organic compounds have been investigated for their physiological and antibacterial activity resulting in a highly fruitful reward in the form of excellent remedies for various infectious diseases as well as diseases caused by other factors. But the success in chemotherapy has been like reaching a destination without knowing the approach roads leading to it.

**Relationship between physiological activity and chemical constitution.**

From the accumulated experience of the last 60 years we are forced to the conclusion that strictly speaking there is no relationship between physiological activity and chemical constitution.

Clark (5), an authority on chemotherapy, in his classical monograph on general pharmacology has concluded that there were 'scarcely any general rules discernible and that every cell drug system was law unto itself'.

This statement receives confirmation by comparing the structures of various compounds which are used for the same
purpose. For example, penicillins (III) and sulphonamides (IV) both are used against streptococci. Morphine (V) and \( \beta \)-diethylaminoethanol (VI) are used as analgesics. Phenylbutazone (VII) and cortisone (VIII) are useful in arthritic and rheumatic diseases.

Isonicotinic acid hydrazide (isoniazid) (IX), \( p \)-amino salicylic acid (X) and ethambutol (XI) are valuable anti-T.B. drugs and there is no relationship between the structures of various drugs in each set quoted above.
Such examples can be multiplied but the above are sufficient to support the point at issue.

In the absence of any definite relationship between chemical constitution and physiological activity, we are confronted with a difficult problem regarding drug design in medicinal research. The two possible courses are:

(1) The empirical approach
(2) The metabolite-antimetabolite approach.

(i) The empirical approach

Even though it has not been possible to establish any relationship between chemical constitution and physiological activity, nevertheless advances in drug chemistry have been made possible through structural variations of all types of physiological active compounds and other systems. A brief account of such features is worth the consideration. Presence of \(-\text{CH}_3, -\text{CH}_2\) \(-\text{CH}, -\text{NH}_2, -\text{NO}_2, -\text{COOH, -COOR (R = alkyl or aryl), -CO-NH-}, -\text{SO}_3\text{H, -SO}_2\text{NH-}, \text{Cl, Br, I in otherwise complicated structures has great influence on their physiological activity.} \)
Methyl group

Introduction of one methyl group in phenol increases its antibacterial action which is further increased by introduction of a second methyl group (6). The two methyl groups in sulphanilamide (II) in the particular positions given in the structure are essential for its activity (7). The best vitamin K activity amongst synthetic 1,4-naphthaquinone derivatives is given by its 2-methyl derivative, Menadione (XIII) only (8). Again replacement of CH$_3$ in vitamin K$_1$ by -OCH$_3$, -OCH$_2$H, -OCH(CH$_3$)$_2$ (isopropyloxy) groups reduces its activity to 1/40, 1/60, and 1/100 respectively and replacement by -H, -OH, -C$_2$H$_5$, -Cl or -Br give rise to inactive structures (9). Vitamins B$_2$, B$_6$, pyridoxine, pyridoxal and pyridoxamine all possess methyl groups in their structures. Amongst the sulphonamides, sulphadiazine (elskoxine) (XIII) ($R = R' = CH_3$) and sulphisoxazole also contain methyl groups (10, 11).
Methoxy group

Quinine differs from cinchonine in having a methoxy group and is a superior antimalarial. Outstanding examples amongst synthetic drugs in which -OCH₃ group is essential for optimum activity are those of mepacrine (12), sulphadimethoxine (XIII) (R = R' = OCH₃) and sulphamethoxy pyridazine (13).

Hydroxyl group

(a) Alcoholic -OH :— Introduction of alcoholic OH group can bring about complex physico-chemical and physiological changes. Methane or ethane are sparingly soluble in water but methyl and ethyl alcohol are freely soluble in water. Glycerine with three OH groups is physiologically less active than propyl alcohol with only one OH group. Hexaldehyde having no hydroxyl group is a toxic substance but glucose having five hydroxyl groups is a valuable food material. According to Burger (14) tertiary alcohols are more active than primary and secondary ones.

Besides the carbohydrates, cardiac drugs and other glucosides, hydroxyl groups are a part of many physiologically active alkaloids, vitamins, enzymes, hormones, steroids, antibiotics and other systems. Systematic studies on introduction of variations in the chloramphenicol (chloromycetin) (XIV) molecule have revealed that the replacement of OH by
hydrogen or alkyl groups leads to compounds which are less potent (15).

(b) Phenolic OH

Phenol is a poison but resorcinol is a mild antiseptic and 4-hexyl-resorcinol is a urinary antiseptic. Morin (XV) having 4-phenolic hydroxyl groups has antimicrobial properties and adrenaline (XVI) is used in cardiac diseases and bronchial asthma.

Phenolic hydroxyl groups are present in vitamins (α-tocopherol), pyridoxine, pyridoxal, pyridoxamine, some alkaloids e.g., morphine (V), 8-hydroxy quinoline which acts as antimicrobial agent by virtue of chelation with metals (16), and in some antibiotics e.g., chlortetracycline (XVII) and (R = H, R' = Cl), oxytetracycline (XVII) (R = OH, R' = H). Therefore, introduction of hydroxyl groups in aromatic or heterocyclic systems can lead to various types of physiological activities.

\[ \text{XIV} \]

\[ \text{XV} \]

\[ \text{XVI} \]

\[ \text{XVII} \]
Amino group

The amino group together with its substituted derivatives is perhaps the most important from the point of view of physiological activity and a brief account under various subheads is considered essential.

A. In aliphatic compounds

(a) As free amino group: The following are some of the important examples of biologically active compounds containing free amino groups.

1) all naturally occurring $L$-amino acids

2) vitamins: pyridoxamine (XVIII)

3) alkaloids: mescaline (XXIX)

4) hormones: serotonin (XXII)

(b) As substituted amino group (other than amidic systems)

1) vitamin choline

2) side chain in synthetic antimalarials e.g., chloroquine (XXI)

3) side chain in synthetic analgesics e.g., 2-diethylamino ethanol (VI)

4) the side chain in adrenaline (XVI)

5) in antibiotics e.g., chlortetracycline (XVII) ($R = H, R' = Cl$) and oxytetracycline (XVII) ($R = OH, R' = H$). 

6) the side chain in synthetic local anaesthetic procaine (XXII)
vii) in vitamins of the pteroyl glutamic acid group e.g., liver \textit{L. casei} factor and yeast \textit{L. casei} factor which differs from first in having two additional -\text{NH-CH-} (\text{C}O\text{CH}) - \text{CH}_2-\text{CH}_2-\text{CO-} groups in the side chain.

B. In aromatic and heterocyclic compounds

(a) As free amino group

i) it is an essential factor in all active sulpha drugs(IV)

ii) co-enzymes systems e.g., flavin-adenine dinucleotide and d.phospho-pyridine dinucleotide

iii) in some vitamins e.g., \textit{B}_1 (thiamine or aneurin) (XXIII) and vitamins of the pteroyl glutamic acid group e.g., liver \textit{L. casei} factor and yeast \textit{L. casei} factor.

iv) some essential metabolites e.g., p-amino benzoic acid
v) some important synthetic drugs other than sulpha drugs e.g., p-amino salicylic acid (X).

vi) the local anaesthetic procaine (XXII) contains an amino group in the benzene nucleus.

vii) the antimalarial daraprim (pyrimethamine) (XXIV)

viii) adenine which is a naturally occurring purine base (XXV)

(b) As substituted amino group

As aromatic side group with an aliphatic side chain in antimalarial amodiaquine (osmoquin) (XXVI).

Amide group

The amide linkage is actually to be regarded as a substitution of the amino group (or of ammonia in simple
cases like acetamide or urea) and is widely distributed in aliphatic and heterocyclic systems. The following are worth mentioning.

i) it constitutes one of the most important groups of all proteins and polypeptide antibiotics including the actinomycin antibiotics

ii) it also forms a part of penicillins (III) (natural as well as synthetic), acetic acid (XXVII), chloroform, oxycycline and chloramphenicol

iii) barbiturates, veronal (XXVII) ($R = R' = C_2H_5$), luminal (XXVII) ($R = C_2H_5$, $R' = C_6H_5$) and others which induce sleep,

uric acid a product of bird metabolism, caffeine and related compounds which are plant products and are sleep destroying,

phenyl butazone (VII) a synthetic drug which is useful in rheumatic fever and phenacetin a strong antipyretic and pain relieving agent contain the amidic groups

iv) the vitamin $B_2$ (riboflavin or lactoflavin), nicotinamide (XXIX) ($R = NH_2$), biotin, pantothenic acid and $B_{12}$ contain amidic linkages

v) coramine (XXIX) ($R = N-(C_2H_5)_2$) a valuable analeptic and LSD (XXX) ($R = H$, $R' = N-(C_2H_5)_2$) the famous psycho-pharmacological agent are diethylamides.
A survey of literature reveals very few drugs which contain a nitro group. The important examples are the naturally occurring antibiotic chloramphenicol (XIV), the synthetic trypanocidal drug, nitrofurazone (XXXI), the fungicidal, furaspor (XXXII) and 5-nitrofurfural oxime. Besides, furazolidone (XXXIII) and furaldantin (XXXIV) have wide antibacterial spectrum (17) and N-(2,5-dimethoxy-4-nitrophenethyl) dichloroacetamide has been reported to be active against Rift Valley Fever (18).
Carboxyl group

The carboxyl group is known to reduce or eliminate toxicity of the various systems e.g., aliphatic amines are toxic but amino acids are essential units of proteins. Phenol is a poison but salicylic acid is a valuable analgesic and p-amino salicylic acid is an anti T.b. drug. Aniline is a poison but p-amino benzoic acid is an essential metabolite. It is a part of all amino acids, the penicillins (III), vitamins, nicotinic acid, biotin, pteroyl glutamic acid, pantothenic acid, linoleic acid and other such unsaturated acids, the hormone thyroxine, the ergot alkaloid lysergic acid (XXX) (R = H, R' = CH) which is an oxytocic agent.

Ester group

The naturally occurring local anaesthetic cocaine is a double ester. Simple esters used for the same purpose are benzocaine and procaine (XXXII).

Sulphonic acid group

The introduction of sulphonyc acid group lowers the toxicity of the parent compound. The trypanocide suramin (II)
and leprosy drug sodium sulfoxone have this grouping (as sodium salt).

**Sulphonamide group**

Like the amino group, the presence of \(-\text{SC}_2\text{NH}^-\) group in para position to the amino in the benzene ring is of vital importance for the bacteriostatic activity of all sulpha drugs. The sulpha drug chemotherapy is important not only because of the discovery of prontosil by Domagk (19) which helped to control streptococcal and gonococcal infections but it also gave evidence for the biochemical aspects of the mode of action and it was established by Pasteur Institute (3) that the real active entity was sulphanilamide. Another far reaching and important effect was the postulation of the metabolite-antimetabolite theory by the English Investigators Woods and Fildes (20). Amongst sulphonamides, sulphathiazole (IV), sulphapyridine, sulphadiazine, sulphasmerizine, sulphamethazine, sulphadimetine (XIII) \((R = R' = \text{CH}_3)\), sulphadimethoxine (XIII) \((R = R' = \text{CH}_3\) \text{O})\), sulphisoxazole and sulphamethoxy pyridazine are important compounds.

**Chloro, bromo and iodo groups**

Presence of chlorine increases the antibacterial or even insecticidal properties. Important examples are the antimalarials chloroquine (XXI), amodiaquine (XXVI) and pyrimethamine (XXIV). The antibiotics chlortetracycline (XVII)
(R = H, R' = Cl) and chloramphenicol (XIV) are powerful antibacterials; chlorpromazine is a highly potent sedative, while DDT and gammexane are important insecticides.

Bromine has been introduced in several steroids. Amongst other compounds bromo isoval (\(\text{CH}_3\text{CHCHBrCONHCONH}_2\)) which is a sedative, is worth mentioning.

Iodoform is a synthetic antiseptic and the presence of iodo groups in the thyroid hormone, thyroxine (XXXV) (R = I) is essential for its activity; the triodo compound (XXXV) (R = H) is said to be more active than the hormone, thyroxine which has 4 iodo groups.

\[
\text{XXXV}
\]

These groups probably bring about the effects outlined above through one and/or more of the following ways.

i) The groups or side chains can add to the geometrical build-up of the main ring systems thus affording possible fitting points with the disease causing factors.

ii) By virtue of their electron release through hyper-conjugation or inductive or mesomeric or electromeric mechanism or through electrostatic attraction through inductive
or mesomeric effect or through Vander Waal's forces, the

groups or side chains can create electron rich or electron
deficient sites which could act as catch points with electron
deficient or electron rich sites of various essential metabolic
systems of the parasites or other disease causing factors e.g.,
penicillin G can afford so many such points as:

![Chemical structure](image)

(iii) The acidic and basic groups can alter the pH values of
the compounds.

(iv) The side chains can be utilised for the introduction of
optical active sites; it being well-known that different
optically active antipodes have markedly different physiological
activities.

(v) The groups or side chains can alter the solubility in
aqueous or lipoid systems thus affording means of being
carried by blood stream and of penetration through membranes.

(vi) The groups are means of chelation with metal parts of
enzyme systems e.g., in oxime (8-hydroxy quinoline) the chelate
could be shown as:

![Chemical structure](image)
A few more additional factors that are known to influence the drug action are outlined below:

(a) **Stereochemistry and biological activity**

Nature exercises a selective role in the synthesis and utilisation of organic compounds with specific configurations as is evident from a few examples given below:

i) Stilbestrol has 14 times greater estrogenic activity than its cis isomer.

ii) Out of the various stereoisomers of hexa chloro cyclohexane only the \( \gamma \) -isomer (gammexane) has outstanding insecticidal activity (21).

iii) Most of the naturally occurring alkaloids are laevo-rotatory and are generally physiologically more active than the dextrorotatory isomers. The same applies to \( \alpha \) -amino acids which occur in various proteins.

iv) Sheehan (22) has established that penicillin (III) \( \left( R = \text{C}_6\text{H}_5-\text{CH}_2- \right) \) prepared from DL penicillamine has only half the activity of the natural product or of that synthesised from D-penicillamine which is very slightly dextrorotatory \( \left( \alpha \right) D = + 0 \) in aqueous solution.

v) The anti T.B. drug ethambutol (XI) is another example in which only the dextro variety is active; the laevoisomer is inactive while meso is only 1/10 as active as dextro (23).
vi) The naturally occurring antibiotic chloramphenicol (XIV) having the D(-) threo configuration is a potent antibacterial agent (24) while the remaining three isomers have no chemotherapeutic utility.

vii) Kepacrine which is racemic is partly utilised by the patient and partly excreted in an optically active form (25). Many drugs are capable of undergoing various conformations thus creating or avoiding chances of interactions with the biological sites.

(b) **Bio-isosterism**

More recently the concept of bio-isosterism involving replacement of certain groups or ring systems by other similar or new approach groups or ring systems with a similar electronic and steric configuration is being developed (26).

Nikethamide (XXXIX) (R = N-(CgHg)g) and diethylamide of m-nitro benzoic acid (XXXVI) have similar analeptic activities due to polar similarities (27) and caffeine and caffeine isoster (XXXVII) exhibit similar diuretic action (28).

![Chemical Structures]

XXXVI

XXXVII

XXXVIIa
(c) The ring systems associated with physiological activity

From the examples already given which are, however, not comprehensive it is obvious that introduction of various types of groups have proved useful. The rings most frequently encountered are: benzene, indole, pyridine, quinoline, acridine, imidazole, thiazole, pyrimidine, purine, pteridine and phenothiazine.

(ii) The metabolite-antimetabolite relationship

Woods and Fieldes (20) put forward a hypothesis which is highly scientific and has potential importance for further development in chemotherapy. Fieldes put his hypothesis as follows:

"Antibacterial substances function by interfering with an essential metabolite and thus inhibit growth. The interference may be (a) by oxidizing a substance which requires to be reduced (b) by molecular combination forming an inactive product and (c) by competition for an enzyme associated with essential metabolites."

It was discovered that various bacteria in the presence of sulpha drug could not utilise an essential metabolite p-amino benzoic acid (PABA) (XXXVIII) for the synthesis of an essential enzyme system and hence the bacteria could not multiply. It was suggested that since sulphanilamide (XXXIX)
(R = H) and other sulpha drugs had identical structures (part shown in XXXIX) with a small difference, the same could interfere with the bacterial enzymic synthesis.

![Diagram of XXXVIII and XXXIX](image)

The theory could be utilised in cases where the nature of the essential metabolites of involving bacteria could be investigated provided these essential metabolites, if released by the uptake of a chemotherapeutic agent by the bacterial system, do not harm the host. Obviously it is equally important that the drug or its complex with bacterial systems do not interfere with the host's metabolism adversely.

A very important issue arises that even when the chemical nature of an essential metabolite is known then what should be the structural features of the proposed antimetabolites. Amongst the various proposals suggested in the 'Designing of antimetabolites' by D.W. Wooley (1961) are the changes of groups and changes in the ring systems. He has given a good example of the stepwise development of a hypertension drug BAS (1-benzyl-5,6-dimethyl serotonin) (XI) (R = OCH₃) as antimetabolite of the widely distributed hormone serotonin (5-hydroxy tryptamine-(5HT) (XII).
Amongst other related physiologically active compounds are LSD (XXX) \((R = H, \ R' = -N(C_2H_5)_2)\) methyl sergide (XXI) \((R = CH_3, \ R' = NH-CH(C_2H_5)_2)\) and reserpine (XLI) \((R = CO-C_6H_5)\).

\[
\begin{align*}
\text{XL} & \\
\text{XLI} & 
\end{align*}
\]

Chloramphenicol (XIV) is a non-competitive inhibitor of phenylalanine \((e \Theta)\) and is a powerful antibacterial. These examples indicate that new chemotherapeutics could be built around the essential metabolites by introducing small as well as more significant changes.

The development of primethamine (daseprim) (XXIV) as a highly potent antimalarial prophylaxis through a study of the active metabolite (XLIII) formed from paludrin or proguanil (XLIII) in animals treated with this drug is primarily due to metabolite-antimetabolite consciousness combined with the most important factor in drug development i.e. the Research Spirit with keen observations.
For the development of new chemotherapeutics we have to build around the structures of vitamins, hormones, and metabolites, steroids, heterocyclic, which form parts of the enzyme systems i.e. pyrimidine and purine derivatives etc. the polyamides, amino acids, natural plant and animal products of known chemotherapeutic values, antibiotics, sugars, modifications of the existing drugs and in short the known systems and the new ring systems not yet investigated by the empirical approach near as well as far metabolite antimetabolite relationships; the group variations in various systems being a very important aspect of research in medicinal chemistry.

In this connection it is worthwhile to quote the observation by James Walker (4).

"The large number of independent or scarcely dependent, variables, often unknown and unsuspected, that are encountered on the biological side of chemotherapy is a great embarrassment to those who are engaged in this field, and is one of the reasons why so much work in chemotherapy is of a seemingly empirical nature. The enormous benefits, however, which modern
society owes to advances in chemotherapy are ample evidence that research work in chemotherapy can be rewarding inspite of its many disappointments, a source of satisfaction to workers in the field, and a stimulus to further endeavour".

"In chemotherapy we have, on the one hand, brilliant practical successes in the treatment of protozoal, spirochaetal and bacterial infections, and on the other hand, almost complete ignorance concerning the biochemical foundations upon which these successes rest. It is only as our knowledge of the fundamental biochemistry of microorganism grows that we may expect to reach a fuller understanding of chemotherapeutic processes and the gaps in the chemotherapy may be filled in. In the meantime new chemotherapeutic agents will continue to be discovered, even if, as yet, they cannot be created".

Secondly even if we concentrate on the study of bacterial metabolism then by the time we completely understand all the biochemical aspects involved in disease causing bacteria and also in the host, small biochemical changes might also crop up in the bacteria giving rise to new problems. The main solution of the whole problem, therefore, lies in the continuation of Research Spirit. An eye on the electronic structures and geometrical shapes might also help in this venture because they possibly offer catch points with bacterial
metabolites, e.g. benzylpenicillin has several major and minor catch points as already stated.

For the development of catch points, polar groups, groups containing double or triple bonds, factors having free pairs of electrons and heterocyclics with so much opportunity of points with varied electronic distributions should be introduced. Another possible important aspect is the pH value of the chemotherapeutics.

With this background of drug design and their development, we are faced with the question: why do we need to develop more of them when we have already got a host of marvellous medicines which have considerably reduced the suffering of mankind. This may be attributed to the following few factors.

(1) From the past experience we know that the continuous use of many drugs over a long period, lowers their curative effect. This is mainly because of the drug resistance property of the microbes (30). Due to this even the best drugs like sulphonamides, penicillins and streptomycin are reported to be becoming lesser effective in curing certain diseases (31).

The danger of drug resistance can be, to some extent, reduced by measures such as administration of large doses of
the drug from the very beginning of the treatment, changing the drug if an infection shows signs of resistance and using two drugs at the same time, such as for example, streptomycin and para amino salicylic acid in tuberculosis (32).

(ii) With the advanced technique of diagnoses we have been able to diagnose numerous microbial enemies of mankind and we are conscious of the fact that we do not have a potent drug which could prove fatal for the disease causing bacteria e.g. the antibiotics have not shown any encouraging results in the treatment of leprosy and cancer.

(iii) As the world population has been growing and there is great deal of stress on automatization, there is stiffer competition for professional opportunities which has raised the number of psychosomatic and mental disorders and their attendant psychological consequence to unexpected levels. So we will have to bear this fact in mind and devote our energies and resources to find a drug which would solve this problem completely.

(iv) Another important factor is the high cost of present day drugs which are, sometimes, beyond the reach of a common man. This aspect also needs a full attention for the discovery and development of cheaper drugs.
Now this introduction equips us to present a discussion of the present work and its object.