PART I

CHEMOTHERAPY OF MYCOBACTERIAL INFECTIONS
Chapter I

General Introduction
Mycobacterium is the generic name of a class of bacteria belonging to the family Mycobacteriaceae of the order Actinomycetales. Mycobacterium tuberculosis and Mycobacterium leprae, the causative organisms of tuberculosis and leprosy respectively, belong to this family. These two organisms and the diseases they cause have a degree of similarity in morphology and pathogenesis respectively and they are, therefore, dealt with together in the present discussion.

**Cellular structure of Mycobacteria**

Both *M. tuberculosis* and *M. leprae* are acid-fast organisms and contain in their structure a large proportion of waxy (lipoid) material. They possess certain prominent cytological peculiarities which endow upon this group of organisms their definitive specificities. The tubercle bacillus is surrounded by a slimy envelope having a high concentration of RNA (Ribonucleic acid) in conjugation with specific polysaccharides and lipids. The slime envelope affords a certain measure of permeability protection to the organism. The cell wall consists of proteins, lipids, polysaccharides and nucleic acid. Next comes the cytoplasmic membrane which appears to be the principal contributor to the permeability specificity of mycobacteria. Much of the lipid constituents of the bacilli are located in this region and the cytoplasmic
membrane appears to be intimately connected with their elaboration. The lipids appear to be present as stable lipid-protein and lipid-polysaccharide complexes, and this combination appears to account for the acid-fast character of the bacilli and endow upon them their highly specific permeability characters. Lipids may constitute as much as 30 per cent by weight of the dried organisms.

Pathogenesis of tuberculosis and leprosy

The tissue reactions due to the presence of bacilli are similar in tuberculosis and in leprosy. In both cases, after entry into the body, the bacilli are phagocytosed by monocytes. In tuberculosis the ingesting monocytes increase in size and become epithelioid cells, and fusion of these epithelioid cells leads to the formation of Langhan's giant cells, which aggregate together to form a tubercle. With the growth of the tubercle, the surrounding blood vessels get into a state of stasis and the blood supply becomes oscillatory. Finally, the blood vessels degenerate and as a result the access of the bacilli to the blood-borne phagocytes is cut off and the tubercle gradually becomes avascular. If at this stage, the bacilli continue to multiply, the central portion of the tubercle becomes necrosed and a caseous mass is formed. Profound biochemical changes take place
around the actively developing tubercle with widespread tissue destruction and inflammation caused by a conditioned hypersensitivity induced by the products of metabolism of virulent pathogens (especially the proteins). Due to this inflammation, the permeability of the blood vessels around this area is considerably altered. As a result of this necrosis certain biochemical changes also take place inside the tubercle.

Similarly, in lepromatous leprosy the monocytes, after ingesting the bacilli, are themselves parasitised and the bacilli multiply in the cytoplasm. As a result, the monocytes are transformed into "lepra cells". Further, lepra bacilli appear to possess a predilection for cutaneous and nervous tissues. Often the first lesion noted after infection is a macule. In the macules the lepra cells arrange themselves in follicles surrounded by small round cells and are seen to contain globe-shaped bodies—the "globi" filled with bacilli. The lepra cells now undergo a curious fatty change with the formation of vacuoles filled with fatty material and masses of bacilli, and are now called "foamy cells of Virchow". The foamy appearance is due to lipid or waxy material, probably produced from the bodies of dead bacilli, forming a matrix in which the living bacilli lie embedded. Externally, the tissue under the epidermis now has the appearance of raised nodules (also called macules or ulcers). In advanced cases the nodules may contain, in addition to
the lepra cells, large amounts of fibrous tissue, which may contract later and result in the hardening of the nodule. Thus in lepromatous leprosy the bacilli are present mainly in the nerve twigs. In the tuberculoid type of leprosy, where the tissue response is more vigorous, the macrophages, after ingesting the bacteria, are rapidly transformed into "epithelioid cells". Immediately new macrophages are mobilized and round-cells concentrate around the epithelioid cells giving rise to the characteristic tuberculoid foci. As in tuberculosis the epithelioid cells coalesce to form the giant cells of Langhan. The bacilli are thus anchored and walled off in the subcutaneous tissues and the spread of infection is inhibited.12,13

Therefore, apart from the rugged morphology of the mycobacteria and their unusual host-parasite relationship, other factors like their intra-cellular mode of existence, the avascular nature of the lesions, the predilection of lepra bacilli for nerves, and the chronic nature of the infections greatly restrict the scope of potent antimycobacterial agents. The ready emergence of resistant strains in tuberculosis further complicates the problem. The biggest obstacle to the progress of chemotherapy of leprosy is the inability to culture M. leprae in an artificial medium or to transmit human leprosy to experimental animals, thereby ruling out direct in vitro and in vivo screening tests for potential antileprosy agents.
Requirements of an ideal anti-mycobacterial agent

From the above discussion of the morphology of the mycobacteria and their histopathogenesis it is clear that an effective antimycobacterial drug should be highly diffusible so that it may reach all tissues including the meninges and the brain. Further, it should be able to penetrate the monocytes, the in vivo habitat of the bacilli, and the avascular necrotic foci, in sufficiently high concentration. It has to be emphasized that mere availability of the drug is not enough; it must be effective in a variety of biochemical environments, particularly those met with in the lesions which are often full of necrotic and caseous tissues. The drug has also to be effective against the various stages of their growth, ranging from organisms actively dividing to those which are dormant. Because of the chronic nature of the disease the drug must also be relatively non-toxic as it has to be administered over long periods. It should stay in the body for a reasonable period without being excreted or chemically changed, so that there may be sufficient time for the drug to exert its full action.

History of the chemotherapy of mycobacterial infections

Ever since the discovery of the tubercle bacillus by Koch in 1882 several thousand compounds have been tested
for the chemotherapy of leprosy and tuberculosis.\textsuperscript{14,15} Till recently, however, no effective drug was available for tuberculosis, though for leprosy, the traditional treatment with chaulmoogra and hydnocarpus oil had found a definite place in clinical practice.

Based upon the effectiveness of chaulmoogra esters in the treatment of leprosy and the fatty nature of the cytoplasmic membrane of the tubercle and lepra bacilli (some ideas of the constitution of which had been obtained by the pioneering work of Anderson's school\textsuperscript{16,17}), the first rational attempt at the chemotherapy of tuberculosis and leprosy was made by Adams\textsuperscript{18} and Rogers\textsuperscript{19} in the U.S.A. They synthesised and tested a large number of straight and branched chain fatty acids and their esters. Later Barry synthesised a number of mono- and di-esters of succinic acid and analogues of the plant product roccelic acid,\textsuperscript{20-24} which had shown some promise in tuberculosis. Although some of these compounds did possess significant \textit{in vitro} antitubercular activity, none was found very effective \textit{in vivo}.

The first advance in the chemotherapy of tuberculosis was the demonstration of the \textit{in vivo} antitubercular activity of sulphanilamide (known since 1908) by Rich and Follis in guinea-pigs.\textsuperscript{25,26} But neither sulphanilamide nor its derivatives sulpha-pyridine, sulphadiazine and sulphathiozole, nor any other compound of the sulphonamide series was found to be useful in experimental tuberculosis.
A more promising field was opened up in 1939 by the demonstration of the high antitubercular activity of diaminodiphenyl sulphone (DDS) by Rist. The chronic toxicity of this compound led to the preparation of a number of its water soluble derivatives such as, Promin (p, p'-diaminodiphenyl sulphone-N:N'-didextrose sodium sulphonate), Diasone (p, p'-diaminodiphenyl sulphone-N:N'-disodium formaldehyde sulphoxylate), Promizole (2:4-diamino-5-thiazolylphenyl sulphone), and Sulphetrone (tetra sodium-p:p'-bis(γ-phenyl propylamino) diphenyl sulphone tetrasulfonate). These were less toxic and showed encouraging results in experimental tuberculosis of guinea-pigs, but their clinical trials were rather disappointing.

By 1940, the similarity between the pathogenesis of tuberculosis and leprosy was established, and this led workers in the field of leprosy to try Promin against leprosy. Clinical trials were started at the National Leprosarium, Carville, U.S.A. in 1941 and after two years of continuous treatment, Faget et al. reported a definite clinical improvement with this drug, and soon sulphones became the drugs of choice for the treatment of leprosy. The role of sulphones in the treatment of tuberculosis and leprosy is described in detail later.

In recent years, a wide variety of organic compounds has been shown to possess antitubercular activity. These include diphenyl amines, amidines, half esters of
aliphatic dicarboxylic acids,\textsuperscript{20} thiocarbanilides,\textsuperscript{41-46} hydrazides,\textsuperscript{47-50} hydrazones,\textsuperscript{51} thiosemicarbazones,\textsuperscript{52} amides\textsuperscript{53,54}, diphenyl sulphones,\textsuperscript{27} non-ionic detergents\textsuperscript{55} and various antibiotics. Of these only Para-amino salicylic acid (PAS), Streptomycin (N-methyl-1-glucosamido-streptosido-streptidine) and Iso-nicotinic acid hydrazide (INH) have been clinically accepted, and Pyrazinamide\textsuperscript{56-57} (Aldinamide), Cycloserine\textsuperscript{58} (Oxamycin or D-4-amino-3-isoxazolidone) and Thiosemicarbazones (p-acetylamino-benzaldehyde-thiosemicarbazone or TB-1/698) are also occasionally used. However, these drugs are bacteriostatic and none of them, individually or in combination with others, is capable of completely eradicating the infection.\textsuperscript{59} Apart from their inability to completely eliminate the bacilli from the system, these drugs lead to the emergence of resistant forms of the bacilli, thus introducing a new problem in the treatment of tuberculosis. This has been partly solved by combination therapy involving the simultaneous use of two and sometimes even three antitubercular agents. Such a course of treatment delays the emergence of resistant forms considerably. Since cross resistance to two or more drugs is rare combination therapy provides as satisfactory a solution of this difficulty as is possible in the present state of knowledge of the factors involved in the chemotherapy of tuberculosis.

The success of sulphones, which had originally received recognition as potent antitubercular agents in
the treatment of leprosy, stimulated the testing of a number of compounds, which had earlier been found to be promising in tuberculosis, for their antileprotic activity, but none of these compounds showed any significant activity except the thiosemicarbazones, which have a limited application in cases of sulphone sensitivity.60,61

As Chaulmoogra, PAS, Streptomycin, INH and Sulphones are the only drugs in vogue for antimycobacterial therapy (leprosy and tuberculosis), their individual merits and drawbacks are discussed separately.

Chaulmoogra oils in leprosy.— The efficacy of Chaulmoogra (Hydnocarpus) oil in the treatment of leprosy has been known in Asian countries since the 14th century and until the discovery of sulphones in 1943, it was the only effective remedy for this disease. Hydnocarpus oil is obtained from the seeds of certain species of Hydnocarpus viz., Hydnocarpus wightiana (South-West India), Hydnocarpus anthelminthes (Siam, Indo-China, Burma) and chaulmoogra oil is obtained from Taraktogenus kurzii (Burma). Chemically these two oils are identical and contain a mixture of two cyclopentenyl fatty acids—chaulmoogric and hydnocarpic acids. The preparations of the oils most commonly used are:

(1) Pure oil (subcutaneously or intramuscularly).

(2) Ethyl esters of hydnocarpic and chaulmoogric acids (intradermally).

(3) Salts of the above two fatty acids; usually sodium hydnocarpate (intravenously).
Chaulmoogra preparations have been of value in the control of the disease and in the suppression of its pathological outbursts. The exact mode of action of chaulmoogra has not been conclusively elucidated, but it has been claimed that the fatty acids of the oil are directly bactericidal in vivo.$^{62,63}$ There is also a belief that the oil exerts a solvent action on the fat containing bacterium, thus liberating an endotoxin which stimulates immunity response.$^{63,64}$ It has, however, been shown recently by Gozsy and Kato that the oil stimulates the phagocytic defence mechanism of the host to increased activity.$^{65,66}$ Chaulmoogra treatment is invariably accompanied by toxic symptoms of local irritation, dizziness, pain and choking in the chest, insomnia, kidney troubles and anorexia. Intravenous administration of sodium hydno-carbate causes, at times, thrombosis of the veins. Chaulmoogra oil and esters bring about a fairly rapid bacteriological response, but clinical improvement is very slow. In recent years though chaulmoogra oil has to a great extent been replaced by the sulphones, it is still important in the treatment of tuberculoid leprosy and sometimes even in early cases of lepromatous leprosy.$^{67,68}$

Para-amino salicylic acid.— In a search for competitive inhibitors of benzoate and salicylate, which increase the oxygen uptake of tubercle bacillus, Lehman$^{69}$ found p-amino salicylic acid (PAS) to be the most effective inhibitor. Subsequent investigations revealed that though
PAS had a strong bacteriostatic effect on the proliferation of the tubercle bacillus, a moderately suppressive effect on experimental tuberculosis in mice, and a definite though limited effect on clinical tuberculosis, it was inferior in its antitubercular activity to sulphones, streptomycin and INH. Para-amino salicylic acid is, however, used clinically mainly as an ancillary drug to streptomycin and INH, its chief advantage being that it delays the emergence of resistant forms and, in the case of INH, also helps in the maintenance of a high blood concentration of the latter.

Para-amino salicylic acid has to be administered in large doses, especially when used alone, and sometimes it causes troublesome gastro-intestinal symptoms. It is rapidly absorbed after oral administration and gets fairly evenly distributed. Its bacteriostatic activity is regarded as being due to its interference with the respiratory enzyme system and the protein metabolism of the pathogenic mycobacteria.

Streptomycin. — Streptomycin (N-methyl-l-glucosamido-streptosido-streptidine), isolated in 1944 from Streptomyces griseus, was shown to be highly effective against experimental tuberculosis of guinea-pigs and mice, and in human tuberculosis. It was soon established that streptomycin exerts a profound effect on the clinical course of pulmonary tuberculosis. However, streptomycin is bacteriostatic and is not able to eradicate the infection
completely. It is fairly toxic and sometimes leads to irreversible damage of the auditory nerve. Further, it provokes the emergence of resistant forms of mycobacteria quite rapidly, but this can be delayed by using streptomycin in combination with PAS or INH.

Streptomycin is highly soluble in water and is administered parenterally. It is well distributed in all the body fluids, but a permeability barrier to streptomycin exists at the cell wall and on the surface of the mitochondria, and hence streptomycin is not very effective against intra-cellular tubercle bacilli or those present in caseous lesions. Its action is confined mainly to extra-cellular bacilli and this would explain the greater success of streptomycin therapy in the treatment of the acute exudative stage of tuberculous infection.

In bacteria, especially E. coli, streptomycin has been shown to inhibit the "oxalacetate-pyruvate" reaction which is essential for the oxidation energy process of the organism. It also inhibits diamine-oxidase and interferes with inositol metabolism. Recently, Umbreit has shown that streptomycin blocks the formation of an essential metabolite, 2-phospho-4-hydroxy-4-carboxy adipic acid from a dicarboxy acid and pyruvate in E. coli. However, the exact mode of action of streptomycin against M. tuberculosis is not known, but it is supposed to interfere with a number of polysaccharide enzyme systems essential for the process of cell division and synthesis of the
Catalytic reduction of the aldehyde group in streptomycin gives dihydro-streptomycin. It is equally effective, well tolerated by patients hypersensitive to streptomycin and has comparatively less neurotoxicity. However, the bacilli resistant to the one are also resistant to the other.

**Isonicotinic acid hydrazide.**—The introduction of isonicotinic acid hydrazide (isoniazid, INH) has provided the most potent single drug up to date for the treatment of tuberculosis. It inhibits the growth of *M. tuberculosis* in concentrations as low as 0.05 ug./cc. and is both bacteriostatic and bactericidal—especially against actively dividing organisms. It produces an impressive therapeutic effect in clinical tuberculosis.

Isoniazid has the great advantage that it can be given orally and in relatively low dosage. It is easily absorbed, gets evenly distributed in the tissues and body fluids including the cerebrospinal fluid, caseous areas and dense fibrous capsules of caseous lesions. As far as it is known there are no permeability barriers to INH. Suter and Mackaness have shown that INH is active against both intra- and extra-cellular bacilli in the same concentration. The exact mode of action of INH is not known, but its remarkably high index of activity indicates that it affects the organism at some site vital to the normal growth and multiplication of the bacterial cell.
The antitubercular action of INH is inhibited \textit{in vitro} by pyridoxal, pyridoxine (although this inhibition does not take place \textit{in vivo}), pyridoxamine, ketoglutarate and pyruvate,\textsuperscript{34} and it has been suggested that INH acts as an antimetabolite against the enzyme, pyridoxal-phosphate-complex, which is essential for transamination.\textsuperscript{95,96}

As compared to other antitubercular drugs, INH is practically non-toxic but it exerts a minor toxic effect on the central nervous system causing hyper-reflexia, peripheral neuritis and toxic psychosis.\textsuperscript{37} Pyridoxine deficiency has been reported with high doses of INH and this can be prevented by giving pyridoxine. The greatest drawback in INH therapy is the rapid emergence of resistant strains of mycobacteria. In a majority of cases resistant forms develop within three months of the treatment. At one time it was thought that these resistant strains were avirulent because of their reduced virulence for guinea-pigs, but it has now been shown that they retain their virulence for the human host.\textsuperscript{38} It has been shown that a combination of INH with streptomycin or PAS reduces considerably the early emergence of resistant strains. Combination therapy has been recognized to be the most suitable form of chemotherapy in the treatment of tuberculosis.

Though the active antitubercular drugs discussed above are widely divergent in their structures, all of them have a basic nitrogenous system and all (except DDS) are capable of chelating heavy metal ions. The presence
of basic centres in the drug molecules may not be purely fortuitous. It is likely that these centres facilitate the approach of the drug molecules and their transport across the acidic slime which surrounds the mycobacteria. In some cases it has been shown that antitubercular activity is directly related to the chelating ability of the molecule. It has been suggested that INH, which forms strong chelates, acts through this mechanism. This is further corroborated by the inability of the N1 substituted INH to chelate and the consequent physiological inactivity of such a molecule. Substitution at N2 does not affect chelation, and N2-substituted compounds are in general biologically active. It may be that the activity of INH is due to its ability to chelate essential metal cations of essential enzyme systems of M. tuberculosis.

Foy et al. have prepared the metal chelates of streptomycin with copper, nickel and cobalt and have shown that although copper chelate is more toxic, it is longer acting than streptomycin.
Antitubercular Detergents

A new concept in mycobacterial chemotherapy has been introduced by the work of Cornforth, Hart and Rees, who have shown that a group of non-ionic surface active agents (detergents), though not active by themselves in vitro, are able to suppress active tuberculosis in mice and also cause regression and healing of an established infection in guinea-pigs. As the action of these agents is mediated through the host, it is possible that such agents may not give rise to the emergence of drug resistant strains—a problem that has assumed considerable importance in the chemotherapy of tuberculosis.

Chemically these compounds are linear or macrocyclic polyoxyethylene ethers, prepared by the successive condensation of \( p \)-tertiary octyl-phenyl with formaldehyde.
and ethylene oxide. The compounds so far reported in this series are, however, toxic and cause damage to the liver and have, therefore, not been tested clinically.

It has been shown that after administration, these detergents concentrate in the monocytes and act on the tuberculous infection by modifying the surface lipids of the tubercle bacilli inside the monocytes, making them more susceptible to phagocytosis. This has been supported by the observation that although tubercle bacilli proliferate readily in macrophages obtained from normal animals, they do not grow in macrophages obtained from animals pretreated with these detergents.

**Present status of sulphones in the chemotherapy of tuberculosis and leprosy**

The sulphones comprise a group of drugs derived from 4,4'-diamino-diphenyl sulphone (DDS). The parent compound was first synthesized by Fromm and Wittmann in 1908 but its high antibacterial action in streptococcal infections was discovered as late as 1937. Diamino-diphenyl sulphone was, however, considered too toxic for administration to man and attempts were made to synthesize its derivatives in the hope of reducing the toxicity. The first derivative to be synthesized was Promin (p,p'-diamino-diphenyl sulphone-N,N'-didextrose sodium sulphonate), but neither Promin nor any of the other sulphone derivatives,
which have since been synthesized, have found favour in the treatment of common bacterial infections. However, the demonstration of antitubercular action of DDS by Rist et al. in 1940 and that of Promin by Feldman et al. in 1941 focused attention on the potential value of sulphones in the chemotherapy of tuberculosis. The results in human tuberculosis were, however, not very encouraging, and about this time the sensational discovery of the powerful antitubercular drug streptomycin was announced. The latter overshadowed the importance of DDS and further work in the field of sulphones as antitubercular agents was greatly retarded.

Faget and his associates, however, showed that Promin gave better results in leprosy than any previously used drug and that it was well tolerated. This was followed by trials with other disubstituted derivatives like Diasone and Sulphetrone which also proved clinically efficacious and were widely adopted for the treatment of leprosy. Although for sometime the various substituted derivatives of DDS were used because of their presumed lower toxicity, it was realized fairly soon that after administration these derivatives were hydrolysed to DDS which was in fact the active entity. This led to the use of DDS in the treatment of leprosy, and now it is known that by controlled dosage and simultaneous antia anaemic treatment most of the toxic effect of DDS can be
Sulphones have undoubtedly brought about a major revolution in the treatment of leprosy and for the first time there are indications that a specific cure for this disease will be found in the future. However, with sulphones it takes four to five years before the patients become bacteriologically negative and in some cases the treatment has to be continued even longer so that relapse may be avoided. With a view to increasing the activity and decreasing the toxicity of this class of compounds, a number of DDS derivatives have been synthesized but none of them has been found to be better than the parent DDS. These derivatives may be classified as follows:

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\begin{align*}
R & \quad \text{HN} & \quad \text{SO}_2 & \quad \text{NH} & \quad R' \\
\end{align*}
\]

1. **N-monosubstituted derivatives** - In these the hydrogen of one of the amino groups is substituted by groups like acyl, alkyl, carboxy or hydroxy alkyl.\textsuperscript{127,128} It was noted that the substitution in the amino group did reduce the toxicity and some of the compounds had a higher bacteriological index and were absorbed better than DDS,\textsuperscript{129} but none has been so far accepted clinically.

2. **N,N-disubstituted derivatives** - Most of the emphasis in sulphones has been on these disubstituted derivatives. In these compounds both the amino groups are substituted with
acyl, or alkyl groups or sodium bisulfite addition products of the corresponding Schiff's bases. Although it was thought in the earlier stages that some compounds like Diasone, Sulphetrone and Promin were active and less toxic, it was soon realized that disubstitution in general reduced the activity and only those compounds which possessed a labile C = N - linkage were active because on hydrolysis by the host metabolism, these could liberate DDS which was the active entity.

3. Heterocyclic sulphones - Bambas and others synthesized a number of analogues of DDS in which one or both the phenyl groups were replaced by heterocyclic moieties, e.g., pyridyl, thiazolyl, thiadiazolyl, quinolyl, benzothiazolyl, etc. In this class only those which had at least one phenyl ring with an amino group in the para position were active. Although some were active and less toxic than DDS, only Promizole (2:4'-diamino-5-thioazolyl-phenylsulphones) showed any promise.

4. Nuclear substituted derivatives - These carried one or two hydroxyl, methoxyl or acetyl sulphonamide groups in the phenyl rings of DDS. Of these only 4:4'-diamino-2:2'-diethoxy (and dihydroxy) diphenyl sulphones and Promacitin (sodium p,p'-diamino-diphenyl sulphone-2-acetylsulphonamide) gave promising results but even these have not found much favour with the clinicians.

Metabolism of Sulphones:

Metabolic studies with the sulphones have been
restricted mainly to DDS and the disubstituted derivatives Sulphetrone, Diasone and Promin.

Several workers\textsuperscript{137,138} have studied the metabolism of DDS and have shown that it is almost completely absorbed into the system after oral administration. After absorption it gets fairly well distributed in the blood and in the various body tissues, the maximum concentration being attained in the liver and kidney. It reaches a maximum level in the blood in 3-4 hours and is then gradually excreted, mainly via the kidney. It is excreted largely as a water soluble derivative and in some cases as much as 80\% is excreted in this form. Bushby and Woiwood\textsuperscript{139} have recently identified the excreted product as the monoglucuronate of DDS and have shown that DDS exists in the body almost entirely in this form. They believe that the activity of DDS is due, at least in part, to its conversion to this mono-substituted derivative.

The disubstituted sulphones—Sulphetrone, Diasone and Promin—are all characterized by a labile C=\text{N} linkage and it has been shown that they are hydrolysed by the stomach acids to DDS. Bushby and Woiwood, who studied the metabolism of sulphetrone in detail, showed that after parenteral administration, sulphetrone is converted into semi-sulphetrone, which actually is the active substance.\textsuperscript{139}

Mode of action of Sulphones:

There have been no real contributions towards the explanation of the mode of action of sulphones. From
their structure it has been suggested that their action may be due to the antagonism of \textit{p}-aminobenzoic acid (PABA). However, PABA has so far not been shown to antagonise the antimycobacterial action of sulphones.

In leprosy, it has been observed that the bacteriological pictures of lesions under regression, with or without sulphone treatment, are similar and it has been suggested that sulphones act primarily on the Virchow cell component, probably altering its metabolism and rendering it unsuitable for the multiplication and survival of bacilli.

\textsuperscript{140,141}