CONCLUDING REMARKS

The pursuit of chemotherapy is a hard task and requires a patient pharmacological understanding of the problem. This again involves the application of scientific knowledge from various branches of science, - chemistry, biochemistry, pathology and medicine. Naturally, the work is one of collaboration, and is time-consuming. Further, chance plays its own role in its success or failure. Nevertheless, the spirit of systematic approach in pharmacology has yielded a rich harvest of new drugs and remedies against the diverse ills of humanity.

The investigations recorded in this Thesis also stem from similar considerations, though limited in its sphere and application. The purpose was to get some idea about a number of synthetic compounds regarding their chemotherapeutic possibilities.

The study started with the testing of certain sulphonamido-acridines and sulphonamido-quinolines. It has been shown that sulphonamido-substitutions in S-amino acridine, known to be a powerful anti-bacterial agent, brings about a lowering in the biological properties. A similar dystherapeutic effect is noted in the sulphonamido-quinoline series as well.
The next line taken up was to study certain $N^1$- and $N^4$-substituted sulphanilamide derivatives synthesized with the purpose of widening the range of activity. The observation of a powerful anti-pneumococcal action of sulhamethylthiazole was made from this laboratory (Part I); a possibility of chronic toxic effects of this compound was also noted at the same time (Part II; Bose, 1941) which had subsequent confirmation from other sources (Beiter et al., 1944; Vandyke, 1943). Some pyrazolone and benzo-thiazole derivatives being inactive, $N^1$-benzoysulphanilamide (sulphanilylbenzamide) was thoroughly studied on account of its powerful bacteriostatic properties in-vitro against various pathogens, causing systemic as well as intestinal lesions. This brought out the significant protective action of the compound against both Streptococcus haemolyticus and Pneumococcus Type I infections of mice, as well as demonstrated the clinical efficacy of the compound in bacillary dysentery (Part I; Bose and Ghosh, 1945). This finding has been corroborated by others as well (Swyvor and Yang, 1945; Majumdar et al., 1945). A thorough toxicological study, distribution of the drug in blood and tissues, and the amount of urinary excretion in various animals and human beings followed rapidly (Part II; Bose, 1944). In order to explain how an absorbable drug like sulphanilylbenzamide could act in the treatment of bacillary dysentery, in view of Marshall's hypothesis of low absorbability and high local concentration in the gut for effective anti-dysenteric action, an extensive work was carried
from a new angle (Bose 1946, 1951). The idea was to find out whether the drug, after absorption was again being re-excreted in the intestines to exert a local chemotherapeutic effect. The study was done by injecting the drug subcutaneously to guineapigs, and examining the washed contents of the lumen of the different parts of the bowel at different intervals of time, generally 4 and 6 hours. The studies showed that sulphanilylbenzamide has a tendency to be excreted more through the caecum and large intestine at the 4th hour in sufficiently high therapeutic concentration (cf. Hawking, 1960). During this period sulphathiazole is excreted more through the small intestine. Sulphapyridine and sulphaguani­dine are scantily excreted under these conditions. Sulphanilamide also does not show such preferential excretion through the large bowel. It has been suggested from these studies that with all anti-dysenteric sulpha remedies, particularly the absorbable drugs, selective re-excretion through the caecum and large intestine might play a useful part in imparting therapeutic activity. Such re-excretion from the gut is further likely to control the subacute, chronic and carrier stages of the disease more effectively than compounds of low absorbability, because the drug can reach the infected ulcers only through such mechanism of systemic circulation (Part III (iii), Bose et al., 1946). Weil (1947) in a later review has stressed the importance of this aspect of the problem by stating "that therapeutically effective sulphonamide is only that which reaches
the tissues; or inversely, activity within the intestinal lumen is of no particular interest as far as dysenteric infection is concerned. Thus, sulphonamides of low water solubility have largely given way to those of high water solubility, particularly to sulphadiazine (Hardy 1946). Sulphathiazole is as effective or nearly as effective as sulphadiazine.

A comparative study with two more proved anti-dysenteric remedies, namely, succinylsulphathiazole and phthalyl-sulphathiazole along with the derivatives, succinyl-sulphabenzamide and phthalyl-sulphabenzamide also brings out the importance of such selective re-excretion through the large bowel (vide Part I, II, and III (iii)). In this respect it has been shown that phthalyl-sulphathiazole possesses pharmacologically more potentiality as an anti-dysenteric remedy than succinylsulphathiazole.

The studies also focus the attention on the phthalyl and succinyl derivatives of sulphanilylbenzamide as possible new chemotherapeutic agents for bacillary dysentery, and allied disorders. In this respect, phthalyl-sulphabenzamide shows more advantages on account of its selective excretion through the caecum and large intestine and a low concentration in blood. The benefit of succinyl sulphabenzamide lies in maintaining the highest concentration in the large intestine, which may serve to tackle
resistant conditions of the large bowel, as found in chronic colitis. However, its high concentration in blood, and a fair proportion of gastric concentration at the same time suggest a careful attention during its trial. Except this compound, all the other three N\textsuperscript{4}-substituted derivatives are of low absorbability, and as such are likely to be well-tolerated.

During the course of the investigations again, certain amidino derivatives of sulphanilylbenzamide and hydroxymethyl amino derivatives of different sulphonamides were studied (Sen Gupta and Bose, 1946). For comparison "Harfanil" and a sulphone from "Harfanil" were also tested both in-vitro and in-vivo (vide Part I). The results do not warrant any possibility for p-amidino-substitutions and Harfanil-sulphone. But the hydroxymethyl amino derivatives or "Formo" derivatives as they are called, showed some definite promise as chemotherapeutic agents. The pharmacology of Formo-sulphathiazole (S.T.F.), has been studied thoroughly by Bhatnagar et al. (1948). In our studies (Bose, 1949) it was found to be a drug with low absorption from the gut, and maintaining negligible concentrations in blood and tissues, except in the kidneys. The hydroxymethylemino derivatives of sulphacetamide (S.A.F.) and sulphanilylbenzamide (S.B.F.) however showed significant characteristics, both in their bacteriostatic action as well as in other pharmacological properties. Thus these two compounds were found to be more active than S.T.F.; and against certain resistant organisms such as Streptococcus viridans, Proteus vulgaris, E. nvecyaneus they were even more active than
sulphathiazole (vide Part I, Bose 1949). Of the two again, S.B.F. appears to be superior in this respect. It seems that the incorporation of CH₂NH₂-group tends to impart some characteristics as well as lability, by which the compounds act effectively on resistant organisms. But the inactivity of S.T.F. shows that the bondage with sulphathiazole is so firm that the compound is unable to liberate the active free amino group on which the action of sulphonamides depends.

These are significant findings, particularly for S.B.F. and brings out its possibility in genito-urinary infections. Toxicologically both the compounds are well-tolerated, though their LD₅₀'s are much lower in comparison with their parent compounds (Part II).

Attempts to widen the range of activity of sulph compounds led to their study in relation to Bell-Robin's theory of correlation of activity with the acid dissociation of a compound. The widened range of activity of sulphanilylbenzamide with a pKa value of 4.78 proves that this compound, like sulphaguanidine, falls outside the range of such correlation. It is further known that N⁴-substitution is generally associated with or without any lowering in activity. The increased activity of the N⁴-hydroxymethylamino derivatives of sulphaacetamide and sulphanilylbenzamide (pKa 4.62 and 4.43 respectively) against certain organisms not so sensitive to a powerful sulphonamide, suggests that this generalisation may not always hold good.
A still powerful compound was however found in \( \text{H}_4 \)-
methyl-sulphabenzamide whose pH value (7.34) was found to be

close to the physiological pH. A close study of this compound

revealed certain significant facts which throw interesting

light on Bell-Robbin's theory (Part I, Rose 1952). It was found

that the shifting of the pH value has led to the development

of an anti-streptococcal activity of the compound, more powerful

than that exerted by sulphanilylbenzamide or even sulphathiazole

in equimolecular proportion. But this activity was not concom-

ittant with a similar increase in action against a pneumococ-

cal infection, rather some lowering of activity was noticed

in this respect. Moreover, toxicological studies showed that

the compound is unusually toxic and maintains a comparatively

low concentration in blood and tissues (Part II).

The chemotherapeutic studies with this compound lead
to the idea that though with respect to streptococcal infection,

Bell and Robbin's theory may well correlate the \textit{in-vivo} activity

of a sulpham compound with its acid dissociation constant, poss-

ibly against pneumococcal infection such correlation may not hold good. This observation may also serve as evidence in favour of the specificity of drugs in different infections, as observed by Marshall (1942). It is, therefore, concluded that newer types of synthesis on similar lines would be worth-

following for obtaining successful chemotherapy against different pathogenic organisms not yet sensitive to known chemotherapeutic agents.
An investigation carried with the object of studying the reactivity of the SO\(_2\)H\(_2\) group in different substituted derivatives also point to a similar impression that sulphamidine derivatives may not all act in a similar manner. Evidence has been brought forward in this study on the dehydrogenase activity of resting Escherichia coli that the 1-heterocyclic derivative, sulphapyridine, acts in a manner contrary to that of sulphamidine or its acyl derivatives, sulphacetamide or sulphamethylybenzamidine (Part III(ii); Bose and Ray, 1946). It has been shown that while in an anaerobic system, sulphamidine, sulphacetamide and sulphamethylybenzamidine reduce methylene blue, sulphapyridine oxidises the leuco form of the substance. Unfortunately the study could not be extended to other heterocyclic compounds; but this finding alone is suggestive of a certain amount of specificity of action on the part of sulphonamides, as reported from other quarters as well (Läuger et al., 1944; Northey, 1948).

With regard to the mode of action of sulphonamides in-vivo, a study on sulphonamide synergy with non-specific agents known to cause a stimulation of the reticulo-endothelial system and leucocytic mobilisation was considered desirable. The work started with the object of investigating as to how peptone, which acts as an antagonist of sulphonamide-bacteriostasis in-vitro, would behave in-vivo. Later, the work was extended to
other non-specific substances such as liver hydrolysate, and milk (Part III(i)). While no significant role of body defences could be observed in these studies, it seems that milk might have some potentiating effect on the activity of sulphanilamide against pneumococcal infection of mice. No clear-cut antagonism of bacteriostatic action of sulphanilamide in-vivo by peptone was however noticed.

These lines summarise the work carried on sulphonamides. No spectacular achievement attended the completion of these studies. But an over-all view of the work will certainly suggest that the studies have brought out certain data which have led to the evolution of some chemotherapeutic compound like, sulphanilylbensamide, and have focussed the significant possibility with others, such as, $N^4$-hydroxymethyl-sulphabenamide (S.B.F.) for genito-urinary infections or phthacyl- and succinyl sulphabenamides as agents for intestinal diseases.

It may be noted here, that the compound S.B.F. is already under clinical trial and a short observation is being annexed in the appendix.