This thesis presents the results of pharmacological studies carried out by the author for evaluating the chemotherapeutic possibilities of certain p-aminobenzenesulphonamide compounds. These belong to the class of sulphonamido-acridines, sulphonamido-quinolines, and N¹- and N⁴- substituted sulphonamides. Some sulphones have also been included in this study.

The subjected matter of the Thesis covers the results of both published and unpublished work carried out in the Bengal Immunity Research Laboratory (Institute). A list of published papers is given as Appendix A. The investigation was started before 1939, when much was not known about the different sulpha drugs. On account of World War II even published literature was meagre and unavailable. Since then, more than a decade has passed yet the knowledge gained about the possibilities of these drugs needs full elucidation. Inspite of much advancement in chemotherapy, the facts presented herein will add to the store of existing knowledge on the subject, and is likely to throw some light on the pharmacology of several sulphonamide derivatives, and also on the chemotherapy with sulpha drugs in general.
The thesis is being presented in three parts:

PART I: CHEMOTHERAPEUTIC STUDIES

This part deals mainly with chemotherapeutic studies, involving bacteriostatic tests in-vitro and protection tests against experimental infections with compounds, all synthesised in this laboratory. These belong to certain sulphonamido-acridines and quinolines, N₁- and N₄-substituted derivatives of p-amino-benzene-sulphonamide and some sulphones, synthesised with the purpose of widening the range of activity of sulpha drugs. For convenience of record and cross reference this part of the thesis has been divided into several sections.

PART II: STUDIES ON TOXICITY, ABSORPTION AND EXCRETION

This part deals with acute and chronic toxicity of many of the compounds studied under Part I, their concentrations in blood and tissues, and their excretion. The LD₅₀ of several compounds have been determined on in-bred mice. Chronic toxicity has been studied with relation to both macroscopic and microscopic changes in different organs.

PART III: STUDIES ON THE MODE OF ACTION OF SULPHONAMIDES

This part deals with some experimental observations towards the elucidation of the mode of action of some sulpha drugs and is divided into three sections. The first section describes experiments which have been carried out to
test whether body defenses can play some synergistic role in overcoming infection. For this, non-specific agents likely to cause leucocytic mobilisation in the tissues, have been used as synergists with sulphanilamide and its derivative. In the second section some experiments have been reported on the behaviour of certain acyl derivatives of sulphanilamide on the dehydrogenase system of resting E. coli. In the third section of this part, the pharmacological basis for the mode of action of sulphanilyl-benzamide with reference to antidiarrhoeal remedies has been discussed.

The most salient features of the observations recorded in this Thesis are:

1) The pharmacological action of sulfa drugs generally bears a close relationship with the chemical structure of the compound. Thus, the alteration of the anilyl group by quinoline or acridine nucleus is being found to bring about a dystherapeutic effect. A similar fall in chemotherapeutic activity is noted when p-amidino substitutions are made in the nucleus of sulphanilamide or even in sulphone molecule. Often again, an extra nuclear substitution in a sulfa drug may alter the efficacy of a drug although its anti-bacterial activity might not have been affected at all. Thus the anti-pneumococcal activity
found in the compound obtained by nuclear substitution in the thiazole part of sulphamethiazole by a methyl group, is overshadowed due to the development of chronic toxic effects in the resulting compound, \(N^1\)-sulphamethylothiazole. Substituting the \(S^1\)-hydrogen atom of sulphonamidine by a benzoyl group a compound of widened activity is obtained, in \(N^1\)-benzoylsulphanilamide (Sulphanilylbenzamide), which exerts an increased bacteriostatic activity against systemic and intestinal pathogens, and possesses powerful anti-streptococcal and pneumococcal action. It is also shown to be a clinically active anti-dysenteric remedy, inspite of its rapid absorption, maintenance of high blood and tissue concentrations, less conjugation and fairly rapid elimination. For these special pharmacological characteristics of the compound its toxicology has been more thoroughly studied. Similarly by substitution of \(N^2\)-hydrogen atom by a hydroxy-methyl group, several \(N^4\)-hydroxy methylamino derivatives of different sulphonamides have been obtained and some of these have been found to exert a significant antibacterial activity against certain organisms generally less sensitive to usual sulphonamides. These studies have led to the
evolution of the therapeutic possibility of \( \text{H}^4 \)-hydroxymethylbenzamide (forme-sulpha-benzamide) in genito-urinary infections.

In order to ascertain how far the acid dissociation in a sulphanilamide compound bears relationship with its chemotherapy property, sulphanilyl benzamide (pKa 4.37) was converted to its \( \text{H}^4 \)-methyl derivative exerting a pKa value of 7.34. In equimolecular dose this latter compound shows a higher anti-streptococcal activity than that exerted by sulphanilyl-benzamide or even sulphathiazole; but this increase in activity is not correlated with a similar rise in anti-pneumococcal potency, pointing out thereby that chemotherapy activity possibly is dependent on some particular specificity of the drug in question. This hypothesis has also been corroborated from a study of the dehydrogenase activity of resting \( \text{Esherichia coli} \).

2) In view of Marshall's hypothesis of low absorbability and high local concentration, an attempt was made to explain how absorbable sulpha drugs, like sulphanilyl benzamide, sulphathiazole and others might act in bacillary dysentery. In a
study of the intestinal excretion of the drugs after subcutaneous injection into guineapigs, it has been shown that the effective drugs have a tendency to be excreted more through the caecum and large intestine, the parts affected in bacillary dysentery, than through other parts of the bowel. It is suggested that this selective re-excretion of the absorbable drugs might play a useful role in imparting therapeutic efficacy. Such a mechanism is also likely to control the chronic and carrier stages of the disease. These studies also reveal that of the known compounds, phthalylsulphathiazole possesses greater potentiality as an anti-dysenteric remedy than succinyl-sulphathiazole, and the new compounds, phthalyl-sulphabenzamide and succinyl-sulphabenzamide, possess certain advantages, which may be useful in tackling different intestinal disorders.

3) The study of the role of leucocytic mobilisation on the mode of action of sulphonamides tends to indicate that though non-specific agent like milk has some potentiating effect, leucocytosis by itself fails to play any significant part in the control of infection by sulfa drugs.
Thus the work that is being presented in this Thesis has led to the evolution of a chemotherapeutic compound, sulphanilyl-benzamide, indicates the possibility of evolution of a drug (\(\text{H}^4\)-hydroxymethylsulphabenzamide) effective in gonito-urinary infections, points to the potentiality of certain drugs (phthaly1- and succinyl-sulphanilylbenzanides) in controlling intestinal infections, and throws an insight into the mode of action of sulfa drugs in general.