Chemical carcinogenesis is thought to consist of two phases known as initiation and promotion. Initiation is considered to involve genetic damage at the first instance due to an interaction between DNA and the initiator followed by cell proliferation involving the replication of damaged DNA. The role of cell proliferation in initiation is not understood at present. Still less understood is the mechanism of promotion phase at the molecular level. In general, promotion has been suggested to be either involved in causing aberrations in gene expression or defective transport of various molecules across the gap junctions of living cells or of processed RNA molecules from the nucleus to the cytoplasm. Interferences by promoters in the interactions of histone and non-histone proteins with DNA (Witschi, 1970) or attachment of ribosomes to reticular membranes (Rabin et al., 1981) have been propounded to be the possible mechanisms of promotion in causing aberrations in gene expressions. The later authors have recently put forward a 'deletion-depletion' hypothesis for explaining the mechanism of action of promoters at the level of ribosome-membrane interactions. According to this hypothesis the specific population of ribosomes which is detached by carcinogens from the ER membranes might be synthesising some control proteins participating either in the structure of gap junctions or cell cycle.
The bases of cancer at present are thought to be either a mutation in DNA or triggering of the oncogenes to action in the chromosomes. Long strides have recently been made in the cloning of oncogenes and understanding their mechanism of action in causing cancer. Till the etiology of this dreadful disease is worked out leading to its curability, it is essential that stringent measures may be taken to prevent the disease. About 80 to 90 per cent of cancers are thought to be caused by environmental contaminants. Many short-term techniques have been devised during the last decade for detection of carcinogenicity of various types of chemicals in human contact. The number of such commercial chemicals is about 80,000 and another 1,000 is added every year. Chemical carcinogens are either organic or inorganic in nature. Most of the techniques devised so far have been used for detecting the carcinogenicity of organic compounds. These techniques fail to detect the carcinogenicity of inorganic compounds like those of chromium, nickel, beryllium and arsenic which are established carcinogens.

The work presented in this thesis was carried out with the following aims.

1. To develop a short-term technique for the detection of carcinogenicity of metals and metallioids.
2. To study the carcinogenicity of metal compounds with the microsomal degranulation technique (Gupta and Dani, 1979) for the first time.
3. To study the dose response curves of some of the organic carcinogens and non-carcinogens on which no work has been reported so far.

4. To conduct in vitro and in vivo experiments to study the carcinogenicity of some commonly used organic dyes in scientific research.

5. To work out the possibility of using interactions between metallic carcinogens and protein molecules (some enzymes) for devising a simple, inexpensive and efficient screening test for carcinogens.

6. To study the effects of known metal carcinogens on histone and non-histone protein levels.

7. To study the anticarcinogenicity of calcium and bleomycin against the carcinogenic microsomal degranulation caused by 2 AAF.

Studies on the carcinogenicity of metal compounds need extensive further research in view of the two lacunae in understanding their carcinogenic action: (1) it is totally unclear at present whether metal carcinogens act as only initiators or only promoters or as both; (2) no information is available whether the metallic carcinogens need to be activated by the microsomal hydroxylase system to proximate or ultimate carcinogens. In view of these lacunae, the major portion of the work presented in the thesis pertains to metal carcinogens. If the metal carcinogens act either as promoters or both as initiators or promoters, it is very important to scrutinize their carcinogenicity as these two actions can play havoc with human
life due to lot of environmental contamination by the metals caused by industrial developments the world over. The promotion phase of carcinogenesis is more dangerous as the initiated cells are still quiescent and do not proliferate to malignancy till repeated attacks by promoters. If the metal compounds act as promoters it is very important to have such short-term tests which can be cheaply and routinely used in various laboratories for their elimination from the environment.

Our efforts have been successful in devising a very simple and effective technique for determining the carcinogenicity of metal/metal compounds employing the measurements of enhanced denaturation and interference with renaturation of highly polymerised DNA (HP-DNA). A study of 46 metals/metal compounds reported in this thesis has enabled us to demonstrate that carcinogenic metals interfere with the double helix formation of denatured DNA, whereas the non carcinogenic metals failed to do so and physiological metals rather stabilize the DNA duplex. This method might be of great utility as there was a dire necessity of a short-term technique for the screening of metal carcinogens. Our experiments have further elucidated that metal carcinogens need not be priorily treated with the microsomal hydroxylase system for their interaction with DNA. However, the microsomal degranulation technique has shown that activated metal carcinogens degranulate the microsomes more efficiently.

Dose response curves with 12 organic carcinogens have
shown that each carcinogen has an optimum concentration for causing maximum microsomal degranulation and further increases in the concentrations of these compounds inhibit the detachment of ribosomes from the reticular membranes. Calcium and bleomycin have been shown to inhibit microsomal degranulation brought about by 2-AAF.

Farmer and Walker (1985) have suggested that future screening techniques should be based on interactions of carcinogens with some proteins like hemoglobin. Their suggestion is based on the fact that these interactions are basically between electrophiles (activated carcinogens) and nucleophiles (nucleic acids and proteins) and methods based on interactions with proteins might be advantageous from two angles: (1) working with mammalian proteins like hemoglobin, whose structure might be altered with metal carcinogens, can be easily extrapolated to human cancer in comparison to results obtained either with microbial systems or non-mammalian assay techniques; (2) protein-carcinogen interactions are irreparable unlike those between DNA and the carcinogens.

In view of the above suggestions, interactions of metal carcinogens with three enzymes (ribonuclease, chymotrypsin and trypsin) were studied and their results have shown that carcinogenic metals have more potentials to inhibit the enzymes but the non-carcinogenic metals are not completely negative in their inhibitory actions. Further, work on some more proteins might provide quite fruitful methodology for the prediction of carcinogenicity of both metallic and non-metallic carcinogens.