Aims and objectives
1. Aims and Objectives

The sensitivity of cells to irradiation is directly proportional to their reproductive activity and inversely proportional to their degree of differentiation (Bergonie and Tribondeau 1959). Since cancer cells have a great reproductive activity and less differentiated than surrounding healthy tissue, they are expected to be vulnerable to the killing action of ionizing radiation. Thus, the findings of Bergonie and Tribondeau (1959) laid the foundation of radiation therapy of cancer. Radiation therapy is considered to be one of the most important and popular tools to cure cancer.

It is now well established that the extent of radiation damage in a tissue is directly related to the degree of oxygenation of that tissue. The findings of Thomlinson and Gray (1955) triggered tremendous interest in oxygen as a factor in radiation therapy. It was suggested that there is a relatively small portion of hypoxic cells in tumors due to rapid fall-off in the concentration of oxygen with increase in distance from blood capillaries with their abundant supply of oxygen. Hypoxic cells are a common feature of human tumors (Brown and Giaccia 1994). Since hypoxia has a dramatic protective effect against ionizing radiation, the presence of hypoxic cells in tumor was suggested to limit the success of radiation therapy of cancer.

To overcome this difficulty, much effort has been expended in the search of agent which will either selectively potentiate the radiation effect or conversely protect surrounding normal tissue and enable the application of relatively higher dose of radiation so as to favor more killing of cancer cells than normal. The possibility of use of radiomodifiers opened newer avenues in the radiotherapy of cancer. The use of radioprotective and sensitizing agents, either alone or in combination of ionizing radiation, is theoretically advantageous particularly in terms of cost/benefit ratios. Moreover, chemical modifiers will be very useful when cancers are already in advanced stage at the time of diagnosis.

Numerous drugs have been tested for their ability to potentiate or to protect against radiation effect (Yuhas et al. 1977, Sugahara 1984, Koch 1985 and von Sonntag 1987). Although many chemical agents were found to have radiomodifying property, but they were not very useful in improving the radiation therapy of cancer even at an
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experimental levels. Because, administration of radioprotectors are likely to protect both
cancer cells as well as normal tissues; and in case of radiosensitizers they are expected to
potentiate radiation damage in cancer cells as well as normal surrounding tissue.
Therefore, to get therapeutic gain a radiomodifier should either protect normal tissues
selectively or potentiate radiation damage of cancer cells also selectively. Indeed a
radiomodifier would be more useful which could differentially protect normal cells and
potentiate radiation damage of cancer cells simultaneously. It may be mentioned that
some drugs like phenothiazines have shown such results. Euoxic radioprotection and
hypoxic radiosensitization have been observed in bacterial and mammalian cells (Shenoy
and Singh 1985). Chemotherapeutic and radiosensitization effects have been
demonstrated in transplantable murine solid tumors in vivo as well as in spontaneously
occurring mammary adenocarcinoma in CBA mice (Shenoy et al. 1982, George and
Singh 1985, Shenoy and Singh 1985, George and Singh 1988, Singh 1990). This is
indicative of a differential radiosensitization of tumors and radioprotection of normal
surroundings tissue by phenothiazines.

Hydroxyl-radical-mediated transient species of these drugs were suggested to be
involved in radiosensitization (Shenoy et al. 1975, Maniar and Singh 1983). The
radiosensitization was also shown to be due to inhibition of post irradiation synthesis of
deyoxyribonucleic acid and protein; and rejoining of DNA single-strand breaks (SSBs)
(Maniar et al. 1984, Yonei et al. 1984).

Their protective effect, on the other hand, has been ascribed to the fluidization of
membranes, facilitating mobility of non-protein sulphhydrlys (NPSH) and allowing
efficient chemical repair of oxygen-specific damage sites (Maniar et al. 1984). The
differential protective effect has also been attributed to their capacity to scavenge the
radiolytically generated oxygen free radicals (Kale and Sitasawad 1990, Varshney and

Formation of transient species and inhibition of rejoining of SSB, DNA and
protein synthesis may also occur in normal cells. On the other hand, fluidization of
membranes and removal of free radicals by phenothiazines may also take place in tumors.
Therefore, these mechanisms can not provide adequate explanation for the differential
modification. Due to this, despite showing initial differential-modifying effects, the
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Phenothiazines and other drugs have not probably been widely accepted for clinical use. A survey of literature suggests that, without addressing or understanding the non-acceptability, the further work on the most of the chemical modifiers was either abandoned or diverted towards the search and testing of new agents. This kind of endeavour helped very little, if at all, in improving the radiation therapy. Therefore, the gap between the present state of knowledge of chemical modifiers and radiation therapy of cancer remained to be bridged.

From results obtained with phenothiazines, it is quite clear that these drugs selectively kill tumor cells and protect surrounding normal tissue but not vice-versa. Thus, phenothiazines offer a unique advantage for radiation therapy of cancer by simultaneously controlling tumor growth and protecting normal stroma. However, for greater application and wide acceptance for clinical use there is need to understand the mechanism of protection as well as radiosensitization by phenothiazines.

Efforts are being made in our laboratory to find out the physiochemical events which make phenothiazine an efficient radioprotector in normal animals and radiosensitizer in tumors. The work related to radiosensitization by phenothiazines in cancer cells has been initiated recently. In the present work, attempt has been made to examine whether the radioprotective action of phenothiazines like chlorpromazine (CPZ), promethazine (PMZ) and trimeprazine (TMZ) is mediated through the bioreductive enzymes.

Since phenothiazines were shown to interact and induce the cytochrome P450 system which provides the ferrous/ferric redox couple (McIntosh and Topham 1972, Mostafa and Weisburger 1980), it could be possible that the radioprotective ability of phenothiazines might be linked to cytochrome P450 system. Therefore, an effect of ionizing radiation on the cytochrome P450 system and its modulation by phenothiazines has been studied. As the cytochrome P450 system was shown to protect cell against oxidative damage (Morichetti et al. 1989), to have a peoxidase activity (O’Brien and Rahimtula 1980, Kappeli 1986, Hollenberg 1992, Thompson et al. 1995, Anari et al. 1995, and Segura-Aguiilar 1996) and is known to partially replace catalase in protecting the cells against oxidative stress; efforts are made to find a link between radioprotective ability of cytochrome P450 system and antioxidant potential of animals using DT-
diaphorase (DTD), glutathione-S-transferase (GST), superoxide dismutase (SOD) and catalase. To support the biochemical pathways involved in radioprotective action of phenothiazines, radioresponse of xanthine oxidase (XO), lactate dehydrogenase (LDH) as well as induction of lipid peroxidation was also probed. Phenothiazines are calmodulin antagonists and are in regular clinical use. The present study might be of considerable significance in improving the radiation therapy of cancer.