Summary and Conclusion
The glyoxalase system is an enzymatic pathway found in the cytosol of all cells. This system is relatively simple consisting of two consecutive enzyme reactions with terminal product- D- lactate, utilizing reduced glutathione as cofactor. The importance of this system is associated with the metabolism of physiological substrate methylglyoxal, a reactive αβ-dicarbonyl compound. The formation of methylglyoxal in glycolytic biological systems is unavoidable. With an impaired or inhibited system, methylglyoxal accumulates to toxic levels. Under dose limiting conditions, methylglyoxal induces initially reversible and later irreversible modifications of proteins. The former may be involved in the metabolic regulation and latter in chronic pathogenesis.

The glyoxalase system is vital for life support from earliest stages of embryogenesis, through maturation and development until death. It has been implicated in control of cell growth, detoxification of α-hydroxaldehydes and a bypass for triose phosphate →pyruvate section of the Embden-Meyerhof pathway. Though it is now known for more than 80 years, the biological function of the glyoxalase has remained unclear.

Since this system is suggested to involve in cell division and considered as a metabolic indicator of cell proliferation, it might play an important role in cellular radiosensitivity, development and ageing, and carcinogenesis. Therefore in the present work we have examined:

1. Effect of radiation on the glyoxalase system.
2. Influence of development and ageing on its activity and
3. Effect of carcinogens on the glyoxalase system.

The findings of the present study revealed that:

1. The glyoxalase system was affected by radiation. The mode and the magnitude of the effect depends on the dose and the type of tissue. Our results have clearly shown that glyoxalase I and glyoxalase II respond differently towards radiation. The effect of radiation on the activity of glyoxalase I was found to be biphasic. These changes may be associated with factors such as unscheduled DNA synthesis and activation of immune response which may be required for repair and later for regeneration. In case of glyoxalase II radiation inhibited the activity at almost all doses. Lowering of the glyoxalase II activity and an increase in glyoxalase I activity may lead to accumulation of S-D- lactoylglutathione which is known to be involved in several biological responses. At
higher doses decrease in the enzyme activities especially that of glyoxalase I, may be indicative of irreversible damage to the cell or to the enzymes themselves.

The effect of different doses on the ratio of glyoxalase I and II (GI/GII) was found to be biphasic, first it increased and then decreased progressively. The similar pattern of GI/GII in liver and spleen is suggestive of control of some common factors on the metabolism of methylglyoxal in these tissues.

Our results have suggested that the effect of radiation on the glyoxalase system persist even in post irradiation period, but for lower doses the activity returns very close to control perhaps suggestive of the recovery of the tissue from radiation damage.

The effect on the glyoxalase system was found to be inversely proportional to the dose rate. Lowering of the dose rate might have allowed the cells to progress through the cell cycle and accumulate in G2 phase.

The radiation induced changes in the activity of glyoxalase system could be modulated by chemical modifiers. Since the glyoxalase system is vital for biological function, Radiation effect on this system may have some serious biochemical consequences.

2. In detailed study of modulation of radiation induced effect it was found that phenothiazines such as CPZ, PMZ and TMZ inhibited the radiation enhanced activity of glyoxalase I but no appreciable change was found in the activity of glyoxalase II. Since phenothiazines are known to scavenge free radicals, the decrease in the activity of glyoxalase I is probably suggestive of their protective action.

Our observation have shown that the protective effect of phenothiazine was diminished to a great extent in presence of Fe$^{2+}$ ions. In other words in combination, phenothiazines and Fe$^{2+}$ ions further enhanced the radiation effect. However it is important to note that in presence of Fe$^{3+}$ ions phenothiazines considerably inhibited the effect of radiation on glyoxalase I. It seems that the redox activity of iron was altered by phenothiazines in such a way that its effect on radiation induced changes of glyoxalase activity were reversed in presence of Fe$^{2+}$ ions, and inhibited in presence of Fe$^{3+}$ ions. It may be one of the reason for their euoxic radioprotection and hypoxic radiosensitization. Our results suggest that the hypoxia in tumour may not be considered as a limitation for the radiation therapy of cancer.
3. The activity of the glyoxalase system changes with age. The activities of glyoxalase I and glyoxalase II vary depending on the age and organ of the animal. Since the growth related increase in glyoxalase I activity correlates with DNA synthesis, it may be indicative of the rapid rate of cell division taking place during this phase of the development. The specific activity of glyoxalase II was low in this period. Towards old age the activities of the enzymes become somewhat irregular particularly that of glyoxalase II. The decline in the activity of the glyoxalase system, may increase free radical formation due to the accumulation of methylglyoxal and S-D-lactoylglutathione leading to the oxidative damage which may contribute to the process of ageing. We have observed reciprocal i.e. inverse relationship between the activities of glyoxalase I and II. The GI/GII ratio was similar in liver, spleen and kidney till about 13 months. The metabolism of methylglyoxal in these organs appears to be under the control of some common factors at least during the development and growth phase.

4. The aged animals were found to be more radiosensitive. The rate of cell division was much lower in case of aged animals as indicated by DNA synthesis studies so the process of recovery may also be slow in these animals as it was seen that the activity of glyoxalase enzymes was much far from normal in aged mice where but they were close to normal incase of young animals after about 72 hours of radiation treatment.

5. Aged mice showed higher incidence of tumours, especially those of 18 months and above. In the old age group both cancerous lesions and visible tumours were more frequent. When examined the activity of glyoxalase system in spontaneously occurring tumours, DEN / DMBA induced tumours, it was seen that the activity of glyoxalase I was higher and that of glyoxalase II was lower in tumour bearing liver or liver showing cancerous lesions compared to normal (non-cancerous) liver. Further study with tumour bearing liver revealed that the different sections of the tumour bearing liver had different activity. The order of activity in these parts was observed to be : LT<LS<LN.

6. The activity of glyoxalase system was modulated in response to both physical and chemical carcinogens. The change in the activity of glyoxalase system was quite similar in regenerating liver of mice exposed to radiation and DEN treatment. In both the cases activity of glyoxalase I increased whereas that of glyoxalase II decreased. These changes might be related to the early events of carcinogenesis.

7. Gemfibrozil is hypolipidemic drug and peroxisome proliferator. Gemfibrozil caused increase in liver size/ weight which could be due to prompt response of liver
peroxisomes to this drug. Hepatomegaly was noticed throughout the period of treatment which could be due to hyperplasia and hypertrophy of liver cells.

Gemfibrozil altered the activity of glyoxalase system. The initial sharp decrease in the activity of glyoxalase I is probably associated with hepatomegaly induced by peroxisome proliferation and other changes in the liver.

The activity of glyoxalase I increased continuously after 12 months of treatment with gemfibrozil. Interestingly the frequency of precancerous lesions and incidence of visible tumours were also found to increase during this period. It is quite possible that the increased activity is related to carcinogenesis. Further study is needed to confirm this possibility so that it may be used as a phenotypic marker of carcinogenesis induced by peroxisome proliferators.

The effect of gemfibrozil on glyoxalase II activity was not straightforward. The carcinogenic effect of gemfibrozil depends on its dose and duration of the treatment.