GENERAL SUMMARY AND CONCLUSIONS

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We are living in an age where people are exposed to a wide variety of pollutants, chemicals which are foreign to the body. These include natural products, food additives, drugs, insecticides, industrial chemicals which are collectively termed as xenobiotics. Besides this, the problem of nutrition is becoming severe day by day with increasing population and changes in the natural environment as a result of disturbance in the ecological balance. In addition to this, the natural calamities like floods, famines, earthquakes etc. pose a further problem. It is well known that nutrition plays a major role in deciding the overall functioning of the body. Any disturbance, abnormality or manipulation in the normal nutritional conditions, naturally reflects on the functioning of the body. We are aware of the fact that a major section of the world's population is passing through a crisis where the manipulation of the food intake/diet becomes indispensable as a consequence of natural or man-made disasters.

Taking into consideration, today's environmental conditions, eating habits, increased exposure to drugs etc., a large number of foreign compounds take their
entry into the body. For survival, the body has to deal with these compounds. This function is accomplished by an enzyme complex system - the mixed function oxidase system (MFOS) or the 'Monooxygenase system' or the cytochrome P-450 linked MFOS, present in the endoplasmic reticulum of the cells of many tissues. The main site of its occurrence has been shown to be the liver. This enzyme complex system, mainly designed for detoxication converts the foreign lipophilic compounds to more lipophobic products so as to facilitate their excretion outside the body. During this process, of metabolism, some compounds are activated, giving rise to harmful intermediates, which if not readily excreted will be harmful. They may even prove to be carcinogenic, teratogenic or mutagenic. This enzyme system has a hemoprotein, cytochrome P-450 and a flavoprotein cytochrome P-450 and a flavoprotein cytochrome P-450 reductase or cytochrome c reductase, as the major components, along with another hemoprotein-cytochrome b5 and other drug metabolizing enzymes (DME). These components may occur in multiple forms in the same cell. Moreover they can be readily induced or inhibited by their own substrates which include a wide array of substances. Any alteration in this system reflects on the metabolism of xenobiotics as well as endogenous substrates.
Alteration in the nutritional status is known to alter the functioning of this system. The literature is replete with evidences describing the alterations caused in the system by the individual or combined macro or micronutrient deficiency, to total starvation or food deprivation. As a matter of fact, these conditions are uncommon, but food restriction or partial food deprivation is widespread throughout the world. Unfortunately, there are very few reports relating partial food deprivation and drug metabolism. The need therefore arises to study this relationship in detail, so as to understand the problems of undernourished people of many of the third world countries. Study of this relationship may help in designing drug therapy.

In this regard we have studied the effect of different levels of food restriction (25, 50 and 75% of the intake of ad libitum fed) for different time periods (30 and/or 45 days) in the young and adult male and female rats. We have observed that the drug metabolizing enzyme system is affected by the stress of food restriction in a manner which is dependent on the level as well as duration of food restriction, besides the age and sex of the animal. In young and adult male
rats we have observed decreased phenobarbital (PB) sleeping time with increase in DME activities (aminopyrine N-demethylase and acetonilide hydroxylase), and electron transport components (ETC) - cytochrome P-450, b5 and cytochrome P-450 reductase. Prolongation of food restriction for 45 days in adult male rats caused a pronounced enhancement in acetonilide hydroxylase activity than aminopyrine N-demethylase. The magnitude of induction was higher in young animals than in adults. In contrast to adult male rats, adult female rats showed a more pronounced decrease in acetonilide hydroxylase than aminopyrine N-demethylase activities, together with a decrease in ETC, with increased PB sleeping time, thereby indicating a sex difference in drug metabolism during stress of food restriction. The occurrence of this sex difference was strengthened by the observation that there is no apparent difference in drug metabolism in young male and female rats subjected to food restriction.

Inducer (phenobarbital/3-methylcholanthrene) treatments during food restriction resulted in increase in the levels of cytochrome P-450, b5 and the activities of cytochrome c reductase, aminopyrine N-demethylase and acetonilide hydroxylase in male as well as female rats, but the magnitude of induction observed in the food restricted
groups was lesser than the ad libitum fed controls. Food restricted females showed no apparent difference in the response to the inducers, from the control rats; the levels of cytochrome P-450 and activities of cytochrome c reductase and acetonilide hydroxylase were higher than the ad libitum fed controls. The results were explained on the basis of the appearance of androgen dependent cytochrome P-450 populations, predominantly present in male rats. The induction in a particular drug metabolizing enzyme activity is explained, taking into consideration the possibility of the survival of a particular population/species of cytochrome P-450 which may be resistant to the stress of recurring cycles of starvation and refeeding. From the results, it can be said that food restriction affects drug metabolism in a manner which differs from that observed during starvation or specific nutrient deficiency.
CERTIFICATE

This is to certify that the work embodied in this thesis entitled "Reactions of Cytochrome P-450", has been carried out by Miss Rafat S. Hashmi under my supervision.

The work included in this thesis is original, unless stated otherwise and has not been submitted for other degree of either Marathwada University or any other University.

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16. 8. 1985
DECLARATION

The work presented in this thesis is original and is carried out by me. It has not been submitted previously for any other degree of either Marathwada University or any other University. References made to the work of others have been cited in the text.

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