INTRODUCTION

Investigation of the mechanism of action of gonadal steroids constitutes an interesting aspect of endocrinology. Generally, this is carried out by studying alterations in biochemical patterns induced by the said steroidal hormones in prime target tissues. It is well known that androgens are responsible for the growth and maintenance of male reproductive structures in mammals (William, 1961). However, they are also equally significant for their influences on metabolic patterns of sex-specific tissues (Farookhi, 1980; Guraya and Arbans, 1981; Tehernitchin and Galand, 1982; Rukhmini and Reddy, 1983) as well as certain non-sexual tissues *viz*.- skin, muscle, liver and kidney (Drofman, 1961; Van Pilsum, 1968; Bergamini, 1969, 72; Dube *et al*., 1975; Max and Toop, 1983). Androgens have been reported to induce *de novo* enzyme synthesis (Umbreit, 1951; Rioton and Fishman, 1953). Although androgenic action is due to the steriod molecule *per se*; more specifically oxygen functions at carbon atoms at positions 3 and 17 are chiefly responsible for androginicity. In recent years it has been increasingly realized that the steroidal as well as non-steroidal androgenic compounds act via the agency of the c-AMP-adenylcyclase system. This has been amply demonstrated by the work of (Robinson and Sutherland, 1972; Singhal, 1973; Spigel *et al*., 1981) on the mechanism of androgen action on prostate gland and seminal vessicles.

Importance of hepatic tissue in the general economy of the bodily functions is a well documented fact. However, information available on androgenic influence on the hepatic functions leaves much to be desired.

Effects of androgens on the accessary reproductive organs have been reviewed as early as in 1939 by Moore, and later by many others like Willams-Ashman et al.(1967), Coffey (1974), Tuohimae and Neimi (1974), Engel et al. (1980), Guraya and Arbans (1981), Franklin and Brandly (1982). Changes induced by testicular androgens are so vivid that their possible influence on the metabolism of the hepatic tissue certainly warrants further investigation.

Though a vast amount of literature is available; regarding the influence of androgens on intermediate metabolism of the hepatic tissue it falls short of a coherent account of the action of testicular androgens on overall physiology and liver. Secondly, most of the literature deals with alterations recorded after few weeks of orchidectomy (Konopkova and Nedvidek, 1972; Moore et al., 1977; Engel et al., 1980; Guraya and Arbans 1981) and after prolonged/repeated hormone therapy. On the other hand, it is also known that different tissues, including accessary sex organs, respond to hormonal deprivation within a few days (Kochakian, 1969; Baulian and Jung, 1970; Santi and Ville, 1971, Chinoy et al., 1973; Pirkko, 1981; Franklin et al., 1982) or even within a few hours (Liang and Liao, 1975; Ambadkar and Gangaramani, 1981; Pirkko, 1981; Max and Toop, 1983; Muddeshwar et al., 1984, Din-udom et al., 1985; Sreedevi and Ooman, 1985). It has also been reported that the effect of testosterone treatment on prostatic tissue could be seen

as early as 30 minutes after the hormone administration (Singhal, 1973). The major issue, therefore, for the present study was to observe the early effects, in terms of few hours of orchidectomy, replacement therapy as well as administration of androgen to intact normal animals on hepatic metabolism of adult male albino rats (Rattus norvegicus albinus).

Previously, an attempt in this direction was made in this laboratory and it was established that maximal alterations in various functional parameters occured by about 48-hours of gonadectomy and that the Spigelian lobe of the liver is more sensitive and intense in its response to alterations in the level of circulating androgens. On the basis of these earlier results obtained in this laboratory, and, in view of the fact that the alterations in certain enzymic activities are a manifestation of hormonal regulation, an attempt is made in the present study to observe the hepatic enzymic levels pertaining to the carbohydrate and protein metabolism at 48-hour post-orchidectomy interval. Further, during the earlier observations different dose levels of testosterone propionate (TP) were administered to the orchidectomized rats so as to counteract the effects of castration and it was found that the maximally effective dose of TP was 0.1 mg, which was capable of restoring most of the parameters then studied to normality.

Hence, in the present study only this effective dose, administered as a single intramuscular injection, was employed to evaluate the effects of replacement. A study of few rate limiting enzymes of carbohydrate metabolism would help understand biochemical alterations better and possibly also the causative factors. In order to substantiate this present work, involving the activities of key enzymes concerning this aspect viz. - Glycogen synthetase and Glucose-6-phosphatase (G-6-Pase) (Chapter-2) was carried out.

Alterations observed in the nucleic acids and protien contents of the hepatic tissue due to orchidectomy and subsequent TP replacement by Gangaramani (1979) provoked the idea of studying 5'-nucleotidase and transaminases (GOT as well as GPT) activity levels under various experimental conditions. 5'-nucleotidase enzyme activity is known to reflect flux in nucleotide pool of the cells. It is worth noting here that this fact has been shown to be dependent on the androgens in case of accessory sex organs (Chalet et al., 1979). The transaminases (GOT/GPT) too, are reported to be affected by androgens (Khilchevs, 1971; Franklinet et al., 1982) (Chapter-3).

An interrelationship between the circulating level of testosterone and ascorbic acid (A.A.-Vitamin C) metabolism has been suggested by Stubbs et al. (1967); Chinoy and Parmar (1975); and Chinoy et al. (1975 a and b). Ascorbic

acid is synthesised in the hepatic tissue of mammals and plays an important role in the oxidation-reduction processes of the tissue. It was evident from the report of Ambadkar and Gangaramani (1981) that the A.A. levels in the hepatic tissue of male rats registered a significant rise after orchidectomy and that it showed a time dependent fall after the initial increase. These workers also reported that in case of 24-hour castrates the effect of replacement therapy was contrary to expected reparative effect of androgen administration. Against this background, it was thought desirable to investigate the influence of such experimental conditions on the whole blood A.A. levels, in order to understand this problem in a wider context. Taking this into consideration; the course of the present investigation was planned so as to bring out possible reflections on the whole blood and hepatic tissue A.A. levels due to androgen deprivation and administration (Chapter-7). In the present study, slight deviation from the previous plan was that instead of 24-hours castrates (where numerically maximum changes were seen by previous workers) the post-orchidectomy interval of 48-hours only was considered for trying out the influence of deprivation and/or replacement of androgens, since the present investigator maintains that this interval is still physiologically quite representative of such experimental manipulations.

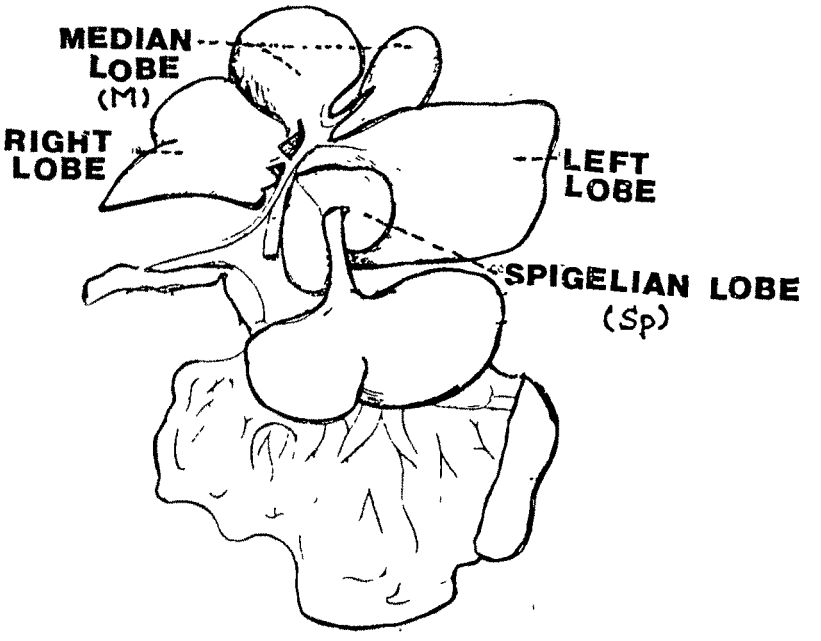
Preceeding study prompted the desirability of an attempt to investigate the early response of hepatic tissue of normal intact rats to exogenous administration of TP as far as blood and tissue AA levels are concerned in order to understand the situation in a wider context and better perspective. With this view, a pilot project was undertaken to elucidate the possible early metabolic response of the hepatic tissue of normal intact adult rats to exogenous administration of TP. Three arbitrarily chosen dose levels of the hormone viz.- 0.1mg, 0.25mg, and 0.5mg were administered intramuscularly as a single injection per head in 0.5ml volume of tributyrine (Vehicle). Rats were sacrificed after 30, 60, 90, and 120 minutes of hormone administration. Quantitative biochemical analysis of the two hepatic lobes (Median and Spigelian - Chapter-1) was carried out to evaluate the early effect of androgen in the normal, intact healthy rats. The main objective of taking up this pilot project was to be forewarned of the metabolic disturbances the hormones may induce, and hence subsequent interference with the overall body welfare. This was specifically thought of in the light of the fact that recent trends in clinical practice tend towards frequent use of natural and synthetic sex-hormones to deal with fertility disturbances, carcinomas and even as anti-fertility drugs.

The data collected during this study were quite confusing and contrary to expectations normally based on existing knowledge concerning the effects of androgenic

hormones. It is a well known fact that the androgens exert an anabolic influence in general, but the present investigation clearly showed that the early response of hepatic tissue was quite contradictory, as was evident from biochemical evaluation of the total hepatic protein content, and the enzymes involved in the protein nucleic acid metabolism. It seems probable from the present findings, (considered along with the previous observations) that normally expected TP-induced generation of c-AMP through activation of adenylcyclase system especially at the early intervals employed in this study is apparantly nullified very fast due to observed high levels of c-AMP-specific phosphodiestrase. This, in its turn, possibly leads to a transient disturbance in the well known 'cascade' effect. Secondly, the raised levels of transaminases might carry such an influence further through accelerated process of deamination leading to formation of more carboxylic acids and thereby reducing the normally available pool of amino acids for protein synthesis (Chapter-5 and 6). On the basis of these observations only tentative suggestions could be made, which need to be dealt with further before anything could be said with confidence. Further, the observed alterations in the carbohydrate metabolic pattern might tangentially point to as yet unnoticed influence of TP on the regulation of hepatic carbohydrate metabolism, perhaps of different etiology than that of either insulin or glucagon (Chapter-4).

FIG : REFLECTED LIVER LOBES OF RAT

(RATTUS NORVEGICUS). REF : GREEN,(1959).



Finally an attempt was made to compare the influence of hormone in normal and 48-hours orchidectomized animals. This was carried out at different time intervals and with different dosages of TP. This would help in understanding the mechanism of hormone action on hepatic tissue (Chapter-8).

Another noteworthy aspect taken into consideration during the entire study was to investigate the median and the Spigelian lobes (nomenclature by Green) of the hepatic gland separately. This is because the Spigelian lobe of the liver was found to exhibit decidedly different response than the remaining lobes to androgen deprivation as well as administration (Ambadkar and Gangaramani 1980, 1981, and 1982). Such a functional difference in metabolic responses of the two different lobes of liver has also been reported in respect of some other physiological adjustments but only by few workers like Hems et al. (1972); and Tyagi and Mishra (1977).

The chapters presented in this thesis are prepared as separate entities for clarity of explanation. Special efforts have been made to avoid repeations, as far as possible. The last chapter "General Considerations" is an attempt to look at the entire data represented herein a comprehensive manner so as to have an integrated picture of the study.