CHAPTER I

GENERAL INTRODUCTION AND REVIEW OF LITERATURE
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The term puberty which is derived from a root meaning hair (Pubes) is used to refer to a period of secondary sexual development which culminates in fertility. For many years considerable efforts have been made to unravel the mechanism responsible for the attainment of puberty and a great deal of information has accumulated as a result of these efforts.

There now appears a general consensus that no single event or sequence of events can be said to trigger the onset of puberty (Ojeda et al., 1980; Ryan and Foster, 1980; Reiter and Grumbach, 1982). Rather, puberty is the result of a final integration of various processes which develop at different pace throughout immaturity. Although the extent to which these changes are influenced by genetic determinants in mammals is unknown and a genetic component may participate in the control of sexual maturation.

The onset of puberty is a process that depends on the occurrence of numerous and complex inter-related maturational events (McCann et al. 1974; Ramirez, 1974) and one such factor involved in the maturational process is assumed to be prolactin (Prl). Earlier observations have
shown that Prl levels rise markedly during sexual maturation, usually around the time the secondary sexual organs begin their pubertal growth spurt and decline steadily to low levels during adulthood (Negro-Vilar et al, 1973; Dohler and Wuttke, 1975; Piacsek and Goodspeed, 1978; Mock and Frankel, 1980).

Sexual maturation in males:

According to Ramaley (1979) early development in males was divided into four intervals:

1. The neonatal period extending from birth until the end of first week of life. In this week testosterone (T) is the main androgen secreted by the testes and the first crop of Leydig cells which develop postnatally either undergo degeneration or enter a quiescent period. As the Leydig cells subside the animals enter the next phase.

2. The early juvenile phase, during which the main testicular androgen is androstenediol, a 5α-reduced product, and the early stages of spermatogenesis, occur rapidly.

3. The late juvenile phase begins around weaning age (21-22 days) as the blood testis barrier closes. The first leptotene spermatocytes move into the newly formed inner compartment of the germinal epithelium and the Sertoli cell proliferation ceases.
4. The peripubertal stage starts around day 30 when mature Leydig cell function begins and the T again becomes the dominant androgen. Puberty terminates as the first sperm is released from the germinal epithelium around 40-45 days of age.

Shortly after birth there is elevated follicle stimulating hormone (FSH) and Luteinizing hormone (LH) in the circulation. Miyachi et al (1973), Rager et al (1975) presented data showing that from about day 20 to day 40 after birth of rats the FSH activity reaches values unparalleled in later maturity and that its maximum occurs on the 33rd day of life. The LH activity increases less dynamically reaching its maximum on day 30 of life and falling thereafter.

Probable role of Prl during sexual maturation in male rats:

There are several lines of evidence suggesting that Prl may be involved in the processes of sexual maturation in the male rat but a distinct role for Prl remains to be defined. It has been found that in the rat Prl levels in the blood are very low during the infantile period (upto 21 days of age) and then rises during the prepubertal and pubertal periods and remained relatively constant until 50 days of age. A secondary" rise was observed thereafter to reach maximal adult levels
at 90 days (Negro-Vilar et al 1973). The studies of Knorr et al (1970); Odell et al (1974); Bartke and Dalterio (1976) have shown that the plasma Prl levels rise markedly during puberty in the male rodents followed by a decline to low levels during adulthood. This rise in Prl coincides with the growth spurt in the accessory sex organs. A similar rise in Prl has been reported in prepubertal lambs (Ravault et al, 1977). Ohlson et al (1981) have shown that Prl is involved in body growth and maintenance of the reproductive tissue weights in the yearling ram.

The discovery of Prl receptors in the testis and epididymis (Aragona and Friesen, 1975) has led to the belief that Prl is directly involved in the regulation of testicular function under normal conditions (Negro-Vila et al, 1977; Reddy et al, 1983). It has been reported by Bartke et al, (1978) that Prl also stimulates spermatogenesis under different experimental conditions. Growth of the epididymis has been obtained by synergistic action of Prl and dihydrotestosterone (DHT) (Kreider et al, 1977). Some of the effects of Prl on the testis seem to be exerted at the level of the Leydig cells affecting the androgen production and secretion (Aragona et al, 1977; Belanger et al, 1979). Prolactin was reported to act synergistically with LH to increase plasma T
incorporation of labelled precursors to T in vitro as well as T output in vitro (Hafiez et al, 1972; Swerdloff and Odell, 1977; Bartke et al, 1978) and to synergize with T to promote the growth and maintenance of the secondary sexual organs (Moger and Geschwind, 1972; Slaunwhite, and Sharma, 1977; Holland and Lee, 1980; Baranao et al, 1981; Nag et al, 1981, 1983). A physiological involvement of Prl in the Leydig cell function in man is also supported by studies of Rubin et al, (1975) correlating peripheral Prl and T levels. Additional experimental evidence indicates that Prl may physiologically increase testicular sensitivity to LH during the course of sexual maturation (Bartke and Dalterio, 1976). These observations indicate that normal circulating levels of Prl would stimulate steroidogenesis through an effect on the Leydig cells acting alone and/or synergistically with LH. In men, on the other hand high serum Prl levels may be inhibitory to testicular function.

The results of other studies have suggested that Prl may also stimulate directly the growth of the prostate gland and/or the seminal vesicle of several species (Grayhack et al, 1955; Chase et al, 1957; Antliff et al, 1960). An increase in prostate and seminal vesicle growth was observed in both castrated or castrated-adrenalectomized rats when Prl was administered (Negro-Vilar et al,
1977). These effects, particularly those seen in castrated-adrenalectomized animals, indicate that Prl may affect accessory sex organ growth even in the absence of any possible source of androgens. According to the study of Maric et al (1980) hyperprolactinemia, when induced in developing rats by grafting one pituitary gland from an adult female under the renal capsule of a 3 week old male, produced exceedingly high levels of serum Prl at the peripubertal age while their own pituitaries showed reduced Prl contents. This hyperprolactinemia did not alter appreciably the peripubertal rise of serum T, it was however, accompanied by a significantly enhanced growth rate of the prostate gland suggesting an increased responsiveness of the target organs to androgen. This data suggests an interdependence between androgen and Prl which establishes itself at the approach of puberty (Maric et al, 1980). In contrast to the low androgen insensitive neonatal Prl levels the peripubertal surge of Prl behaves as highly androgen dependent. It was observed in castrated animals that Prl also augments the testosterone induced weight responses of the accessory sex organs.
Sexual maturation in female rats:

Ojeda et al (1980) have proposed to divide the interval between birth and puberty into four phases:

1. A neo-natal period which comprises of the first postnatal week.
2. An infantile period which extends from day 7-21.
3. A juvenile period which extends from day 21 to about 32 or precisely until the first manifestation of increased estrogen activity as seen by presence of intrauterine fluid.
4. A peripubertal phase which includes the day encompassing the first ovulation.

The three basic components which interact to bring about sexual maturity are brain, pituitary gland and the gonads.

The two gonadotrophic hormones FSH and LH have been measured in immature male and female rats by several laboratories (Goldman et al 1971; Swerdloff et al 1971; Ojeda and Ramirez, 1972; McCann et al 1974) and it was shown that FSH is high at 10 days of age and falls progressively until the time vaginal opening occurs and estrous cycles are present. LH falls between 10 and 21 days of age and is constant. Development of a preovulatory follicle takes place about 19 days from its inception in
the infantile period and it is observed that the elevated levels of FSH found in the infantile rats are important for the initiation of a wave of follicles destined to ovulate at puberty (Schwartz, 1974; Hage et al, 1978). Although the infantile ovary can respond with steroid secretion to both endogenous and exogenous gonadotrophins (Andrews et al, 1981; Funkenstein and Nimrod, 1982) it is at puberty the greatest degree of responsiveness is observed (Advis et al, 1979). Actually, the Estrogen (E$_2$) and progesterone (p) response to gonadotrophins increases gradually during the juvenile period and then abruptly during the few days preceding the first ovulation (Advis et al, 1979). These changes in the ovarian steroidogenic function as well as the development of the gland in general are determined by both intrinsic and extrinsic factors (Smith-White and Ojeda, 1981).

Role of Prl during sexual maturation in female rats;

Other pituitary hormones known to play an important role in determining the time of puberty in the female rat are growth hormone (GH) and Prl. There is an increased secretion of these two hormones during the prepubertal period at the same time when serum gonadotrophins are low. Prolactin favours the onset of puberty by acting at both the CNS (Voogt et al, 1969; Wuttke and Gelato, 1976) and
Prolactin favours follicular development at the ovarian level and thereby increases the steroid responsiveness to the gonadotrophins (Advis and Ojeda, 1978). Prolactin appears to exert these effects by facilitating LH actions through maintenance and/or increased formation of LH receptors (Rolland and Hammond, 1975; Advis et al., 1981). An anatomical substrate for the actions of Prl in the ovary has been provided by the demonstration that Prl binds specifically to granulosa cells of developing follicles (Rolland and Hammond, 1975; Richards and Williams, 1976) and to granulosa cells differentiating into luteal cells (Richards and Williams, 1976). An observation which suggests that during normal prepubertal development the rising Prl titers seen after day 20 (Voogt et al., 1970) may accelerate the pace of follicular development by interacting with circulating levels of FSH to induce the formation of LH receptors in granulosa cells. Casper and Erickson (1980) have demonstrated that FSH can induce LH receptors in granulosa cells in a serum free medium and the replacement of FSH by Prl was very effective in maintaining LH receptors at maximal levels thereby preventing the loss in the receptors observed after the removal of FSH. This experimental situation is similar to that of the prepubertal female rat in which serum FSH levels are extremely elevated during the first week of life (Ojeda
and Ramirez, 1972) and decreases at the time when serum Prl levels begin to increase (Voogt et. al, 1970).

In contrast to the mechanism of Prl action peripherally the mechanism(s) underlying the central effect of Prl are not well understood. Voogt et al., (1969) had shown that Prl, when implanted in the hypothalmus, released FSH but subsequent studies failed to detect any changes in plasma LH or FSH (Advis et al, 1982). It has been postulated by Lamberts and Wuttke (1981) that Prl desensitizes dopamine (DA) receptors (by increasing DA turnover) and thus releiving LHRH from an inhibitory dopaminergic tone. However, chronic blockade of DA receptors failed to elevate serum LH and a LH surge is observed only after ovarian activation has occured (Advis and Ojeda, 1978). It has not yet been discovered at what level during the developmental sequence of follicular growth Prl acts. Speculations are that it may facilitate the passage of small to medium size follicles to more advanced phases of development a step at which adrenal gland may also be important. Nevertheless, neither Prl nor adrenal hormones are absolutely essential for the completion of follicular development. Since in either hyperprolactinemia (Advis et al, 1980) or adrenalectomized rats (Gorski and Lawton, 1973} Ramaley, 1974) puberty is delayed but not prevented.
Role of Prolactin during pregnancy:

It has been well established that Prl constitutes a part of the luteotrophic complex necessary for the maintenance of the corpus luteum and its secretory activity during pregnancy in the rat. The corpus luteum is stimulated by Prl during the early lutenizing period to develop an increased binding capacity for LH and hOG and to produce P (Holt et al., 1976; Richards and Midgley, 1976). The serum Prl levels rise at least 16-24 hrs after coitus and LH levels increase for the first 8 hr (Spies and Niswender, 1971; Walter et al., 1973). These authors have also demonstrated that pelvic neurectomy prevents this postcoital increase of Prl. Interruption of pelvic nerves is known to prevent normal pregnancy (Kollar, 1953; Carlson and De Feo, 1965). Since pelvic stimulation increases serum levels of Prl and/or LH it seems likely that these hormones might be involved in conversion of the corpora lutea of pregnancy.

The early phase of luteal function during pregnancy appears to depend on pituitary hormones since hypophysectomy of the pregnant rat prior to day 11 results in the termination of pregnancy. The administration of Prl, LH or FSH cannot prevent this effect although Prl adjuncted by either estrone or FSH can support pregnancy in the
hypophysectomized animal (Greenwald and Johnson, 1968). Pituitary Prl secretion during the first 3 days of pregnancy is higher than during the following 18 days. The Prl levels rise again on day 22 of pregnancy and on the day of parturition reach a higher level.

An overwhelming evidence indicates that the mating stimulus induces the release of Prl which in turn rescues the corpora lutea of the cycle and prolongs the ability of these structures to secrete progesterone (Smith et al, 1975; Smith et al. 1976; Smith, 1980). These Prl surges are responsible for the maintenance of corpus luteum through early pregnancy (Morshige and Rothchild, 1974). A luteotrophin secreted from the rat's placenta during the second half of pregnancy maintains P secretion through this period (Kelly et al, 1976; Yogev and Terkel, 1978; 1982; Voogt et al, 1982; Gorospe and Freeman, 1985). Hence the pituitary prolactin levels are low during the second half of pregnancy.

**Historical background of Prolactin:**

Prolactin is possibly phylogenetically the oldest of the hormones secreted by the anterior pituitary gland in the vertebrates. The importance of Prl in reproduction was established soon after its discovery (Strieker and
Grueter, 1928). Evidence for other significant functions of Prl was gained more slowly. The effects of Prl on the mammary gland are most widely known and frequently reviewed aspects of the physiology of the hormone. These mammotrophic effects are reflected in the alternate terminology for Prl, mammotrophin or lactogenic hormone. The gonadotrophic action of Prl was established by Astwood, (1941), Evans and his colleagues, (1941) when they demonstrated the effectiveness of crude pituitary extracts in maintaining functional corpora lutea. This finding gave an additional synonym for Prl viz., luteotrophin. Riddle (1963) emphasised that Prl was also an important regulator of growth and metabolism. It is now well documented that Prl is a multi-function hormone that has diverse regulatory roles among the vertebrates.

Prolactin has been recognized as a separate adenohypophysial hormone in a variety of animal species for many years. Prolactin is a protein which circulates in the plasma in several forms having different molecular size. The ovine Prolactin (oPrl) generally used in research, has been shown to be composed of 198 amino acid residues and has a molecular weight of 22,550 (Li, 1974).
Control of secretion of Prolactin;

It has been known for a long period of time that if the pituitary is transplanted to another site away from the hypothalamus Prl is released in copious amounts. In 1963 Talwalker, Ratner and Meites, using a hemipituitary incubation system, reported that if a crude hypothalamic homogenate was added to the incubation medium there was an inhibition of Prl release from the anterior pituitaries. This finding led to the postulation of Prl inhibiting factor (PIF). Since then there have been several investigations into the nature of PIF.

Prolactin secretion from the adenohypophysis is controlled by tonic inhibition and mediated by the secretion of hypothalamic PIF. Convincing evidence obtained in the rat suggests that dopamine (DA) secreted by the tuberoinfundibular system is the main inhibiting factor involved in the control of Prl secretion (Macleod and Lehmeyer, 1974; Labrie et al, 1978; Vijayan and McCann, 1978a,b). According to Fuxe (1964) DA released from the nerve endings in the median eminence is transported to the pituitary by the hypothalamo-adenohypophyseal portal blood to act on lactotrophs. In support of such a physiological role for DA at the pituitary level on Prl secretion, presence of DA has been demonstrated in
the portal blood (Ben-Jonthan et al., 1977) and a typical dopaminergic receptor has been characterized in the anterior pituitary gland (Caron et al., 1977, 1978: Calabro and Macleod, 1978; Cronin et al., 1978).

**Drugs affecting Prolactin secretion:**

The hypothalamus also contains substances which can positively influence release of Prl (McCann et al., 1980). It has been evident that a host of neurotransmitters and neuropeptides are also involved in the control of Prl secretion (Mcleod, 1976; McCann et al., 1978; Neill, 1980; Vijayan, 1985). Consequently, drugs capable of altering neurotransmitter or neuropeptide function can alter Prl secretion in a positive or negative fashion (Muller et al., 1983). Some of these neuropeptides and neurotransmitters are listed in Fig. 1. Recent studies have provided evidence for the existence of GABA-ergic receptors in the pituitary involved in the control of Prl secretion. In addition to proven or putative neurotransmitters, a host of neuropeptides may inhibit or stimulate Prl secretion although the physiological significance of the action of most of these peptides has yet to be clarified. Stimulation of Prl release via a CNS mediated mechanism(s) by endogenous opioid-peptides, bombesin, cholecystokinin (CCK), Vasoactive intestinal
Fig. 1. Neurotransmitters and neuropeptides affecting PRL secretion.
peptide (VIP) and by direct pituitary action by VIP, substance P, neurotensin (NT), angiotensin II and vasotocin have been reported. Inhibition of Prl release via CNS-mediated mechanism(s) by gastrin, NT, bradykinin and vasotocin and bombesin have also been demonstrated (McCann, 1982). Thyrotrophin releasing hormone (TRH) is a potent Prl releasing agent in mammals. Although it does not seem to represent a physiological PRF (Szabo and Frohman, 1970) Prl acts on specific peripheral target gland or tissue which possesses a mechanism to control its secretion. It is operated via a short loop feedback by circulating Prl levels which increase the activity of the tuberoinfundibular neurons which releases DA into the portal blood.

Drugs which lower serum Prl levels are DA, DA agonists like L-Dopa, ergot alkaloids, Piribedil and apomorphine, all of which exert a marked inhibitory effect (Frantz and Kleinberg, 1978). This characteristic is shared though in different degrees by antiserotonin drugs and monoamine oxidase inhibitors.

Among the drugs capable of rising serum Prl levels are phenothiazines, Butyrophenones (Haloperidol), Pimozide and Benzamides (Sulpirid, Metoclopramide) all of which antagonise DA receptors (Frantz and Kleinberg, 1978).
a) Bromocriptine:

b) Pimozide:

c) Muscimol:

d) Baclofen:

Fig. 2. Drugs Affecting Prolactin Secretion
Other drugs with different mechanism of action as reserpine and methyldopa (Blood pressure lowering drugs which cause depletion of central catecholamines), 5-OH-Tryptophane (Serotonin precursors), Cimetidine (H2 Histamine receptor blocker) Morphine and Methadone (Opium derivatives), estrogens and TRH increase serum concentration. GABA has also been shown to participate in controlling Prl secretion. Muscimol and Baclofen are two GABA mimetic drugs. Among the drugs mentioned above the following were used in the present investigation.

**Bromocryptine;**

This is a semisynthetic ergot alkaloid. These ergot alkaloids contain the tetracyclic ergolene or ergoline ring system. These are divided chemically into four groups. 1. Peptide containing ergot alkaloids, 2. Lysergic acids, 3. Lysergic acid amines, 4. Clavines. Substitution of the aliphatic group for a cycle-alcohol, gives rise to the family of the ergopeptenes of which ergocryptine is the most potent, much more so if a bromine atom is introduced at C2, which is then 2-bromo-ergocryptine. Bromocryptine (Bc) is a 2α-bromoergocryptine which is an 8-substituted 9-ergolene (with a double bond in 9-10 position) belonging to the peptide alkaloid group (Fig. 2a).
Bromocryptine is a directly acting DA agonist. Although Bc was developed in 1967 it was introduced into clinical research in 1969. It was later shown to directly stimulate neuronal DA receptors (Hokfelt and Fuxe, 1972; Corrodi et al, 1973) and to compete with the specific binding of $^3$H-dopamine to DA receptors of isolated bovine pituitary membranes (Calabro and Macleod, 1978). Because of its ability to affect $\alpha_1$, $\alpha_2$ and $\beta$ adrenergic and serotonin receptors. Bromocryptine induces an early agonistic effect at central norepinephrine (NE) receptor sites, while later its effect is more consistent with the post synaptic NE receptor blockade. The Prl inhibiting properties of ergot derivatives extend to all vertebrate species tested so far, including humans and do not require the integrity of the hypothalamo-pituitary connection. Bromocryptine and ergot derivatives directly inhibit Prl release from anterior pituitaries both in vitro (Nagasawa et al., 1973; Macleod and Lehmeyer, 1974) and in vivo (Fluckiger et al, 1976). Probably the action of Bc on the hypothalamus is secondary. Bromocryptine stimulates DA receptors of lactotrophic cells and then through a mechanism not involving changes in cAMP it antagonizes potassium action and interferes with calcium influx polarising pituitary cell membranes. In this way the drug lessens the exocytotic release of Prl granules which thus accumulate into the cells.
Pimozide:

Pimozide (Pirn) is a DA receptor antagonist. Dopamine receptor antagonists increase Prl secretion in either animals or humans and this is due to direct blockade of DA receptor sites located on the pituitary lactotrophes which are under continuous modulation by DA delivered through the hypophysial portal vessels (Weiner et al. 1979). Both high and low affinity binding sites for DA antagonists have been evidenced in membranes from anterior pituitary glands (DeLean et al, 1981). Pimozide, a neuroleptic drug was developed by Janssen et al, 1968 which specifically blocks DA receptors, represents a useful tool for the study of the participation of DA in the regulation of hypothalamic and pituitary function (Fig. 2b).

GABA mimetic drugs:

In recent years, some proven or putative neurotransmitters have been proposed to participate in controlling Prl secretion. One among them is GABA. Recent data support the existence of a dual GABA ergic control of Prl secretion in rat, although the precise nature of its intervention is controversial. One is stimulatory exerted on a CNS site and the other inhibitory occurring
at the level of the anterior pituitary (Vijayan and McCann, 1978a; Locotelli et al, 1979; McCann et al, 1982). A number of events favour the existence of either GABA ergic component for the control of Prl secretion. GABA is a neutral amino acid found in high concentrations in the mammalian CNS (Awapara et al, 1950; Roberts and Frankel, 1950). A number of GABA agonists and antagonists have been developed in recent times. A substance may antagonize the action of GABA directly by competing with GABA for its receptors or indirectly by allosterically modifying the receptor and by blocking GABA activated ionophores.

**Muscimol;**

The action of Muscimol, a psychotomimetic isolated from the mushroom *Amanita muscaria* as a GABA like amino acid was first reported by Johnston et al (1968) and this isoxazole is widely used as a selective and potent GABA agonist. It shows a remarkable selectivity in its interaction with GABA receptors, the 3-isoxazole moiety acts as a marked carboxyl group which is recognized efficiently by GABA receptors but not by other macromolecules that interact with GABA in the brain. Muscimol (Fig. 2c) is not a substrate for GABA transaminase and is transported inefficiently by GABA uptake system (Johnston et al, 1978).
Baclofen is a lipophilic derivative of GABA which is better able to penetrate the blood brain barrier. Much indirect evidence suggests that Baclofen (Fig. 2d) has a GABA mimetic action but is not a direct GABA agonist and is relatively ineffective in displacing GABA or bicuculline bound to brain membranes (Johnston, 1978). Its GABA mimetic properties are perhaps related to GABA release since it has been shown to enhance the release of GABA from slices of rat globus pallidus (Kerwin and Pycock, 1978) and from rat brain synaptosomes (Roberts et al, 1978).

Scope of the present investigation:

Prolactin which has a regulatory role in androgen biosynthesis during sexual development is also involved in reproductive changes in seasonal breeders and in rodents. In man it exerts inhibitory and facilitatory effect. Thus Prl has a dual role on testicular function in men or in experimental animals. This situation can be explained by the biphasic action of Prl where low levels were stimulatory and high levels inhibitory to gonadal function. In rat and mouse hyperprolactinemia"
can reduce plasma LH and FSH levels. Whereas in golden hamsters it stimulates the synthesis and release of FSH. These observations indicate important differences between species and experimental conditions used. Keeping this in view, the present investigation is an attempt to study the effect of Prl releasing/inhibiting drugs in sexually maturing and adult intact rats by evaluating the changes in some hormone sensitive biochemical markers.

Testicular hyaluronidase and glucosamine 6-phosphate synthase activities, two enzymes involved in testicular function and glucosamine 6-phosphate synthase activity in the ventral prostate has been evaluated. Circulating plasma cholesterol levels were also measured to see the modulatory role of Prl, if any, on steroidogenic response. Glycogen concentration and glucosamine 6-phosphate synthase activity in the uterus were also determined in rats treated with Prl releasing/inhibiting drugs.

Hyaluronidase enzyme (EC 3.2.1.35) concentration in the rat testis is related to the functional status of the germinal epithelium (Mancini et al, 1964; Blackshaw, 1970). The acrosome of the mature spermatozoa is considered to be a lysosome like structure, containing hydrolytic enzymes which are utilized in the process of fertilization. The enzyme hyaluronidase in the testis
has been localized exclusively to the acrosome of developing spermatids and mature spermatozoa by immunofluorescent staining of the intact cells (Mancini et al. 1964). The emergence of hyaluronidase activity correlated with the formation of the cap phase of spermatid (Males and Turkington, 1970). This rapid rise of enzyme activity occurs during the period of development of spermatid cap into the acrosome which takes place during the sexual maturation of the testes. Hence this enzyme has been chosen as a biochemical marker for the study of Prl effect on testicular function.

Glucosamine 6-phosphate synthase (E.C. 53.1.19) catalyses the transfer of the amide group of L-glutamine to fructose 6-phosphate to form glucosamine 6-phosphate. This is a rate limiting enzyme in the formation of UDP-N-acetyl glucosamine. It appears that all N-acetyl amino-sugar units of glycoproteins, mucopolysaccharides and glycolipids are synthesized through the reaction catalyzed by glucosamine 6-phosphate synthase. Activity of this enzyme was shown to fluctuate during estrous, early pregnancy and in the male reproductive organs of rat (Rukmini, 1981). Since the synthesis of glycoproteins occur during spermatogenesis this enzyme was studied as a biochemical marker of spermatogenesis and glycoprotein synthesis during hypo-and hyperprolactinemic condition.
Cholesterol is an obligatory precursor for steroid hormone synthesis (Bransome, 1968). The circulating cholesterol levels are a potential source for steroid hormone production as well as membrane synthesis. Luteal cells have three potential sources for cholesterol, it may be synthesized de novo from acetate, derived from sterol esters stored within lipid droplets or enter cells from the blood. Although each of these sources may contribute sterol for progesterone synthesis the interrelationship between these pools and their relative importance is poorly understood. The effects of Prl stimulatory and inhibitory drugs on circulating plasma cholesterol, in sexually maturing rats were also evaluated. Since Prl is known to be involved during early pregnancy and lactation the effect of inhibition of Prl during pre-and post-implantation period on uterine glucosamine 6-phosphate synthase activity, gestation period and litter size were also evaluated.