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Neonatal-Prepubertal Hypothyroidism on Postnatal Testis Development

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1. Introduction

Thyroid hormones stimulate oxidative metabolism in many tissues in the body, however, testis is not one of them. Therefore, in this sense, testis is not considered as a target organ for thyroid hormones. However, recent findings clearly show that thyroid hormones have important functions on the testis development during neonatal-prepubertal life. Testis is an exocrine organ because it produces sperm and it is also an endocrine organ, because it produces hormones. In this chapter, general organization of the adult mammalian testis is first described to understand the organization of the adult testis. Thereafter, the general organization of the mammalian testis at birth is described, followed by how the neonatal-prepubertal hypothyroidism affects the testis development during this period, Establishment of the Sertoli and Leydig cell numbers in the adult testis during the neonatal-prepubertal life, is critical to the general maintenance and reproductive functions of the adult mammalian male; thyroid hormones play a crucial role in these processes. The effects of hypothyroidism on neonatal-prepubertal testis are discussed in this chapter using the observations generated with rodent models, focusing on testicular testosterone secretory capacity and sperm production, which are an essential function to the male mammal.

The hormone testosterone is essential for the mammalian male for maintenance and proper functioning of many organ systems of the body such as muscle, bone and skin, in addition to its requirement for the reproductive function. Leydig cells in the testis are the primary source of testosterone in the male mammal. There are two populations of Leydig cells in mammals studied to date; fetal and adult Leydig cell populations. Fetal Leydig cells are differentiated during the fetal life and are still present at birth. However, the adult population of Leydig cells differentiate postnatally from the mesenchymal stem cells in the testis to establish the adult population Leydig cells of the sexually mature testes; they are the main source of testosterone during adult life. Therefore, establishing the adult population of Leydig cells in the postnatal testis, which occurs during the neonatal-prepubertal life, is an essential process in the mammalian testis for the well being of the adult mammalian male. Research with several rodent species has shown that Leydig stem cell differentiation in the postnatal testis is arrested with hypothyroidism, but can be stimulated by supplementation with thyroid hormones. Transient neonatal hypothyroidism causes larger testis at

adulthood, although the process of Leydig cell differentiation is arrested during the period of hypothyroidism. Differentiated Leydig cells in these animals after the hypothyroid period is withdrawn, are smaller in size but two-fold in number compared to the euthyroid animals. Therefore, the fertility and circulating testosterone levels in these transiently neonatal animals at adulthood are similar to euthyroid animals. Under hypothyroid conditions during the neonatal -prepubertal period, fetal Leydig cells continue to function normally with no change in their testicular testosterone secretory capacity, although the postnatal differentiation of adult population of Leydig cells are absent. However, prolonging the hypothyroid condition beyond the neonatal-prepubertal period fails to maintain the fetal population of Leydig cells; they undergo cell atrophy and lose their testosterone secretory capacity, in addition to the arrest in differentiation of adult population of Leydig cells. During the hypothyroid period, in the neonatal-prepubertal animals, Sertoli cells in the seminiferous tubules fail to mature, but continue to proliferate. When the hypothyroid status is withdrawn, these Sertoli cells mature and are now greater in number per testis compared to a euthyroid testis, because they were subjected to prolonged proliferative period because of hypothyroidism. Because of this reason, testes of transiently hypothyroid animals become larger in volume and weight at adulthood and produce greater numbers of sperm compared to the control animals.

These studies have revealed the importance of thyroid hormone for postnatal testis development in the mammalian testis.

2. Thyroid hormones

J.F. Gudernatsch (1912) provided the first evidence for thyroid hormones and their task in cellular differentiation. It is established now that thyroxine (T_4) and triiodothyronine (T_3) are produced by the thyroid gland and triiodothyronine is at least five times more potent than thyroxine. The most characteristic effect of thyroid hormones is their ability to stimulate oxidative metabolism in tissues in the body. However, in this sense, testis is not considered as a target organ for these hormones. Thyroid hormone secretion is regulated by the thyroid hormone releasing hormone and the thyroid stimulating hormone from the hypothalamus and the anterior pituitary, respectively.

3. General organization of the adult mammalian testis

Testes produce sperm for reproductive function and androgens (male hormones) which are necessary for general maintenance of many organ systems in the male and the reproductive function which includes libido. Testis has two compartments. The tubular compartment or the seminiferous tubules and the testis interstitium which lies out side of the tubular compartment (Figure 1). As stated earlier testis has exocrine and endocrine functions. Seminiferous tubules are comprised of Sertoli cells and germ cells (Figure 1). The testis interstitium has Leydig cells, which are the primary source of androgens (male hormones) of the adult mammalian male, the blood vessels, lymphatics, and many other cell types (Figure 1), such as fibroblasts, macrophages and plasma cells. Testes are encapsulated by three distinct layers; the innermost tunica vasculosa, the outer most tunica vaginalis and the tunica albuginea is in the middle. All of these are structures are suspended in the scrotum in many mammalian species (Davis et al., 1970).

3.1 Seminiferous tubules

The seminiferous tubules are of two kinds, the convoluted seminiferous tubules, which have Sertoli and germ cells, and the straight seminiferous tubules, which are continuous with the rete testis (Banks, 1986). Rete testis is connected with the efferent ducts and continuous with the epididymis, which is continuous with the ductus deference/vas deference that is connected to the male urethra which leads to the external orifice of the penis. In this review, only the structural organization of the convoluted seminiferous tubules and the Leydig cells are described, because of the relevancy to the title of this chapter,

Convoluted seminiferous tubules. comprise approximately 90-92% of the volume of the adult testicular parenchyma in mammalian species studied to date (Mendis-Handagama et al., 1987, 1988, 1990). Beyond this point, convoluted seminiferous tubules will be referred to as seminiferous tubules throughout this chapter. Each seminiferous tubule is separated from the testis interstitium by a well defined basement membrane (Figure 1). Sertoli cells (Figure 1), first described by Sertoli in 1865, reside on the basement membrane of each seminiferous tubule and extend from the basement membrane to the lumen of the seminiferous tubules. Different stages of male germ cells are found in the seminiferous tubules (Figure 1); spermatogonia, primary spermatocytes, secondary spermatocytes, round spermatids and elongated spermatids. Sertoli cells together with the germ cells form the seminiferous epithelium, which is a stratified epithelium. In addition to the Sertoli cells, spermatogonia (stem cells for male germ cells) are also reside on the basement membrane of the seminiferous tubules. All the other germ cells are attached to the Sertoli cells with their differentiation and maturation and move towards the lumen. Sertoli cells, spermatogonia and primary spermatocytes are diploid cells and secondary spermatids, round spermatids and elongated spermatids are haploid cells.

Sertoli cells provide seminiferous tubular integrity. Moreover, The adjacent Sertoli cells in each seminiferous tubule form Sertoli-Sertoli junctions (tight junctions, Brokelman, 1963; Flickinger and Fawcett, 1967; Nicander, 1967; Rosas, 1970) close to the basement membrane, which divides each seminiferous tubule into two compartments; the basal compartment and the adluminal compartment (Banks, 1986). More importantly, Sertoli-Sertoli cell junctions form the blood-testis barrier to protect the developing germ cells (Dym, 1973; Setchell and Waites, 1975). The basement membrane and the associated myoid cells of the seminiferous tubules contributes to the blood-testis barrier to a lesser extent (Dym and Fawcett, 1970; Fawcett et al., 1970). Sertoli cells function as 'nurse' cells for the developing germ cells; they provide nutrition and hormones (androgens) required for spermatogenesis, which is the process of producing sperm from spermatogonia. Different species demonstrate different cellular associations during the cycle of the seminiferous epithelium; six stages in the human (Clermont, 1963), twelve stages in the monkey (Clermont, 1969), and 14 stages in the rat (Leblond and Clermont, 1952)

Sertoli cells produce tubular fluid (Setchell and Waites, 1975). They transport and maintain a high concentration of androgens in the seminiferous tubules and secrete androgen binding protein (ABP; French and Ritzen, 1973) and the hormone inhibin (de Kretser et al., 2002), which are important in maintaining spermatogenesis. Also, it serves as a phagocytic cell to recycle residual bodies that arise as a byproduct of spermatogenesis (Lacy, 1967). It is also

reported that Sertoli cells have a significant role in the process of spermiation, i.e. release of sperm into the seminiferous tubular lumen (Sapsford and Rae, 1968; Fawcett and Phillips, 1969). It is also important to document that the testicular size and sperm producing capacity of a testis is positively correlated with the number of Sertoli cells in the testis (Berndtson et al., 1987; Moura et al., 2011).

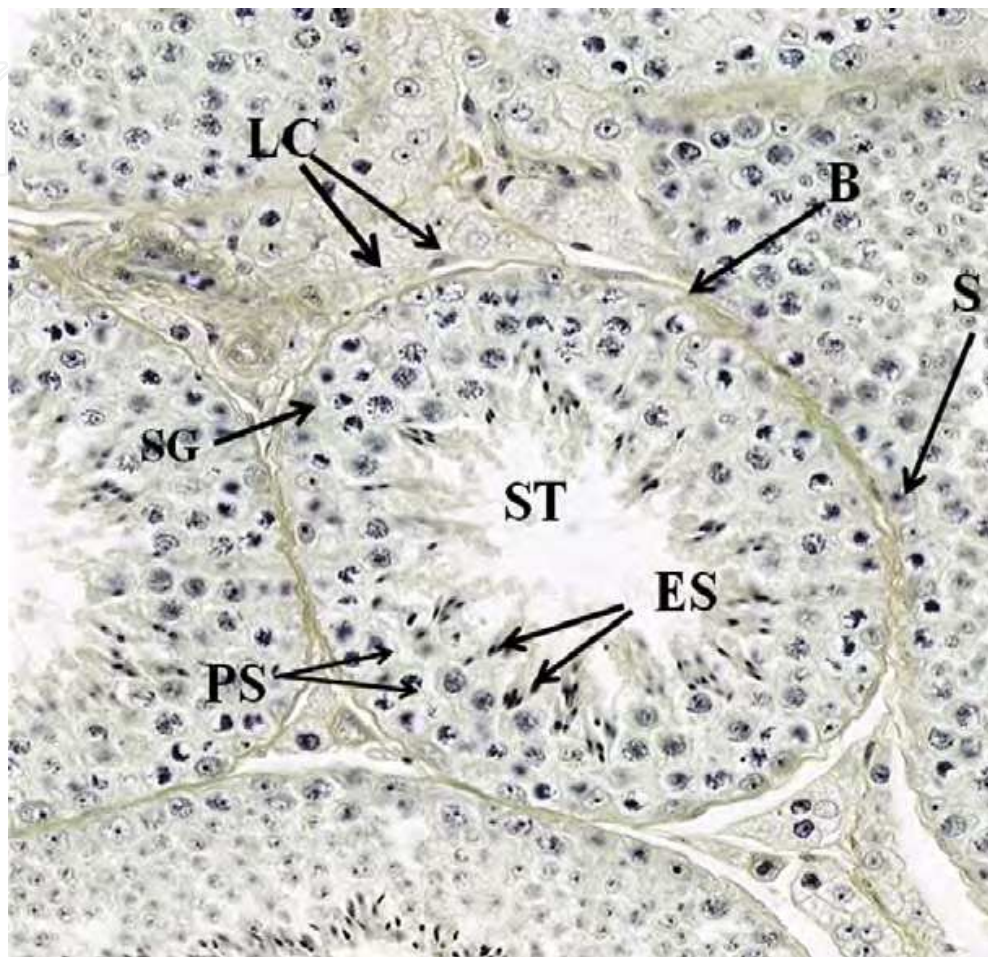


Fig. 1. A representative light micrograph of an adult dog testis to show general organization of the testis parenchyma. LC=Leydig cells in the testis interstitium, ST=seminiferous tubules, B=basement membrane, S=nucleus of a Sertoli cell, SG=spermatogonia, PS=primary spermatocytes, ES=elongated spermatids.

3.2 Testis interstitium

The testis interstitium can be considered as the skeletal frame work of the testis and is approximately 8-10% of the adult testicular parenchyma (Mendis-Handagama et 1987, 1988, 1990). Leydig cells reside in the testis interstitium (Figure 1). Among species, variations are seen in Leydig cell number, size, morphological characteristics and their relationship to blood vessels and other surrounding structures; these are unique to each species (Fawcett et al., 1973) and will not be discussed in this review. Luteinizing hormone (LH) produced by the gonadotrophs of the anterior pituitary gland, is considered as the primary regulator of Leydig cell structure and function in the adult testis.

It is universally accepted that Leydig cells, which were first discovered in 1850 by Franz Leydig as large polyhedral cells, are the source of androgens. Bouin and Ansel (1903) are credited with the concept that the primary androgen secreted by the testis is testosterone. In 1929, Gallagher and Koch also showed that the primary androgenic hormone secreted by the adult testis is testosterone. Later, Christensen and Mason (1965) and Hall et al., (1969), demonstrated that the principal site of testosterone synthesis in the testis is Leydig cells. Although the testosterone production by the Leydig cells is greatly influenced by the environment of the testis interstitium, this review will be primarily focused on Leydig cells.

The volume percentage (2-6%), the absolute volume (depends on the testis size), number ($2-4500 \times 10^6$) and the size ($1500-3000 \mu\text{m}$) of Leydig cells in the adult testis varies among species (Kaler and Neaves, 1978; Mori and Christensen, 1980; Mori et al., 1980; Johnson and Neaves, 1981; Mori et al., 1982; Mendis-Handagama et al., 1987, 1988 and 1990). The steroidogenic enzyme 3β -hydroxy steroid dehydrogenase ($3\beta\text{HSD}$) was exclusively localized histochemically in Leydig cells of mice (Baillie, 1964), the rat (Levy et al., 1959) and in many other mammalian species (Wattenburg, 1958). At present $3\beta\text{HSD}$ is used as a marker for Leydig cells (Ariyaratne and Mendis-Handagama, 2000; Ariyaratne et al., 2000a-d; Figure 2). Moreover, 11β -hydroxy steroid dehydrogenase 1 ($11\beta\text{-HSD1}$) is a marker for postnatally differentiated adult type Leydig cells, which is present as early as postnatal day 21 in the newly formed adult Leydig cells in the rat testis (Mendis-Handagama et al., 1998; Figure 3) and will be discussed later in this review.

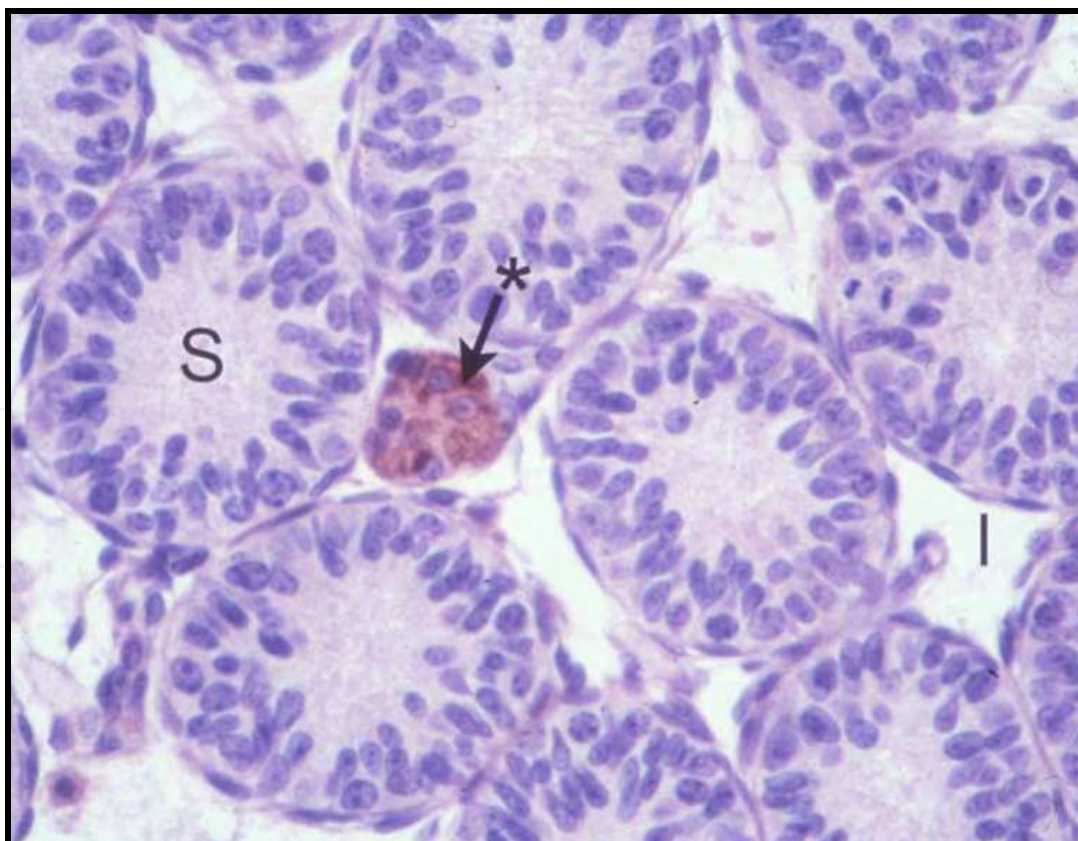


Fig. 2. A representative light micrograph of a 7 day old rat testis. S=seminiferous cord, I=testis interstitium, The arrow with an asterisk (*) depicts a cluster of fetal Leydig cells immunolabeled for $3\beta\text{-HSD}$.

4. General organization of the mammalian testis at birth

4.1 Seminiferous cords

At birth, tubular compartment of the testis does not contain a lumen and therefore, referred to as the seminiferous cords (Figure 4). These cords contain only two types of cells; the Sertoli cells, which are located on the basement membrane of the cord and the gonocytes (Figure 4). Sertoli cell nucleus is much smaller than the nuclei of gonocytes which are easily distinguishable from the Sertoli cells due to their large and circular appearance in section (Figure 4).

During the postnatal growth of the testis, the immature Sertoli cells undergo cell proliferation, although at a steadily declining rate, until the adult Sertoli cell population is established. Studies on rats have shown that the migration of gonocytes to the basement membrane and become spermatogonia from that point onwards and the differentiation of spermatogonia to primary spermatocytes in the neonatal/prepubertal testis are associated with the restriction of Sertoli cell proliferation, but before the blood-testis barrier is formed (Vitale et al., 1973). Sertoli cell proliferation gives a stable population of Sertoli cells in the adult testis (Bishop and Walton, 1960; Attal and Courot, 1963; Sapsford, 1963). With the initiation of spermatogenesis occurring soon after birth in rodents and at various later times in ruminants and primates, the immature Sertoli cells in the seminiferous cords undergo maturation and gain adult type Sertoli cells observed in the adult testis (Sapsford, 1963; Flickinger, and Fawcett, 1967; Vitale et al., 1973; Nagano and Suzuki, 1976; Ramos and Dym, 1979). Sertoli cell maturation in the developing testis is also accompanied by formation of the blood-testis barrier (Vitale et al., 1973; Nagano and Suzuki, 1976; Ramos and Dym, 1979).

4.2 Testis interstitium

In this section of the review, the author focuses on the Leydig cells in the neonatal/prepubertal testis interstitium. The fetal population of Leydig cells differentiate during the fetal life and is still present at birth (Figure 5) in all species studied to date (Lording and de Kretser, 1972; Mendis-Handagama et al., 1987; Kerr and Knell, 1988; Chemes, 1996;

Ariyaratne and Mendis-Handagama, 2000; O'Shaughnessy et al., 2002, 2003) and continue to be present in the postnatal testis in rodents studied to date (Kerr and Knell, 1988; Ariyaratne and Mendis-Handagama, 2000; O'Shaughnessy et al., 2002, 2003). However, in humans, it is reported that fetal Leydig cells undergo cell atrophy postnatally (Chemes, 1996).

Leydig cells in the adult testis, which are identified as the mature adult Leydig cells are differentiated postnatally during the neonatal pre-pubertal period (Roosen-Runge and Anderson, 1959; Mancini et al., 1963; Niemi and Kormano, 1964; Baillie, 1964; Lording and de Kretser, 1972; Mendis-Handagama et. al., 1987; Ariyaratne et al., 2000d) from the peritubular mesenchymal cells (Figure 6), which are the stem cells of adult Leydig cells. The peritubular mesenchymal stem cells differentiate through a series of cell stages in the Leydig cell lineage (progenitor cells, newly formed adult Leydig cells, immature adult Leydig cells) and become the mature adult Leydig cells (Figure 6). In this differentiation process, a spindle-shaped peritubular mesenchymal cell, which does not have the steroidogenic potential, gradually achieve appropriate enzymes and receptors for steroid

hormone biosynthesis and steroidogenic potential and finally become a large polyhedral mature adult Leydig cells (Figure 6); a non-steroidogenic mesenchymal stem cell gaining the steroidogenic status, e.g. gaining 3β -HSD enzyme activity can be visualized by performing immunocytochemistry (Figure 7).

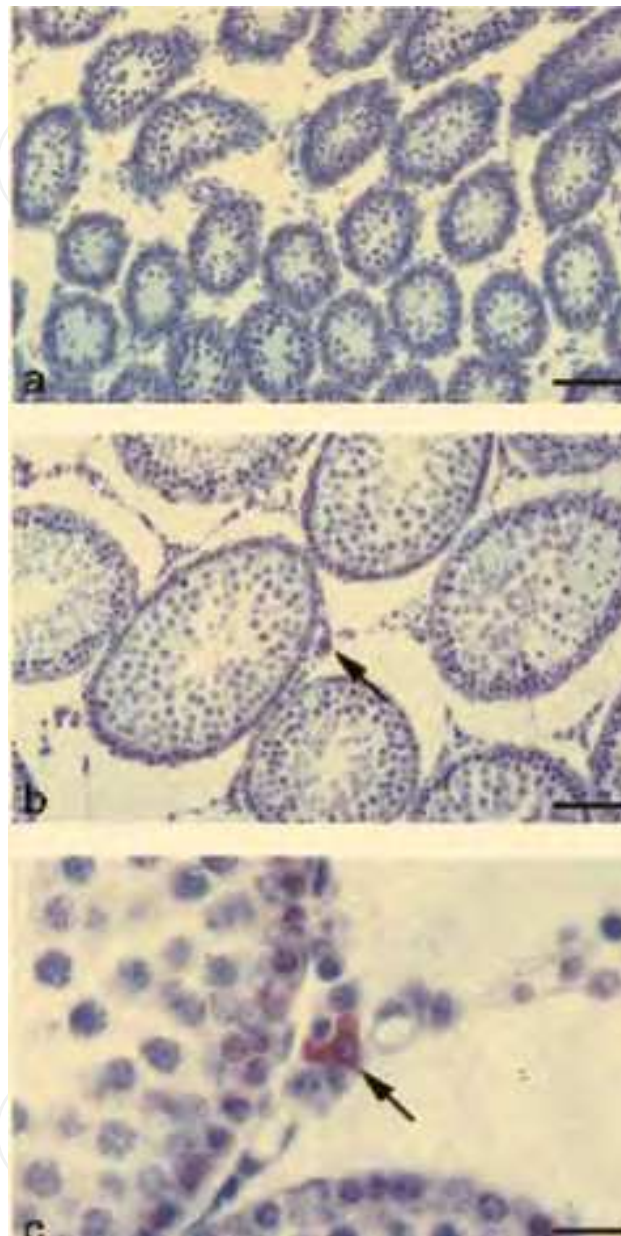


Fig. 3. Representative light micrographs to show the presence and absence of Leydig cells immunolabeled for 11β -HSD1 (marker for adult Leydig cells) immunocytochemistry in testis interstitium of 21-day-old rats. (a) Low power micrographs of a hypothyroid rat where 11β -HSD1 positive cells are absent (bar= $5.38\mu\text{m}$) and (b) a control rat where 11β -HSD1 positive cells (newly formed adult Leydig cells) are present (bar= $5.38\mu\text{m}$). (c) A higher-power view of the region located by the arrow in b. of a 21-day-old control rat I, Seminiferous tubule diameter is much reduced in the PTU/hypothyroid rat testis shown in (a). Bar= $5.12\mu\text{m}$. (Used with permission from the publisher, Mendis-Handagama et al., 1998, Biol. Reprod.59: 351-357.

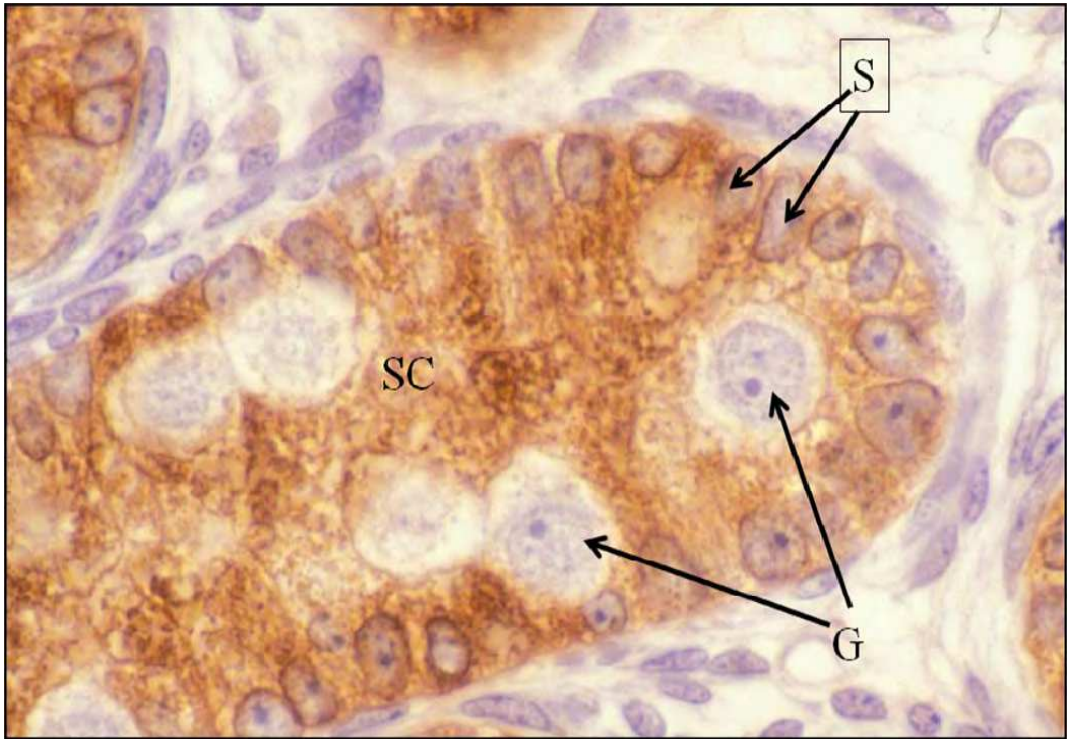


Fig. 4. Representative high power light micrograph of a 1 day old rat testis immunolabeled for anti-Müllerian hormone (brown stain) .SC=seminiferous cords, G=Gonocytes/Germ cells,, S=nuclei of Sertoli cells, (Used with permission from the publisher, Mendis-Handagama et al., 2008, Histology and Histopathology, 23:151-156, Figure modified).

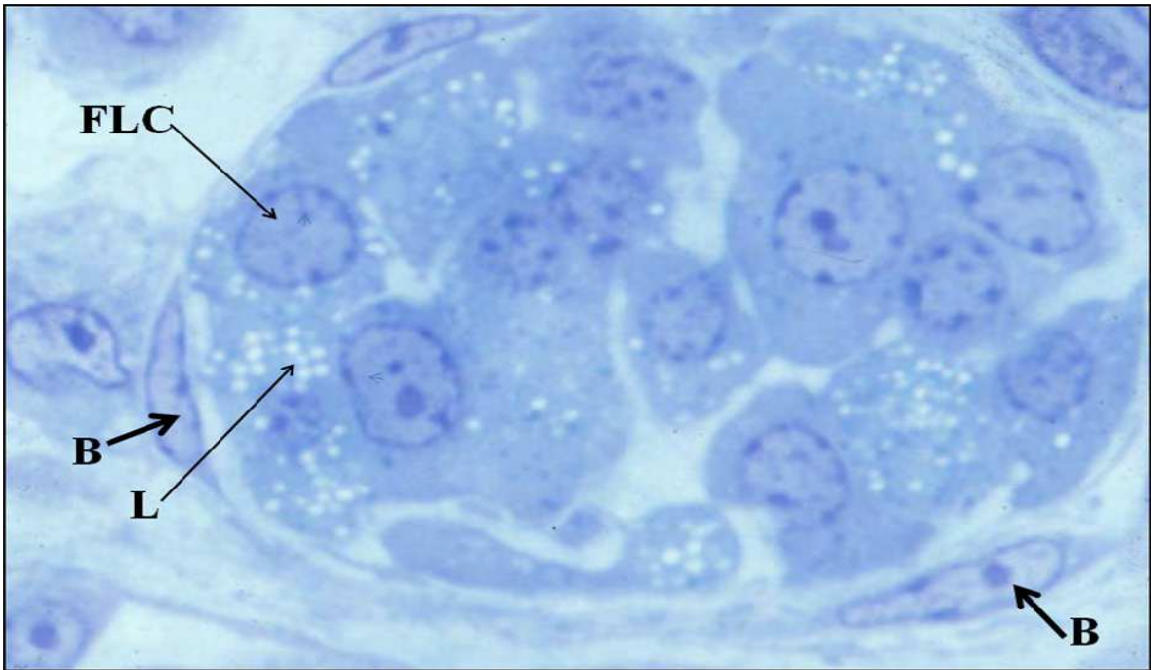


Fig. 5. Representative light micrograph to demonstrate fetal Leydig cells (FLC) in a 1 day old rat testis. L=cytoplasmic lipid droplets in fetal Leydig cells. B=basement membrane components surrounding a fetal Leydig cell cluster, a characteristic feature associated with fetal Leydig cells.

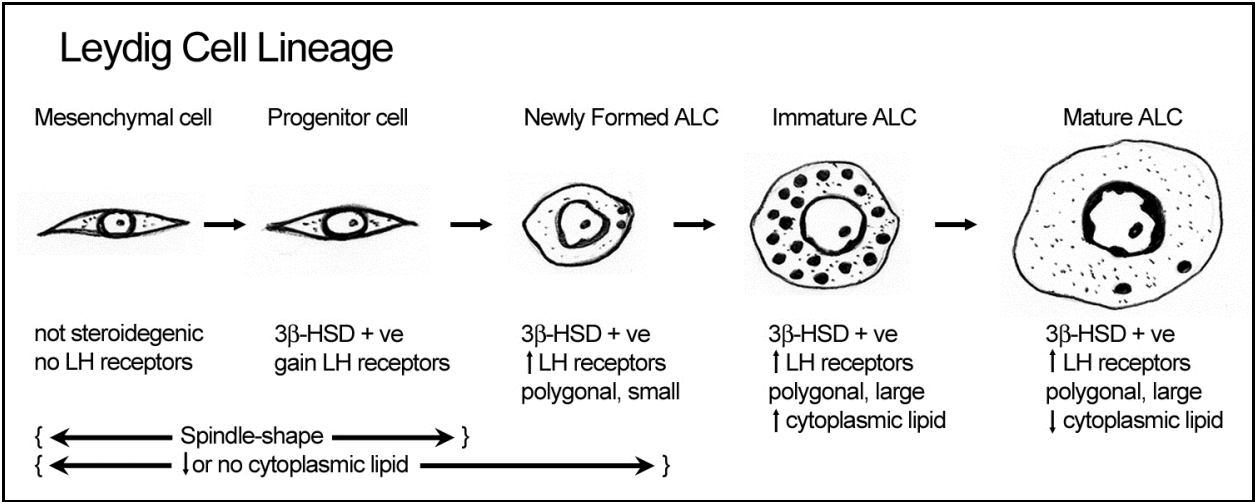


Fig. 6. Schematic diagram of Leydig cell lineage. (used with permission from the publisher, Mendis-Handagama and Ariyaratne, 2001, Biol.Reprod. 65:660-671). The stem cells for Leydig cells are the mesenchymal cells in the testis interstitium, which are spindle-shaped and non-steroidogenic. They first differentiate into progenitor cells, which are also spindle-shaped, but possess few steroidogenic enzymes (e.g. 3 β -HSD) and LH receptors. Thyroid hormone is critical to stimulate the mesenchymal cells to differentiate into the progenitor cells (the first step in Leydig cell differentiation) to begin the process of Leydig cell differentiation. Progenitor cells differentiate into mature adult Leydig cells through stages of newly formed adult Leydig cells and immature adult Leydig cells, respectively. (Used with permission from the publisher, Mendis-Handagama and Ariyaratne, 2001, Biol. Reprod. 65:660-671.).

5. Thyroid hormone action on the neonatal-prepubertal testis

Until recent years, little was known about the effects of thyroid hormones on the neonatal-prepubertal testis development. In many investigations on the effect of neonatl-prepubertal hypothyroidism, the hypothyroid status was insduced in the experimental animals immediately after birth by feeding their lactating mothers the reversible goitrogen, 6-n-propyl-2-thiouracil (PTU), 0.1% (w/v; Cooke et al., 1991, 1992; Mendis-Handagama et al., 1998; Teerds et al., 1998; Ariyaratne et al., 2000a.) or 0.05%(w/v) methimazole (Antony et al., 1995; Maran et al., 1999) in their drinking water until the pups were weaned on day 21.

5.1 Leydig cells

In mammalian species studied to date, the adult Leydig cells are absent at birth. Therefore, the fetal Leydig cells are the only source of testicular androgens at this age, which is primarily testosterone. In control euthyroid (normal thyroid hormone levels) rats, adult type Leydig cells are observed as early as postnatal day 10 (Mendis-Handagama et al., 1987) and concomitantly increase in number (Mendis-Handagama et al., 1987). This is in addition to the fetal Leydig cells already present in the postnatal testis. From birth to 21days, fetal Leydig cell number in the normal rat testis do not change (Mendis-Handagama et al., 1987,1998; Ariyaratne and Mendis-Handagama, 2000). They could be differentially identified from the postnatally differentiated adult type Leydig cells using their morphology

(Mendis-Handgama et al., 1987,1998; Ariyaratne and Mendis-Handagama, 2000) and using 11 β -HSD1 immunocytochemistry, as early as postnatal day 21 in the rat (Mendis-Handgama et al., 1998; Figure 8). These newly formed adult type Leydig cells primarily secrete androstenedione.

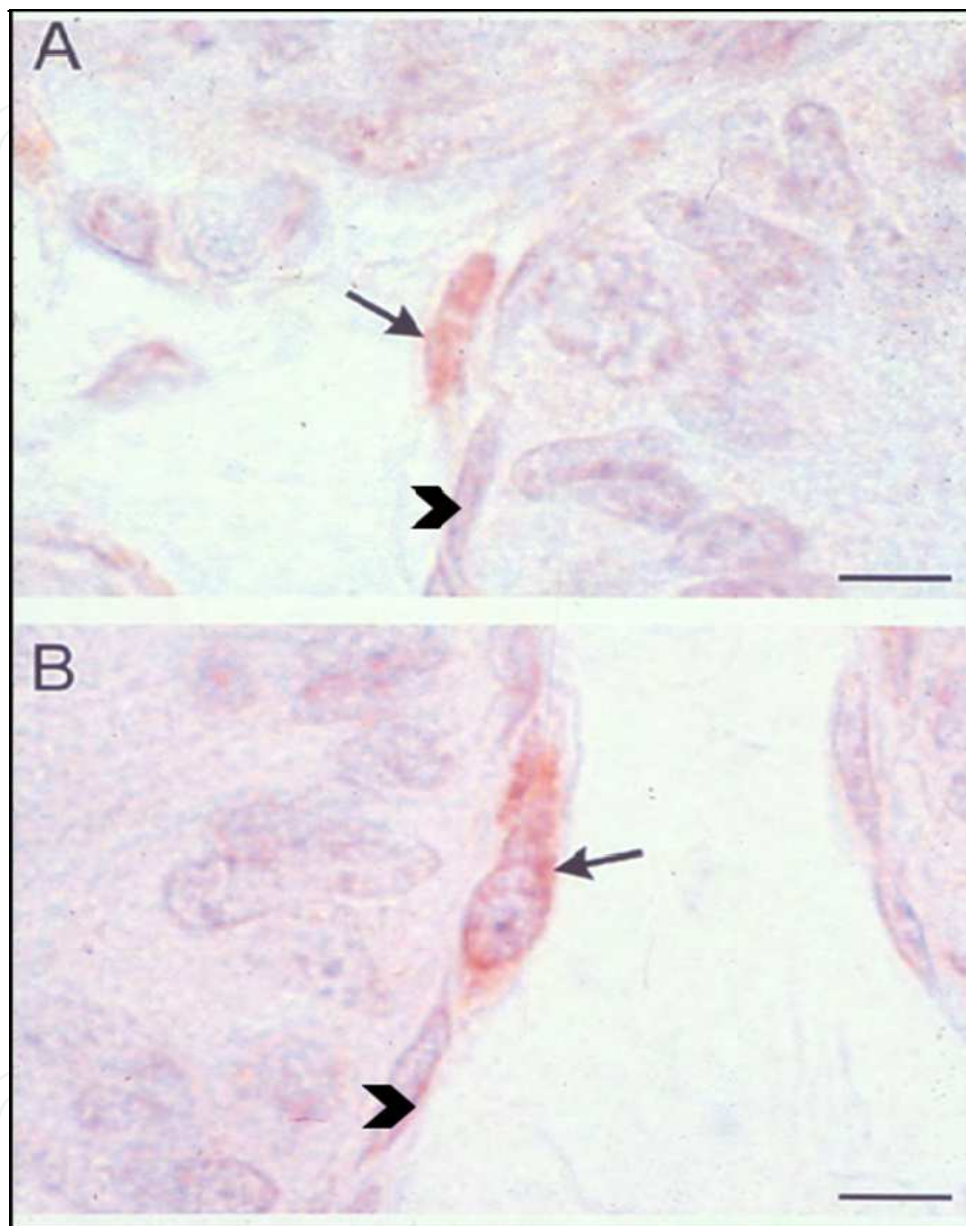


Fig. 7. Representative light micrographs from a 10 day old rat testis immunolabeled for 3 β -HSD (shown in brown color) and demonstrate early steps in Leydig cell differentiation. With thyroid hormone stimulation, mesenchymal cells (arrow heads) in the periphery of the seminiferous tubules (S) differentiate into progenitor cells (arrows in Figures A, and B), which are still spindle-shaped; with the progression of their differentiation towards the newly formed adult Leydig cells, they become rounder in shape (compare cells depicted by arrows in Figures A and B, with A) and move gradually away from the peritubular region towards the central part of the testis interstitium. (used with permission from the publisher, Ariyaratne et al., 2000, Biol. 63:165-171., figure modified).

Postnatal Leydig cell differentiation in the neonatal-prepubertal testis is arrested with hypothyroidism (Mendis-Handagama et al., 1998; Teerds et al., 1998; Ariyaratne et al., 2000a) and therefore, these testes do not contain newly formed adult Leydig cells, evident by the absence of 11 β -HSD1 labeled cells in their testes interstium (Figures 8c and f) in contrast to age-matching euthyroid rats (Figures 8a and d, respectively); they show 11 β -HSD1 labeled Leydig from postnatal day 21 (Figure 8a). From birth to postnatal day 21, testes of hypothyroid rats contain only the fetal Leydig cells, which are fully functional, evident from their morphology and testosterone secretory capacity (Mendis-Handagama et al., 1998; Ariyaratne et al., 2000a). Additionally, an increased number of mesenchymal stem cells are also generated in the hypothyroid rat testes (Mendis-Handagama et al., 1998; Ariyaratne et al., 2000a). The fetal Leydig cells in control rats show cell atrophy on postnatal day 21 (Mendis-Handagama et al., 1987 and 1998; Ariyaratne and Mendis-Handagama, 2000), which is not seen in the 21day old hypothyroid rats (Mendis-Handagama et al., 1998), suggesting that the fetal Leydig cells in the neonatal-prepubertal testis do not regress under a hypothyroid status up to 21 postnatal day. Therefore, serum testosterone levels in these neonatal-prepubertal hypothyroid rats are maintained similar to the control rats up to this age, although the total number of Leydig cells in these rats are significantly lower compared to the age-matching control rats. This is because that the testosterone-producing capacity per fetal leydig cells at neonatal ages is significantly greater than the adult Leydig cells, even at day 90 (Tapanainen et al., 1984; Huhtaniemi et al., 1982). Control 21day old rats have shown greater serum androstenedione levels than their age-matching hypothyroid rats (Mendis-Handagama et al., 1998) indicating the greater numbers of newly formed adult Leydig cells in those testes. Absence of newly formed adult Leydig cells.

In testes of 21 day old hypothyroid rats agrees favorably with their lower levels of serum androstenedione (Mendis-Handagama et al., 1998).

When the hypothyroid status is extended beyond postnatal day 21 in the rat, fetal Leydig cells undergo cell atrophy together with the absence of newly formed adult Leydig cells in their testis interstitium, evident by the absence of cells labeled for 11 β -HSD1 in the testis interstitium, the marker for adult Leydig cells (Figures 8c and f). By contrast, when hypothyroid status is stopped at postnatal day 21, newly formed adult Leydig cells are still absent on postnatal day 28, but present at day 40 (Figures 8b and c), greater in number compared to age-matching control/normal rats (Figures 8a and d). However, although these newly formed adult Leydig cells are greater in number (Figure 9a) they are smaller in size than their age-matching controls (Figure 9b). When prolonging the hypothyroid status from day 21 to day 40, testicular testosterone and androstenedione secretory capacity is also diminished (Mendis-Handagama and Ariyaratne, 2004; Figures 9c and d) and could be attributed to the fact that the regression of the fetal Leydig cells and arrest in the differentiation of adult Leydig cells with extended hypothyroidism in these rats.

When the hypothyroid status is discontinued at weaning of the pups at day 21 and raise them under euthyroid conditions until adult hood, which is referred to as transient neonatal hypothyroidism, the adult testis size of these rats become extremely larger (Cooke et al., 1991, 1992; Meisami et al., 1992; Mendis-Handagama and Sharma, 1994) and contain twice the number of Leydig cells per testis compared to the age-matching untreated controls (Mendis-Handagama and Sharma, 1994). However, these Leydig cells in the adult testes of the transiently hypothyroid rats are smaller in size and has 50% of testosterone secretory

capacity (Mendis-Handagama and Sharma, 1994). Nevertheless, the testosterone secretory capacity per testis is maintained in these transiently hypothyroid rats at adulthood, because of doubling of the Leydig cell number per testis (Mendis-Handagama and Sharma, 1994). This is because, in rats subjected to neonatal hypothyroidism from birth to 21 days of postnatal age accumulate an abundance of mesenchymal stem cells in their testes due to their proliferation but undifferentiation to Leydig cells during the hypothyroid period. Thus, when the hypothyroid status is withdrawn at postnatal day 21, the inhibition of these mesenchymal stem cell differentiation to Leydig cells is ceased and therefore, they begin to differentiate and first appear in these testes interstitium at day 40 as newly formed Leydig cells (Figure 8e; Figure 9a) in significantly greater numbers than their age-matching euthyroid rats and continue to increase in number up to adulthood (i.e. 90days; Figure 9a). However, as stated before, these Leydig cells are smaller in size and capable of producing only 50% of testosterone secretory capacity per cell. However, they maintain the serum testosterone levels at adulthood because they are greater in number (Mendis-Handagama and Sharma, 1994).

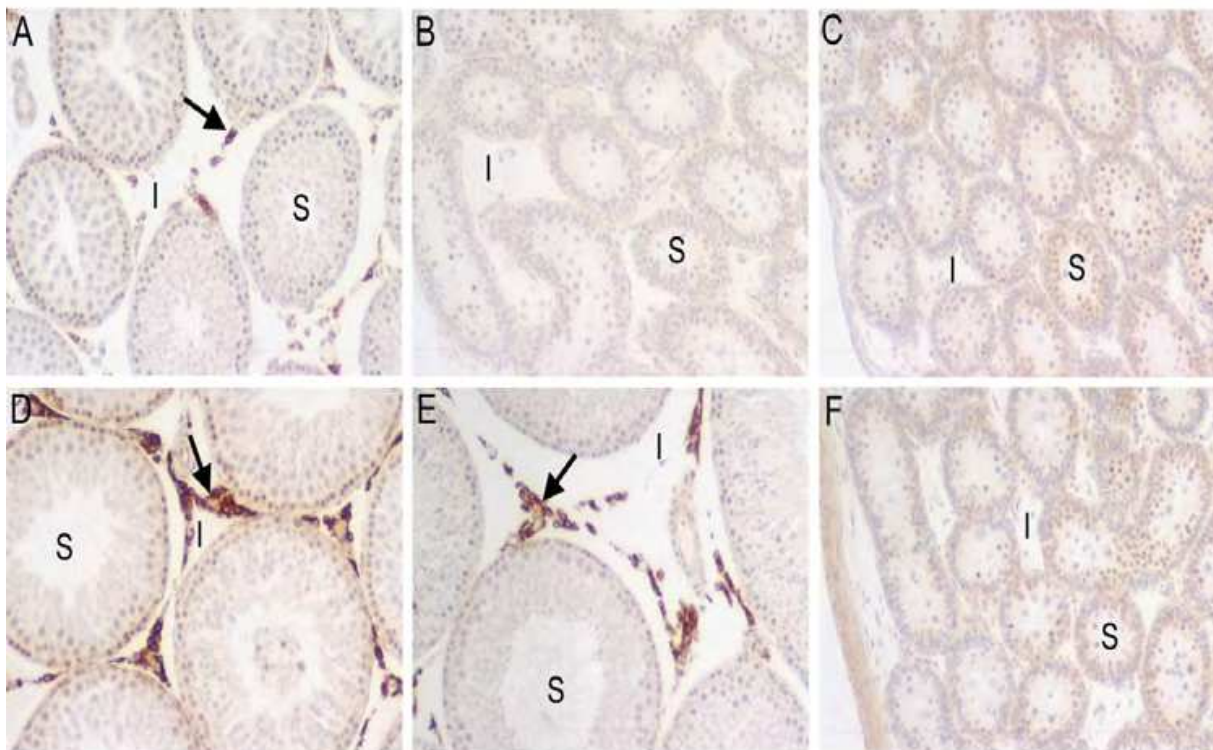


Fig. 8. Representative micrographs to show 11bHSD1 immunocytochemistry in testes interstitium of 28 and 40 day old control rats (A and D), PTU-water rats/transiently hypothyroid (B and E) and PTU/hypothyroid rats (C and F), respectively. 11bHSD1 positive cells (i.e. newly formed adult Leydig cells; arrow) were present in control rats in few numbers at day 28 (a) and more at day 40 (D), were absent at day 28 (B), but present at day 40 (e) in PTU-water/transiently hypothyroid rats, and were absent in PTU/hypothyroid rats at both days (C and F). Seminiferous tubule (S) diameter is much reduced in the PTU/hypothyroid rats compared to the other two groups. Interstitium of the testis. Bar=35 μ m. (used with permission from the publisher, Mendis-Handagama and Ariyaratne 2004, Archives of Andrology 50:347-357)

Continuous exposure of lactating mothers to polychlorinated biphenyls results in significant effects on Leydig cells structure and function in the adult offspring males: Leydig cells hypotrophy and reduced capacity to produce testosterone *in vitro* in response to luteinizing hormone stimulation (Kim et al., 2000). It is reported that polychlorinated biphenyls disrupt the thyroid gland function in humans (Langer et al., 1998; Cheek et al., 1999; Nagayama et al., 1998) and in many other mammalian species, e.g. the rat (Collins, 1980; Saeed and Hansen 1985;

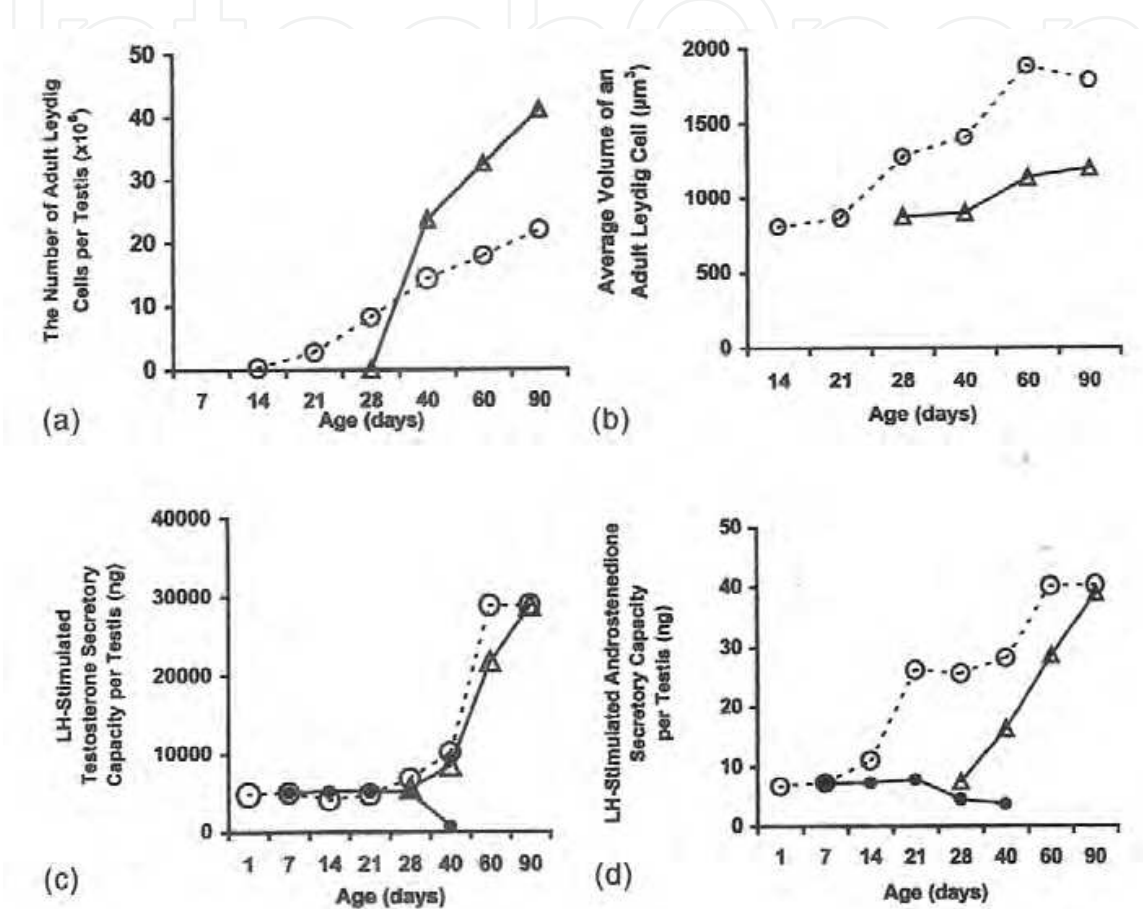


Fig. 9. Control rats – open circles, PTU-water rats/transiently hypothyroid – triangles, PTU/hypothyroid rats – filled circles. (a) The number of adult Leydig cells (ALC) per testis in control rats and PTU-water/transiently hypothyroid rats, ALC were first detected at day 14 in few numbers in control rats. In PTU/hypothyroid rats the ALC were absent, In PTU-water/transiently hypothyroid rats few were seen at day 28, but increase numbers were seen at day 40 onwards. (b) Average volume of an ALC. (c) LH-stimulated (LH, 100 ng per ml) testosterone production per testis *in vitro* for three hours. (d) LH-stimulated (LH, 100 ng per ml) androstenedione production per testis *in vitro* for three hours. (used with permission from the publisher, Mendis-Handagama and Ariyaratne, 2004, Archives of Andrology 50:347-357)

Ness et al., 1993; Cooke et al., 1996; Kato et al., 1998 and 1999; Desaulniers et al., 1999) and the grey seal (Wolstad and Jensen, 1999). Based on the observations of Cooke et. al (1996) and Kim et al. (2000), it appears that polychlorinated biphenyl exposure during the neonatal period has subjected these rats to undergo a transient hypothyroid status, which has caused an interference in the normal process of Leydig cell differentiation in the developing testis

and produce a defect in the steroidogenic function of the Leydig cells in the adult. Moreover, it is important to note that in neonatal Syrian hamsters, Leydig cells differentiation is arrested with experimental exposure to extreme darkness (Hance et al., 2009), which causes low levels of thyroid hormones. This finding agrees favorably with the concept that mesenchymal stem cell differentiation into Leydig cells is arrested under low levels of thyroid hormones. Therefore, neonatal-prepubertal testes of these hamsters do not show peritubular mesenchymal stem cell differentiation into progenitor cells and newly formed adult Leydig cells in the prepubertal testes, in contrast to euthyroid control hamsters; they contain only the fetal Leydig cells (Figure 10).

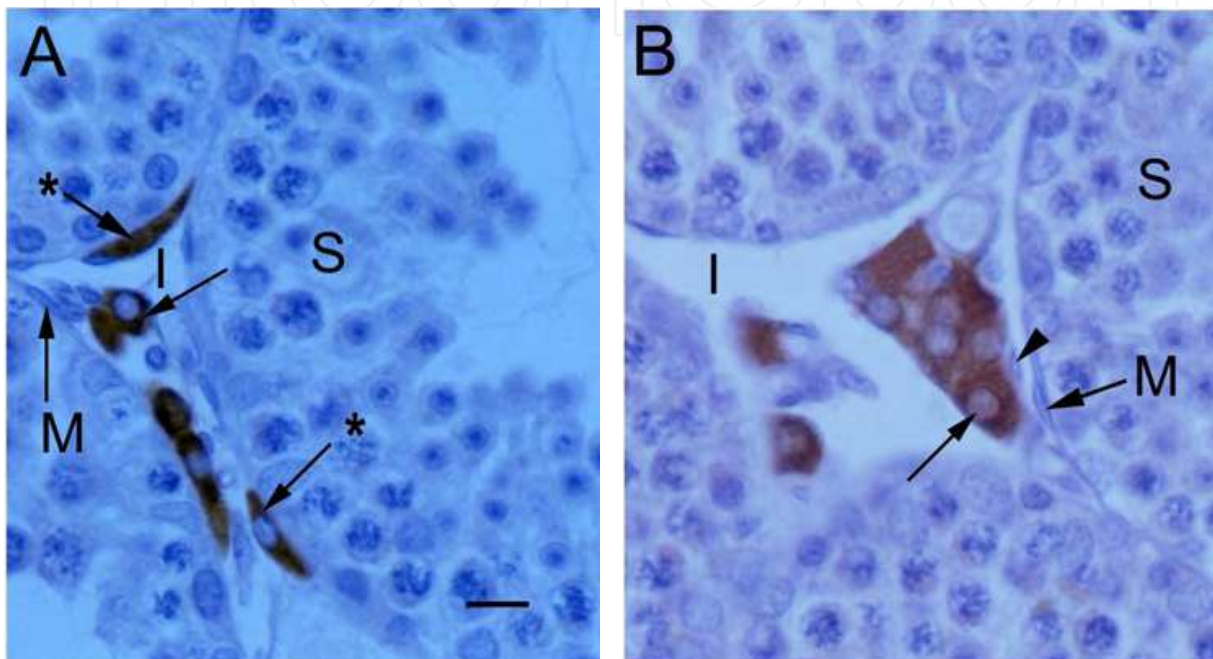


Fig. 10. Representative light micrographs of hamster testis of (A) 14 hours of light and (B) 1 hour of light exposed hamsters, immunolabeled for 3β -HSD. S=seminiferous tubules, I=testis interstitium, Bar=20 μ m for both A and B; same magnification). A. Single arrow depicts a newly formed adult Leydig cell positive for 3β -HSD in a 14 hours of light exposed hamster testis. Arrows with asterisks (*) depict Leydig progenitor cells, which are spindle-shaped cells located at the peritubular region and are positive for 3β -HSD. Their presence indicates that Leydig cell differentiation is occurring in testes of these hamsters. Leydig stem cells / mesenchymal cells (M) are negative for 3β -HSD. B. Single arrow depicts fetal Leydig cells in a 1 hour of light exposed hamster testis. They are primarily observed in clusters surrounded by basement membrane components (arrow head). Leydig cell progenitors (Spindle-shaped cells located at the peritubular region and positive for 3β -HSD) were absent in 1L hamster testis. Leydig stem cells / mesenchymal cells (M) are negative for 3β -HSD. (Hance et al., 2009, *Histology and Histopathology*, 24: 1417-1424)

5.2 Seminiferous tubules

Hypothyroidism induced in new born male rats up to postnatal day 60 has shown reduced diameter of seminiferous tubules, arrest in proliferation and differentiation of germ cells, reduction in number of germ cells and plasma testosterone levels, estradiol and sex hormone binding globulins (Maran and Aruldhas, 2002), which are essential for normal testicular

development. Transient neonatal-prepubertal hypothyroidism in rats causes significantly reduced body weight (Figure 11a) and significantly increased testis weight at adulthood, i.e. at 90days (Figure 11b; Mendis-Handagama and Ariyaratne, 2004; Lagu et al.,2005).

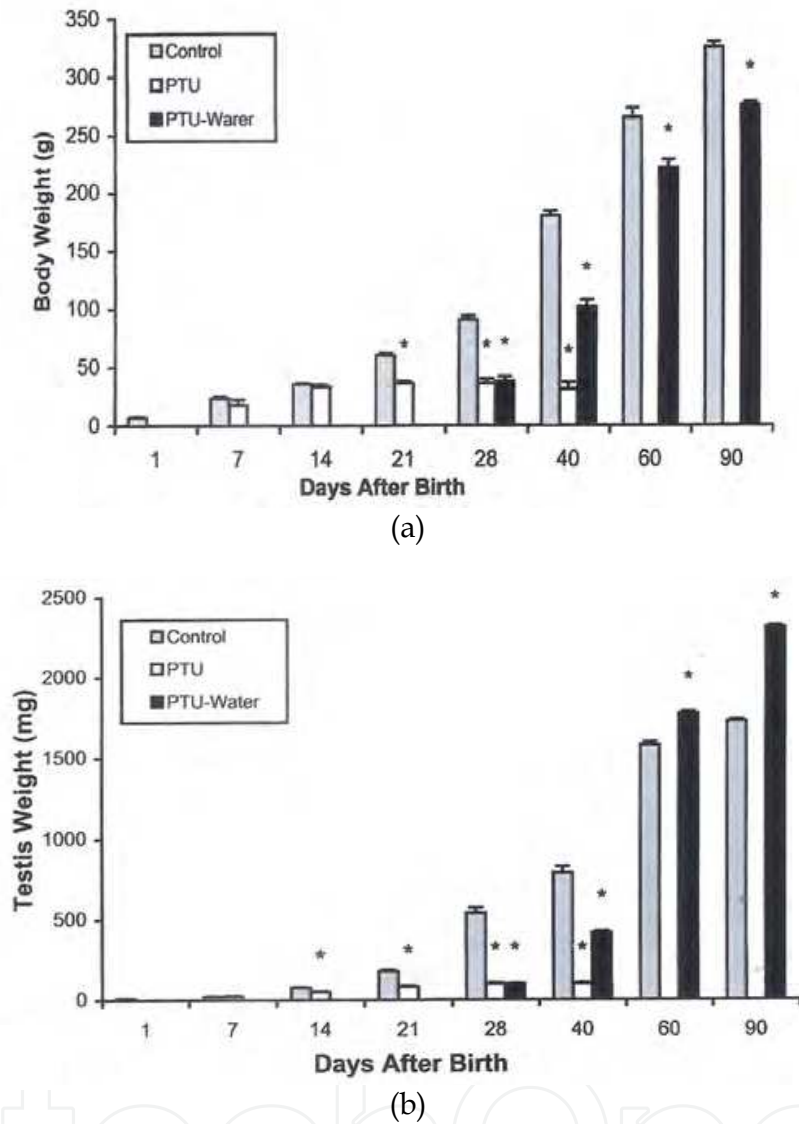


Fig. 11. (a) Body weights of control, PTU/hypothyroid and PTU-water treated/transiently hypothyroid rats. (b) Testis weights of control, PTU/hypothyroid and PTU-water treated/transiently hypothyroid rats. Mean±SE (n=5 rats per group). Asterisks (*) depict significant differences ($P<0.05$) from the control value at each age. (used with permission from the publisher, Mendis-Handagama and Ariyaratne, 2004, Archives of Andrology 50:347-357)

This increase in testis weight following transient neonatal hypothyroidism in these rats is due to the increase in number of Sertoli cells and germ cells (van Haaster et al., 1993; de Franca et al., 1995; Maran et al., 1999). van Haaster et al. (1993) showed that neonatal hypothyroidism in Wistar rats (from birth up to postnatal day 26) retards the morphological differentiation of Sertoli cells, prolongs their immature status and proliferation of these cells up to postnatal day 30. Sertoli cell numbers per testis in these hypothyroid rats determined

at day 36, were increased compared to controls. These findings revealed that neonatal-prepubertal hypothyroidism delays maturation of Sertoli cells (van Haaster et al., 1993; de Franca et al., 1995) and extend their period of proliferation, which increase their numbers. Therefore, this increase in the number of Sertoli cells per testis in the transiently hypothyroid rats produces larger testes at adulthood (Meisami et al., 1992; Mendis-Handagama and Sharma, 1994). This increase in the number of Sertoli cells in the adult rats subjected to transient neonatal hypothyroidism is associated with increased daily production of sperm (Cooke et al., 1991, 1992).

It is also being reported that neonatal hyperthyroidism causes opposite effects on testis development. However, because 'hyperthyroidism' is not relevant to the title of this chapter, it is not discussed further.

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7. References

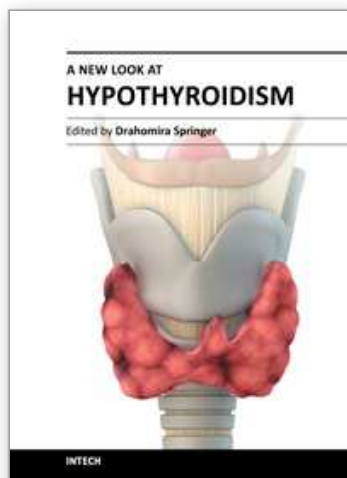
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A New Look at Hypothyroidism

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Hypothyroidism is the most common thyroid disorder. It can cause a variety of changes in women's menstrual periods, reduce their chances of becoming pregnant, as well as affect both the course of pregnancy and the neuropsychological development of babies. During pregnancy there is a substantially increased need for thyroid hormones and a substantial risk that a previously unnoticed, subclinical or latent hypothyroidism will turn into overt hypothyroidism. The thyroid inflammation caused by the patient's own immune system may form autoimmune thyroiditis (Hashimoto's thyroiditis). Congenital hypothyroidism (CH) occurs in approximately 1:2,000 to 1:4,000 newborns. Nearly all of the developed world countries currently practice newborn screening to detect and treat congenital hypothyroidism in the first weeks of life. "A New Look at Hypothyroidism" contains many important specifications and innovations for endocrine practice.

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