



HISTOGENESIS OF HUMAN TESTES AT DIFFERENT AGE GROUPS

Anatomy

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ABSTRACT

The testes are primary reproductive organs or gonads in males, which are responsible for production of testosterone and secondary sexual characters.

Aims & Objectives: The present study is done to observe testicular histology at different ages.

Materials & Methods: A total number of 64 testes of pre and post natal age groups from 17 male foetal cadavers, 6 autopsies of Forensic department, One cadaver of Anatomy department, 16 from pathology department. The prenatal specimens were collected from aborted embryos and dead foetuses of 6-40 weeks gestation. The postnatal testes were collected from individuals of 9-78 years of age. All the specimens were cut into two halves for recording the observations on lobules of testis, seminiferous tubules and tunica albuginea. Sections of 5 microns thickness were cut and stained with haematoxylin and eosin and mounted in Canada balsam. Cut sectional views were photographed and images were transferred to a computer and analyzed.

Results: The embryos of 6-10 weeks post conceptional age gonads primordial germa cells could be identified suspended by mesentery. In the foetuses of 13-20 weeks gestation tunica albuginea, rete testis, sex cords with spermatogonia, interstitial cell cords with foetal leydig cells were identified. At 24-28 weeks of gestation tunica propria was observed. At 9 years of age thick stratified epithelium was observed. In pubertal age seminiferous tubules with epithelium was observed. At 22-45 years of age different spermatogonic cells were observed. At 52-78 years of age atrophic, sclerosed, hyalinised seminiferous tubules were observed.

Conclusion: There is marked delay in the appearance of the PGC, termination of indifferent stage and establishment of gonadal sex during 1st trimester and a slight delay in the differentiation of various components of testes during 2nd and 3rd trimesters

KEYWORDS

Testes, Sertoli Cells, Leydig Cells, Primordial Germ Cells, Tunica Albuginea

INTRODUCTION

Key event in mammalian development is acquisition of a sexually dimorphic phenotype. At the time of fertilization genetic sex is determined by the presence or absence of a Y chromosome that directs the bipotent embryonic gonads to differentiate in to either testes or ovaries. In a male embryo or fetus subsequently, hormones produced by the testes trigger development of male phenotype. In the absence of testes and their biochemical products, female phenotype including the gonads develops.

The testes are primary reproductive organs or gonads in males, which are responsible for production of testosterone and secondary sexual characters. Male infertility depends on supply and maturation of germ cells i.e., spermatogonic cells. The human testis proceeds through periods of profound morphological and functional changes from birth to maturity.

There is relationship between intrauterine development and pubertal and adulthood variations of testes. Age related changes in the testes are indicated by formation, differentiation and growth of seminiferous tubules and number of sertoli and leydig cells.

Testicular histogenesis comprises formation of genital ridge, migration of primordial sex cells, formation of sex cords and its canalization and formation of seminiferous tubules, formation of sertoli and leydig cells. There are very limited studies on histology of testes at different periods of life.

AIMS & OBJECTIVES: The present study is done to observe the histology of human testes at different ages.

MATERIAL & METHODS: This work was conducted in the Department of Anatomy with the cooperation of the departments of Obstetrics and Gynaecology, Forensic medicine and pathology at RIMS, Ongole. Institutional ethics committee approved collection of embryonic tissue after obtaining informed consent from patients. Materials studied include spontaneously aborted/ dead foetuses of different periods of intra uterine life as well as testes representing prepubertal, pubertal, reproductive and andropausal ages.

A total number of 64 testes of pre and postnatal age groups were collected from 17 male fetal cadavers, 6 autopsies of Forensic department, one cadaver of Anatomy department, 16 specimen received for histopathological examination by department of pathology. The

prenatal specimens were collected from aborted embryos and dead foetuses of 6-40 weeks gestation. The postnatal testes were collected from individuals of 9-78 years of age. This study was conducted from November 2016 to October 2017.

Prenatal Specimens: A total of 17 embryos and foetuses were studied in the prenatal group. A total of 34 sets of testes were collected from 17 dead male foetuses at Government General Hospital, RIMS, Ongole. The gestation ages of foetuses ranged from 6 weeks to 40 weeks.

Postnatal Specimens:

- Prepubertal age – A total of 2 testes specimens were collected from an autopsy body of 9 year old male received by Forensic Department.
- Pubertal age – A total of 3 testes of 11-20 years age were collected from Forensic autopsies and a specimen received by department of pathology for histopathological examination after surgical removal.
- Reproductive age – A total of 14 testes were collected from Forensic Department autopsies and a specimen received by department of pathology for histopathological examination. The specimens were obtained from individuals of 21-45 years of age.
- Andropausal age – A total number of 11 testes of 46-78 years were collected from male cadaver from department of Anatomy, Forensic autopsies and histopathological specimen received by pathology department.

All the specimens were cut into two halves for recording the observations on lobules of testis, seminiferous tubules and tunica albuginea. Among the 64 testes collected and preserved in 10% formalin 43 testes of different age ages collected from 40 individuals were subjected to routine tissue processing by dehydration in graded alcohols, clearing in xylol and were embedded in paraffin. Sections of 5 microns thickness were cut and stained with haematoxylin and eosin and mounted in Canada balsam. Representative sample from each of the 43 testes sections of various ages were observed for developmental chronology and age related changes in the testes. Cut sectional views were photographed and images were transferred to a computer and analyzed.

RESULTS**DISTRIBUTION OF SPECIMENS OF TESTES COLLECTED**

A total number of 64 testes of pre and postnatal age groups were studied (Table-1) for histological appearance at different ages. In the prenatal group 34 testes of 0-40 week's gestational ages were collected from 17 male fetal cadavers received from Department of Obstetrics

and Gynaecology, RIMS, Ongole. In the postnatal group 30 testes were collected from cadavers of Forensic autopsies, Anatomy and also specimen received by Pathology department for histopathological examination after surgical excision. The postnatal specimens were collected from individuals of 9-78 years of age.

TABLE 1: Categorization Of Specimen Collected

Type of specimen	No. Of cases	Right	Left	Total
Prenatal	17	17	17	34
Postnatal	23	15	15	30
Total	38	32	32	64

The prenatal specimens were categorized into those of 0-12, 13-28, 29-40 weeks of gestational age (Table-2). In the prenatal age group the 2 smallest embryos of 6-10 weeks gestational age were subjected to serial sectioning.

TABLE 2: Categorization Of Prenatal Testes

Gestational age	Right	Left	Total
0-12 wk	3	3	6
13-28 wk	3	3	6
29-40 wk	11	11	22
Total	17	17	34

The postnatal testes were categorized into prepubertal (0-10yrs), pubertal (11-20 yrs), reproductive (21-45 yrs) and andropausal (>45 yrs) age groups (Table-3).

TABLE 3: Categorization Of Postnatal Testes

Category (Age in yrs)	No. Of cases	Right	Left	Total
Pre pubertal (0-10)	01	1	1	2
Pubertal (11-20)	02	1	2	3
Reproductive (21-45)	11	8	6	14
Andropausal (46-78)	09	5	6	11
Total	23	15	15	30

The details of source of specimens in pre and postnatal age groups are shown in table-4.

Among the 17 dead foetuses utilized in the present study 16 were apparently normal and one was a case of anencephaly. The gestational age of foetuses ranged from 6-40 wks post conception and their CRL varied from 12-310mm. The weight of foetuses ranged from 1-2500 gm.

Among the postnatal specimens 2 testes were removed from one of the dissection hall cadavers. The specimens obtained from department of Forensic medicine include 12 testes collected from 6 males who died in road traffic accidents. 16 testes were collected after surgical procedures. Among the postnatal specimens include those collected from one case of infertility, one case of undescended testis and 2 cases of sertoli cell only syndrome.

TABLE 4: Origin Of Specimen Of Testes

Origin of specimen and No.of cases	No. Of specimens
Prenatal Testes	
1. P.I.H (1)	2
2. Spontaneous abortion (3)	6
3. I.U.D (11)	22
4. Abnormal presentation-Breech (1)	2
5. Fetal Anamolies-Anencephaly (1)	2
Postnatal Testes	
1. R.T.A (6)	12
2. Surgical cases (16)	32
3. Dissection hall cadaver (1)	02

OBSERVATIONS ON THE HISTOLOGY OF PRENATAL TESTES

A total of 20 testes in the prenatal age group were processed (Table-5) for histological study. This includes the three small embryos of less than 10 weeks gestational age that were embedded as a whole and were serially sectioned. Histological observations of 6 to 40 weeks gestational ages are described here under and depicted in (Fig-1-15)

TABLE 5: Age-wise Distribution Of Testes Studied For Histological Observations

Type of specimen	Number collected	No. Of testes studied for histological features
72		

Prenatal		
0 -12 weeks	06	06
13 – 28 weeks	06	03
29 – 40 weeks	22	11
Post natal		
Prepubertal	02	01
Pubertal	03	02
Reproductive	14	11
Andropausal	11	09
Total	64	43

HISTOLOGY OF GONADS IN 0-12 WEEKS OF GESTATIONAL AGE

At 6 weeks of post conception and Carnegie stage 16 the indifferent gonads were seen along the posterior abdominal wall, retroperitoneally at the lumbar level as a projection known as gonadal ridge (Fig-1). The gonadal primordium was lined by cuboidal epithelium and a gonadal mesentery could be identified. In the centre of the gonadal primordium, primordial germ cells were observed (Fig-2)

At 7 weeks of post conception and Carnegie stage 17 the indifferent gonads were observed at lumbar level of serial section. At this stage urogenital mesentery supporting mesonephros and gonadal blastema could be identified. This mesentery was separated from the root of gut mesentery and parietal coelomic epithelium by medial and lateral coelomic bays respectively (Fig-3). Gonadal blastema with mesonephric and paramesonephric ducts could be identified. In the gonadal blastema dark cords of cells extending from flat coelomic epithelium were observed (Fig-4).

At 10 weeks gestational or 8 weeks post conceptional age sex of the specimen as testis could be established. Mediastinum and sex cords in the form of long cords embedded in the interstitial tissue are identified at this stage (Fig-5). The sex cords showed branching. The tunica albuginea covering testis is thin indicating early stage of formation. Epididymis also could be identified at this stage.

HISTOLOGY OF GONADS IN 13-28 WEEKS GESTATIONAL AGE

At 20 weeks tunica albuginea could be identified clearly. Seminiferous sex cords arranged in small compact groups, rete testis and interstitial cell cords were seen (Fig-6). Spermatogonia could be identified in seminiferous sex cords. In interstitial cell cords abundant foetal leydig cells (Fig-7) could be identified. The seminiferous sex cords are lumen less. The spermatogonia are identified but their large size and clear cell out line. The large pale colored fetal leydig cells are seen in clusters (Fig-7).

At 24 weeks of organization of sex cords as round or oval shaped groups, leydig cells and fibroblasts could be identified (Fig-8,9). Early stage of formation of tunica propria lining sex cords was observed. The division of gland into lobules could be identified. Few leydig cells are seen.

At 28 weeks better structural clarity was observed with the appearance of interlobular septa. There is considerable growth in the cords. Cellular aggregations in the seminiferous cords were observed. A very thin tunica propria incompletely surrounding the sex cords (Fig-10) was observed. Eosinophilic cytoplasm of leydig cell could be seen clearly (Fig-11) and the leydig cells are widely spaced.

HISTOLOGY OF GONADS IN 29-40 WEEKS OF GESTATIONAL AGE

Immature seminiferous tubules that were not canalized and a clear basement membrane and degenerating leydig cells are seen (Fig-12). In the anencephalic male foetus of 38 weeks though the testes were located at the neck of scrotum they were normal in architecture.

OBSERVATIONS ON THE HISTOLOGY OF POSTNATAL TESTES

A total of 23 testes in postnatal age group were processed for histological study. Histological observations of 9-78 years age are described here under and depicted in Fig-13 to 31

HISTOLOGY OF PREPUBERTAL TESTES

In the prepubertal specimen lumen of seminiferous tubule with a clear basement membrane that was thick and a stratified epithelium showing early stages of spermatogenesis (Fig-13) could be identified. Leydig cells are few in number.

HISTOLOGY OF PUBERTAL TESTES

Mature seminiferous tubules with a clear basement membrane could be observed (Fig-14) distinct spermatogenic cells showing orderly arrangement and surrounded by sertoli cells (Fig-14) were observed in seminiferous epithelium. Various spermatogenic cells viz. Spermatogonia, primary spermatocyte, spermatid could be identified individually (Fig-15). Few leydig cells and blood vessels are observed.

HISTOLOGY OF REPRODUCTIVE TESTES

Microscopic features of all testes of reproductive age group showed highly active spermatogenic tubules (Fig-15-19). Orderly arranged spermatogenic cells in different stages of development could be seen. There is mild thickening of basement membrane as age advances. Leydig cells clusters are seen.

In infertile testis of 30 years only sertoli cells (Fig-21,22) with associated aspermatogenesis and thickened basement membrane were observed. In this section of infertile testis few leydig cells and spermatocytic arrest was giving wind washed tree top appearance. In the reproductive age group histological section of 27 years age showed absence of spermatocytic and leydig cells (Fig-20) and presence of only sertoli cells. It is a case of unilateral undescended testis. In two specimens of 22 and 40 years age only sertoli cells without spermatocytosis and leydig cells were observed (Fig-23,24). This is known as sertoli cell only syndrome.

HISTOLOGY OF ANDROPAUSAL TESTES

In this age group all the sections showed thickening of basement membrane that increased with age (Fig-25-31) Gradual decrease in spermatogenic activity with increasing age from 52 years age (Fig-25,26) to no spermatogenic activity at 66 years (Fig-30) were observed in the present study. In a section of 78 years old some of the seminiferous tubules showed decreased spermatogenic activity while some are showing significant empty space within the tubule indicating inactive tubule (Fig-31). Leydig cell clusters were observed in some of the sections (Fig-28,29,31) and some were showing very few leydig cells (Fig-27). Atrophic seminiferous tubules with sclerosis and hyalinization (Fig-28,29) were observed in a 60 year old testis. Crystals of Reinke were observed in some of the sections in this age group (Fig-31). Accumulation of lipid globules in sertoli cells were observed at 78 years (Fig-31).

DISCUSSION

A total of 64 testes collected from prenatal and postnatal age group males of 6 weeks gestational age to 78 years andropausal age were included in this study. All the specimens collected were broadly categorized in to prenatal and post natal age groups. The number of cases in these two broad categories and the number of testes observed for histological features were shown in (Tables-5)

All the embryos and foetuses observed were apparently normal except one case of anencephalic foetus with associated GIT, renal and gonadal abnormalities. In the postnatal age groups, specimen collected were from apparently normal individuals of 9 years to 78 years age excepting a case of unilateral undescended testis, one case of infertility and 2 cases of sertoli cell only syndrome.

A total of 34 testes of prenatal and 30 testes of post natal category were observed for age related histological parameters. Representative samples of 43 among 64 collected for this study were subjected to tissue processing, sectioning and staining for observing developmental histology and age related histological features. Among the 34 prenatal specimens observed in this study except for two specimens collected from anencephalic male foetus of 38 weeks gestation all the other specimens are from apparently normal foetuses. Among the 30 postnatal specimens studied 16 testes were received by pathology department for histopathological examination after surgical removal for various reasons viz. Undescended testis, infertility etc. other than malignancy.

DEVELOPMENTAL HISTOLOGY DURING PRENATAL PERIOD

In the prenatal group the gonadal blastema was identified at lumbar level during embryonic stage. The gonads of 6 and 7 weeks age observed in this study are of different stage. In this age gonadal blastema projecting in to the coelomic cavity with a clear gonadal mesentery could be identified. These observation are in agreement with those reported by Hamilton, Mossman and boyd(1972)¹, satoh(1991)², Rodeck and whittle(1999)³, Healy et.al(2005)⁴ and Standing and Collins(2005)⁵ according to whom the gonadal

primordium projects in to the coelomic cavity during 6 th week of gestation.

In the present study the indifferent stage extended upto 7th weeks. At 8weeks post conception or 10 weeks gestational age only the gonad could be clearly identified as testis. Arey(1966)⁶, Hamilton, Mossman and Boyd(1972)¹, Standing and Collins(2005)⁵ and Healy et.al(2005)⁴ observed termination of indifferent stage at 6 weeks of post conception or 8 weeks of gestation with clear identification of testes. There is a delay of one week in the present study in termination of indifferent stage and in establishing gonadal sex with certainty when compared to those reported in literature.

In the prenatal category sagittal sections of embryo of 6 weeks post conceptional or 8 week gestational age was the smallest of all the specimens collected for this study. It corresponds to stage 16 of Carnegie staged embryos based on the external features. In this urogenital ridge on the dorsal aspect of embryo could be identified. The two constituents of urogenital ridge i.e. nephrogenic cord that contributes for the development of urinary system and the genital ridge that gives rise to the gonads could be identified. Satoh(1991)² and Healy(2005)⁴ reported the first indication of genital ridge in the 5th week of Intra uterine life and can be compared to with stage16 of Carnegie. In the present study also it corresponded with Carnegie stage though it did not correlate with the size and the age at which they observed. The discrepancy in age can be explained as they did not mention the method employed for calculating the age of embryo. In the present study the age of the embryo is determined based on ovulation age rather than menstrual age which will be two weeks more than the ovulation or conception age. In the present study up to 10th week post conception or post ovulation week Carnegie staging was followed.

The urogenital ridge was observed at the upper lumbar level at 6 weeks. The gonadal primordium with covering cuboidal germinal epithelium, Primordial germ cells in the center of gonadal blastema were present at 6 weeks. This finding is in agreement with that reported by Jirasek (2004)⁷, Healy et.al.(2005)⁴ and Sadler(2006)⁸. According to them gonadal development starts during 5th and 6th week after ovulation with migration of PGC from the yolk sac into the gonadal blastema.

In the embryo of 7 weeks post ovulation age or 9weeks gestational age corresponding to Carnegie stage 17 the gonads are still in indifferent stage. The gonadal primordium could be identified as an oval projection into the coelomic cavity on either side of dorsal mesentery. Primary sex cords were found extending from flat germinal epithelium towards the base of the gonadal blastema. Hamilton and Mossman(1972)¹, Satoh(1991)², Healy et.al(2005)⁴ and Standing and Collins(2005)⁵ observed primordial sex cords in late 5th week. When compared to these reports in the present study there is a delay of 2weeks for the appearance of primordial sex cords.

In the embryo of 8 week post conception or 10 weeks gestational age corresponding to Carnegie stage 19 the gonads could be clearly identified as testis. At this stage the epididymis could be identified. The testis was oval in section and presented a thin non-epithelial covering the tunica albuginea. Primordial sex cords were found radiating from the hilum to the periphery. Mediastinum testis could be identified; at this stage rete testis is not formed. The observations in the present study are in agreement with that of Keith (1949)⁹, Pelliniemi and Niemi(1969)¹⁰, Sahama(1985)¹¹.

At 20 weeks thin tunica albuginea, rete testis, long and branching seminiferous sex cords extending from base to periphery of gonad and interstitial cords could be seen clearly. Spermatogonia could be clearly identified in seminiferous sex cords. In between these sex cords pale foetal leydig cell clusters could be identified. Sniffen(1950)¹² reported these findings in 9 weeks foetus. In the present study due to non-availability of more specimens in the 13-24 weeks age group significance of this finding couldn't be highlighted. Leydig cells were identified at 20 weeks in the present study, finding in agreement with that of pellini and neimi(1969)¹⁰. 24weeks to 28 weeks are the early stages in the formation of tunica propia in the present study. Sniffen(1950)¹² reported the appearance of it by 20 weeks of development. Inter lobular septa separating lobules were found developing from 24-40 weeks. Rounded spermatogonia could be identified in the midst of plenty of sertoli cells. Immature seminiferous tubules without a lumen and a clear basement membrane and degenerating leydig cells are seen at full term.

HISTOLOGY DURING POSTNATAL PERIOD:

Prepubertal seminiferous tubules with a lumen, a clear basement membrane and a thick stratified epithelium showing spermatologia and sertoli cells could be identified. Leydig cells are few in number. Active spermatogenic process was not seen. In pubertal age seminiferous tubules that were not coiled, clear basement membrane and seminiferous epithelium showing orderly arranged cells were identified. Various spermatogenic cells and sertoli cells could be identified. Few Leydig cells, and blood vessels were observed.

Microscopic features of all testes of reproductive age group showed highly active and coiled spermatogenic tubules. Various spermatogenic cells Viz. spermatogenic, primary spermatocytes, spermatid clusters, spermatozoa and sertoli cells were identified. Numerous compact and eosin stained leydig cells are seen in inter tubular area. The findings in the reproductive age are in agreement with those reported in the literature by various authors (Douglas et.al. 1983¹²; Datta, 2000¹³).

Presence of only sertoli cells with associated aspermatogenesis, thick basement membrane and few leydig cells was observed in infertile testis. In the reproductive group in a histological section of unilateral undescended testis except hypo spermatogenesis, it did not show the atrophic changes as quoted by Irkilata et.al., (2005)¹⁵. In the two specimens of 22 and 40 years age only sertoli cells without spermatocytosis and leydig cells were observed. This is known as sertoli cell only syndrome.

Increase in thickness of basement membrane, gradual decrease activity and number of leydig cells are observed age with increase in age. Some of the seminiferous tubules are atrophied, sclerosed and hyalinised. Crystals of Reinke were observed in the some of the sections in this age group. These findings are the agreement with the reported by Sniffen (1950)¹², Kaler and Neaves (1978)¹⁶, Irkilata (2005)¹⁵ and Schachter (2007)¹⁷.

CONCLUSION

There is marked delay in the appearance of the PGC, termination of indifferent stage and establishment of gonadal sex during 1st trimester and a slight delay in the differentiation of various components of testes during 2nd and 3rd trimesters in the population observed in the present study. There is no gross variation in the postnatal development in the present study.

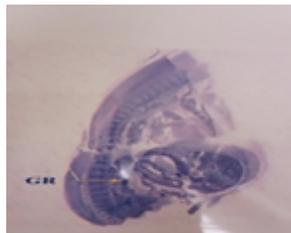


FIG 1: 6wks post conception-CS 16 stage sagittal section-Gonadal ridge in lumbar region

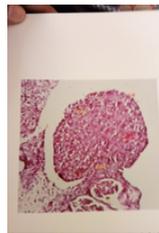


FIG 2: Cuboidal germinal epithelium, Gonadal mesentery, and PGC.



FIG 3: 7 weeks - Indifferent gonads - Urogenital Mesentery, Gonadal Primordium.



FIG 4: 7 weeks - Indifferent gonads - Urogenital Mesentery, Gonadal Primordium- Mesonephric and Paramesonephric ducts.



FIG-5: 10 weeks foetus- Epididymis, Mediastinum testis, Primordial sex cords.



FIG-6: 20 weeks- Rete testis, seminiferous tubules, Interstitial cell cords.

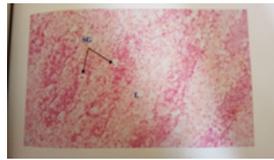


FIG-7: 20 Weeks Fetus- Spermatogonium, Leydig Cells

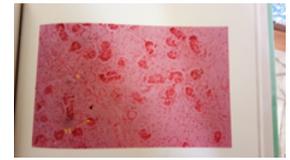


FIG-8: 24 weeks- seminiferous tubules, septa

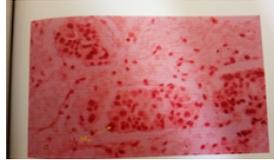


FIG-9: 24 weeks fetus- spermatogonium

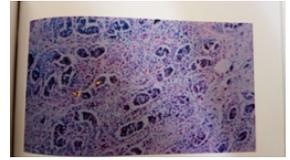


FIG-10: 28 weeks fetus- seminiferous tubules (immature)

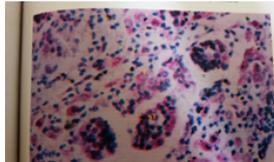


FIG-11: 28 weeks fetus- seminiferous tubules, leydig cells

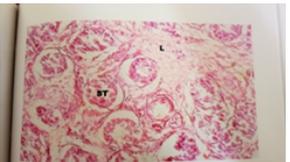


FIG-12: 40 weeks fetus- Immature seminiferous tubules, leydig cells

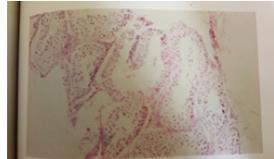


FIG-13: 9 years- Normal BM, Rim of spermatogenic epithelium with few leydig cells

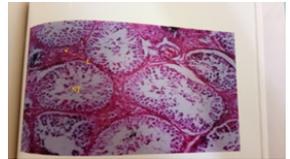


FIG-14: 17 yers testes- seminiferous tubules, leydig cells

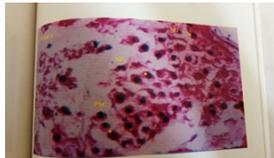


FIG-15: 17 years testes- Primary spermatocyte, spermatid, spermatogonium

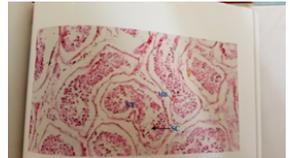


FIG-16: 22 years- Reproductive period- seminiferous tubules, basement membrane, active spermatocytosis



FIG-17: 28 years- Normal spermatogenesis- Leydig cells

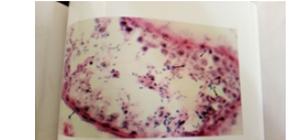


FIG-18: 28 years- sertoli cells- spermatozoa- spermatids- BM with myoid cells- Primary spermatocytes

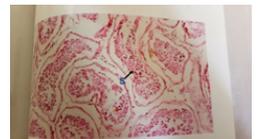


FIG-19: 45 years -



FIG-20: 27 years - undescended testes- No few leydig cells- spermatocytes- Thickened basement membrane only sertoli cells without leydig cells.



FIG-21: 30 years - infertility- only sertoli cells with out spermatocytosis- thickened basement membrane

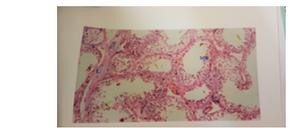


FIG-22: 30 years infertility- Thickened basement membrane- spermatocytic arrest- few leydig cells



FIG-23: 40 years- sertoli cell syndrome

FIG-24: sertoli cell only syndrome

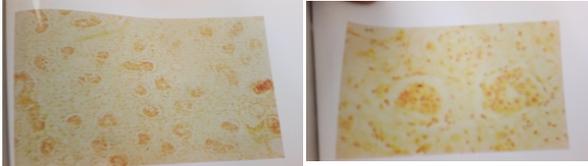


FIG-25: decreased spermatogenesis

FIG-26: Decreased spermatogenesis

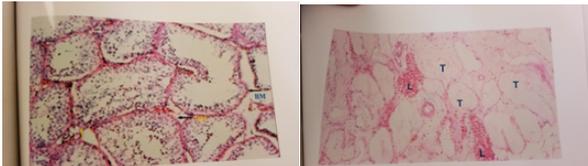


FIG-27: Thickening of Basement membrane- Active tubules-Few leydig cells

FIG-28: 60 years-Atrophic tubules showing sclerosis and hyalinization



FIG-29: Leydig cell clusters

FIG-30: Thick basement membrane



FIG-31: Leydig cell clusters, Reinke crystals, BM Thickening

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