THE EFFECT OF ALTERATIONS IN SPERMATOGENESIS UPON GONADOTROPHIC HORMONE EXCRETION IN MAN

by

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THE EFFECT OF ALTERATIONS IN SPERMATOGENESIS UPON GONADOTROPHIC HORMONE EXCRETION IN MAN.

Absence of testes is accompanied by a marked increase in the amount of pituitary gonadotrophins excreted in the urine. There are two ways in which the testes may influence gonadotrophins secreted by the anterior pituitary:

1) The testis could secrete a hormone whose site of action is the anterior pituitary gland, the process involved being suppression of gonadotrophic secretion.

2) The gonadotrophins, whose site of action is the testis, could be inactivated during the process of stimulating testicular activity.

Three hypotheses concerning the control of the gonadotrophins by the testis have held the attention of physiologists; two hypotheses concern themselves with the possibility of testicular secretions inhibiting the pituitary, and the third with the possibility that gonadotrophins are acted upon by the testis directly.

A. The earliest hypothesis was that gonadotrophin secretion is inhibited by the amount of androgen in the systemic circulation of normal, adult male mammals. It is well established that castration in the male causes a 10-20 fold increase in gonadotrophin content of hypophysis, blood and urine. It is also well established that gonadotrophins in normal or castrated males can be inhibited by administration of large amounts of androgen. The rise in gonadotrophins following orchiectomy was therefore attributed to androgen withdrawal, i.e., "release of the brake" upon the hypophysis. However, it has been

demonstrated for man and laboratory animals that smaller amounts of androgen, sufficient to prevent castration changes or to restore a castrate to normalcy, do so without lowering hypophyseal gonadotrophin content or the gonadotrophin output in the urine.(1,2,3)

Evidence will be included in this report which indicates that gonadotrophins may be elevated in the presence of normally functioning and normal appearing Leydig cells; therefore, elevation cannot be due only to "release of the brake" on the pituitary by androgen withdrawal.

B. A less widely held view has been that the testis secretes an elusive substance that defies concentration or isolation, but when present, keeps gonadotrophins at normal levels. This substance has been named "inhibin".(4) Castration presumably permits rises in gonadotrophin because "inhibin" has been removed. It has been suggested that the Sertoli cell secretes this substance.(5)

Evidence will be included in this report which indicates that gonadotrophins may be elevated in the presence of normal Sertoli cells. Therefore, elevation in gonadotrophins cannot be due to the failure of Sertoli cells to produce "inhibin". If, as other believe, the Leydig cells produce "inhibin", the same evidence that excludes Leydig cell androgen secretion as being the physiological regulator of pituitary gonadotrophins also excludes Leydig cell "inhibin" secretion.

C. The third hypothesis holds that gonadotrophins are inactivated by the testis.(6) Thus, fluctuations in urinary gonadotrophins should correlate with testicular activity, a decrease in testicular activity being reflected by an increase in gonadotrophin levels.

The objective of the current study was to elicit information bearing upon these three hypotheses.

Man as an experimental subject is more satisfactory than laboratory animals, because the variety of spontaneous alterations in spermatogenesis and Leydig cell function which occur are difficult or impossible to reproduce in animals. In animals, it is also difficult to make observations regarding dynamic alterations in gonadotrophins, since the amounts of hormone available in blood and urine are generally too small to measure with current methods. In the rodent, for example, observations are largely limited to assessment of the content of gonadotrophins in the pituitary at autopsy. In man, on the other hand, the levels of gonadotrophic hormones in the urine are sufficient to make repeated observations feasible.

Before continuing the discussion of the effects of the testis on gonadotrophic excretion, it may be well to summarize the established facts concerning the actions of the gonadotrophins upon the testis (Chart 1).

The testis is a dual organ composed of two distinct elements, the germinal, which produces spermatozoa, and the hormonal, which produces testosterone. Each element is controlled or stimulated by a separate pituitary hormone. The germinal function of the testis is controlled by follicle stimulating hormone (FSH), and the hormonal portion by interstitial-cell stimulating hormone (ICSH), also known as luteinizing hormone (LH).(7) The third gonadotrophin, lutectrophic hormone, has recently been detected in human male urine in our laboratory, but its function in the male remains unknown.(8)

In addition, testosterone is necessary for maintenance of the seminiferous tubules and appears to stimulate spermatogenesis.(9) For normal function, therefore, the tubules are dependent upon both

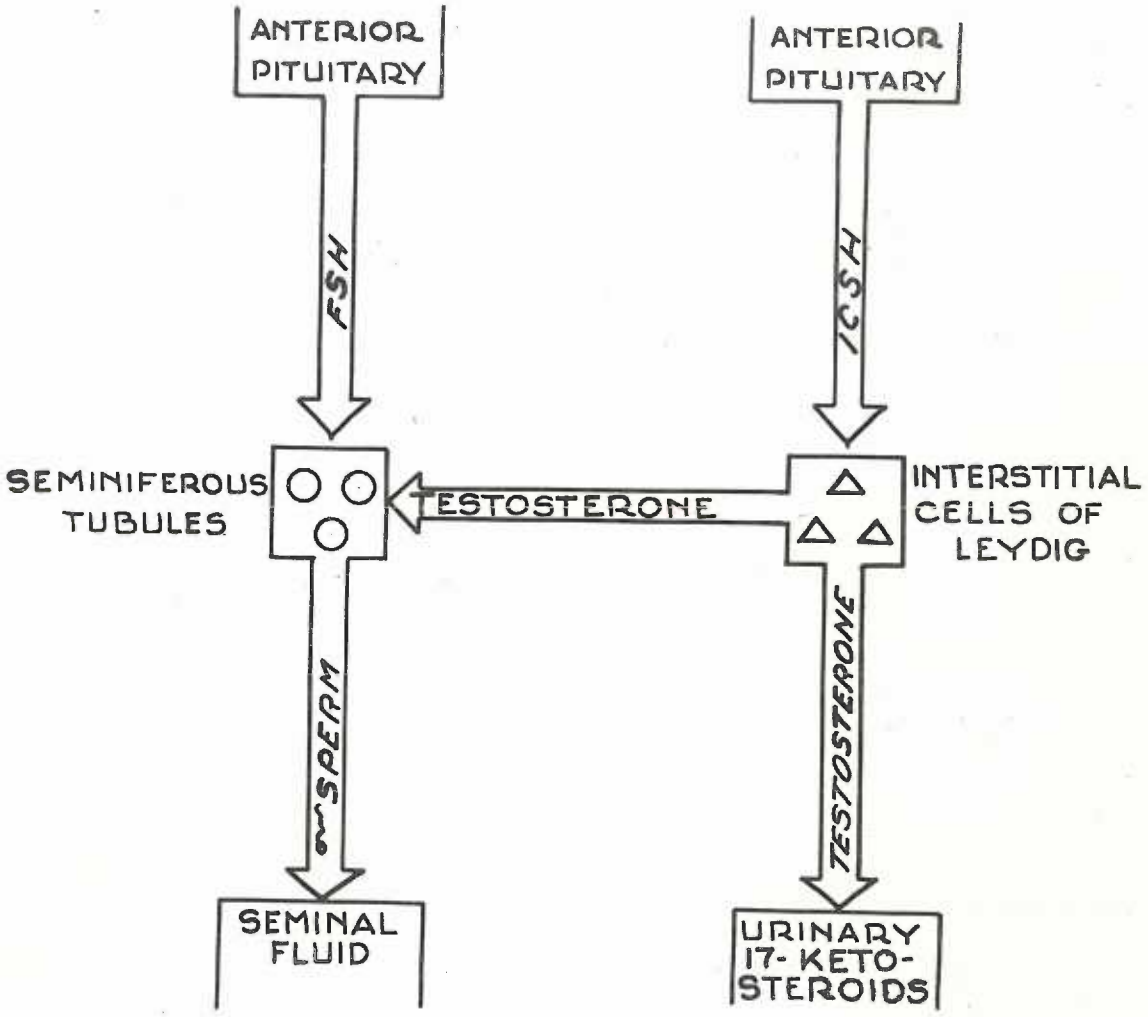

ANTERIOR PITUITARY
ANTERIOR PITUITARY
FSH
ICSH
SEMINIFEROUS TUBULES
ESTOSTERONE
INTERSTITIAL CELLS OF LEYDIG
SPERM
TESTOSTERONE
SEMINAL FLUID
URINARY 17-KETO-STEROIDS
GERMINAL SYSTEM
HORMONAL SYSTEM

Chart 1

FSH and testosterone.

Relatively little information is currently available regarding such questions as 1) the relation of the spermatogenic processes to gonadotrophins, 2) the relation of the supporting cells of Sertoli to gonadotrophins, and 3) the relation of the interstitial cells of Leydig and their secretions to gonadotrophins. Precise information is lacking because of the difficulty in experimentally altering one of the three testicular elements without concurrently altering the other two. For example, the two classical and most workable methods for altering testicular function experimentally are to expose the testis to body heat (experimental cryptorchidism), and to expose the testis to roentgen rays. However, the alterations in spermatogenesis so produced are accompanied--but more slowly--by alterations in Leydig cell function.

In infertile, impotent, or eunuchoidal men, disease processes or congenital malformations may cause alterations in the testis affecting one or two of the testicular components, while allowing the other to remain intact. For example, during the period of this study, more than 30 men were encountered who lacked all germinal cells and whose seminiferous tubules contained only Sertoli cells. In the majority, Leydig cell function remained intact. Thus, the effect of absent germinal cells, intact Sertoli cells and intact Leydig cells; and absent germinal cells, intact Sertoli cells and failing or absent Leydig cells upon gonadotrophins could be observed and compared, and conclusions could be reached regarding the role of the Sertoli cell. Similar observations and comparisons were made regarding Leydig cells, hyalinization of the tunica propria of the seminiferous tubules, and

various stages of germinal maturation.

MATERIALS AND METHODS

The patients comprising this study were selected because of hypogonadism of one of three general types: infertility, eunuchoidism or the male climacteric. No cases of hypogonadism secondary to pituitary failure were included.

Seminal fluid examinations were performed on the majority of patients, and were repeated as often as a dozen times in order to establish a basic pattern for a given individual. Specimens were examined within one hour after collection in a clean glass container. Condom collections were avoided, because the chemicals contained therein may alter motility, morphology and total count. The number of spermatozoa in each cc. was determined, along with observations on motility and morphology.

Urinary gonadotrophin assays were conducted in each patient. Four 12-hour overnight urine collections were made by each patient. In several instances, a second and occasionally a third set of four collections were made. The protein hormone was concentrated from the 48-hour pooled sample by ultrafiltration(10) on collodion membranes, the membranes dissolved in alcohol-ether solution, and the precipitated hormone taken up in water after drying. The hormone was assayed by injecting 12-hour aliquots into immature female albino rats in six divided doses, over a 3-day period; 24 hours later, autopsies were performed on the rats, and the increase in uterine and ovarian weights noted.

Testicular biopsies were performed on each patient, using local novocaine anesthesia. After incising the tunica albuginea, by gentle pressure on the testis, a small amount of testicular parenchyma was extruded, which was cut off. The tissue was fixed in Bouin's solution and stained with Masson's trichrome stain. Both testes were biopsied if there was any disparity between them.

DATA

The testicular biopsies, sperm counts and urinary gonadotrophin excretion of 115 men with hypogonadism have been analyzed. The data are summarized in Table 1.

Each testicular biopsy was analyzed for the severity of sclerosis of the basement membrane and tunica propria, for the activity of spermatogenesis in the tubules, for the relative numbers of each of the main spermatogenic cell types, and for the numbers and appearance of the Leydig cells.

Sclerosis

Classification of the Degree of Sclerosis in Individual Seminiferous Tubules: The term "sclerosis" is used throughout to denote thickening and hyalinization of either the basement membrane or the tunica propria of the seminiferous tubules. The thickening consists of a multiplication of the connective tissue layers surrounding the tubules, and is accompanied by an increase in number of connective tissue cells, as is well seen by comparing the large number of connective tissue cells in Figures 3 and 4, illustrating sclerosis, with the small number in the normal testis, Figure 1. The process of sclerosis is invariably accompanied by hyalinization of the layers in the

most severe instances of thickening, as illustrated in Figure 6. Hyalinization may or may not be encountered in earlier stages of thickening. Both multiplication of layers and hyalinization are encompassed by the term "sclerosis".

The degree of sclerosis of a seminiferous tubule is graded on the following basis:

0 — no sclerosis

+ — minimal sclerosis

++ — moderate sclerosis

+++ — severe sclerosis

++++ — complete sclerosis

The degrees of 0 and 1+ sclerosis (none and minimal) are considered normal, since tubules of these degrees of thickening are frequently encountered in testes of normal young men and are compatible with normal spermatogenesis. Any greater degree of sclerosis is always accompanied by defective to absent spermatogenesis.

Examples of the various degrees of sclerosis in individual tubules are illustrated in the following figures:

Fig. 1 — 0 sclerosis

Fig. 2 — 1+ sclerosis

Fig. 3 — 2+ sclerosis without hyalinization

Fig. 4 — 3+ sclerosis without hyalinization

Fig. 5 — 3+ sclerosis with hyalinization

Fig. 6 — 4+ sclerosis with hyalinization

Classification of the Degree of Sclerosis in the Testicular Biopsy as a Whole: Following the above plan of classification of the degree of sclerosis in individual seminiferous tubules, the number of tubules

Figure 1

Normal Testis

0 - sclerosis

Good spermatogenesis

The basement membrane is very thin, showing no evidence of sclerosis. Spermatogenesis is proceeding in an orderly fashion, with all stages present: spermatogonia, primary and secondary spermatocytes, spermatids and sperm. The lumen of the tubule is clear. The Sertoli cells are not prominent, as they are greatly outnumbered by the spermatogenic cells. Leydig cells are numerous and show granulation and numerous crystalloids. X 450. (KL 246)

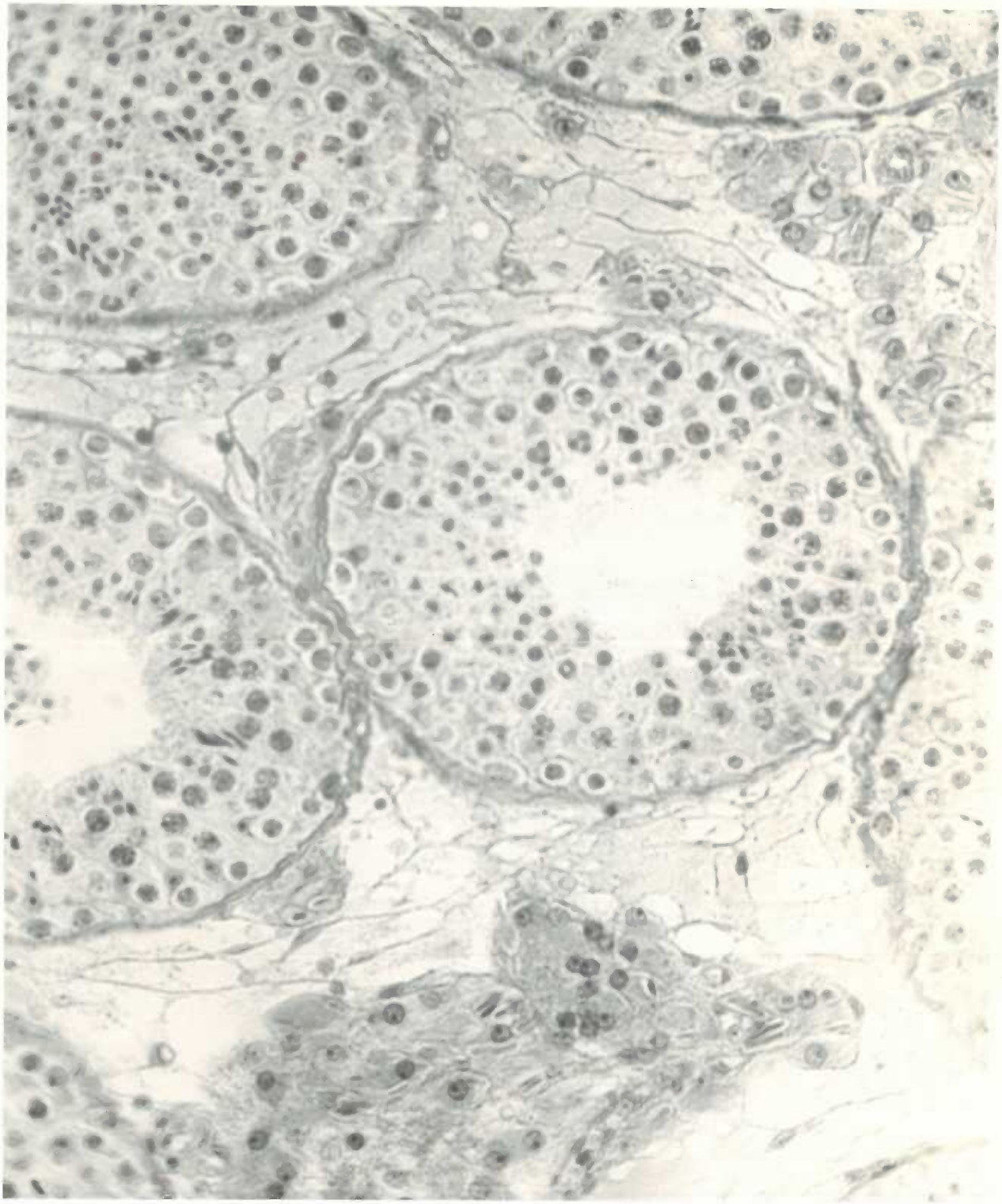


Figure 1

Figure 2

It sclerosis

The tunica propria shows minimal thickening with an increase in the connective tissue layers. Spermatogenesis in the upper tubule is fair, and in the lower tubule is poor. Leydig cells are normal in number and appearance.
X 450. (Kl 196)

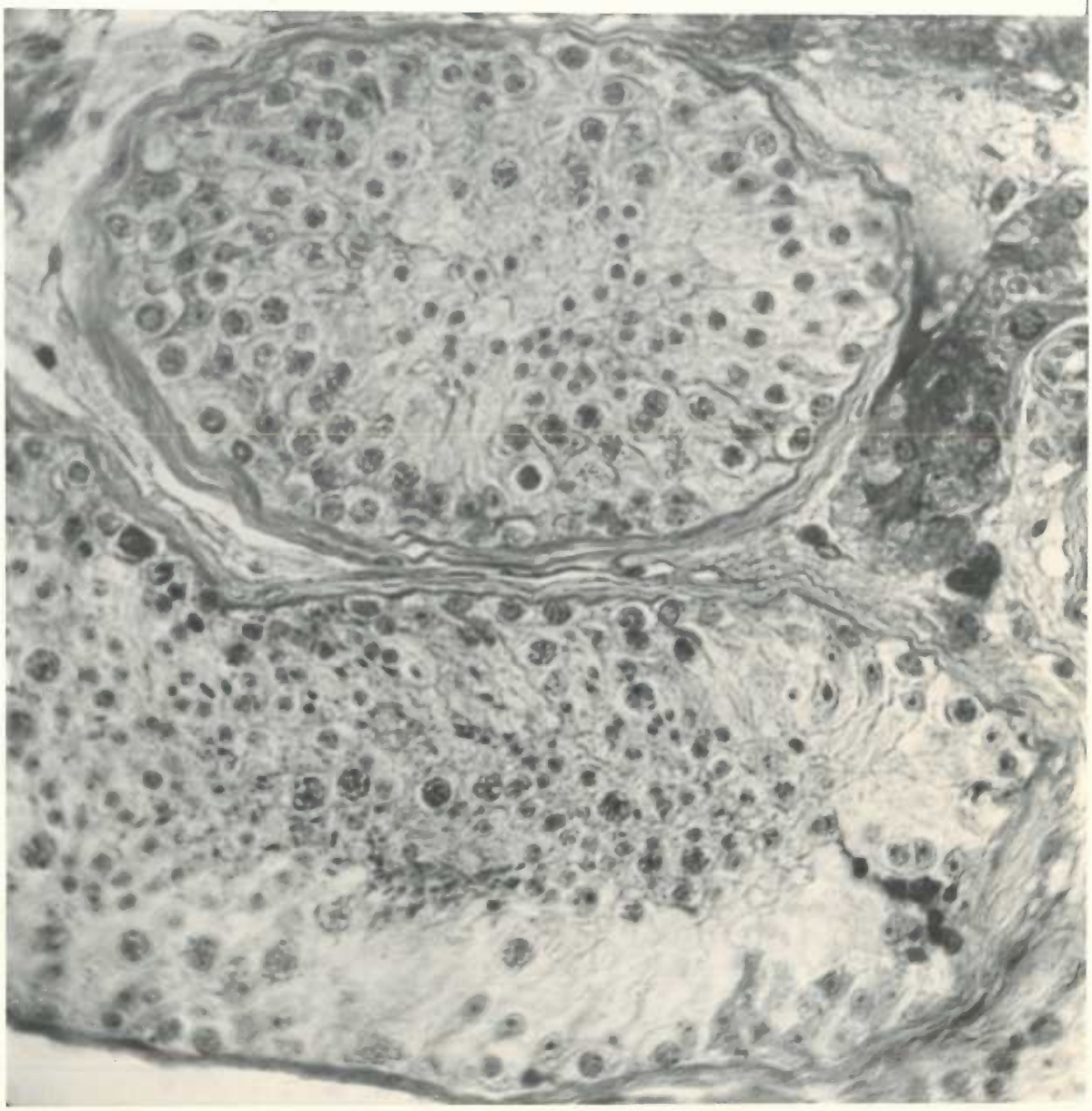


Figure 2

Figure 3

2+ Sclerosis without hyalinization

The tunica propria and the basement membrane show moderate thickening with an increase in connective tissue cells and cell layers about the tubule. There is no hyalinization of the thickened membrane. Spermatogenesis is poor. Leydig cells are normal in number and appearance. X 450. (KI 307R)

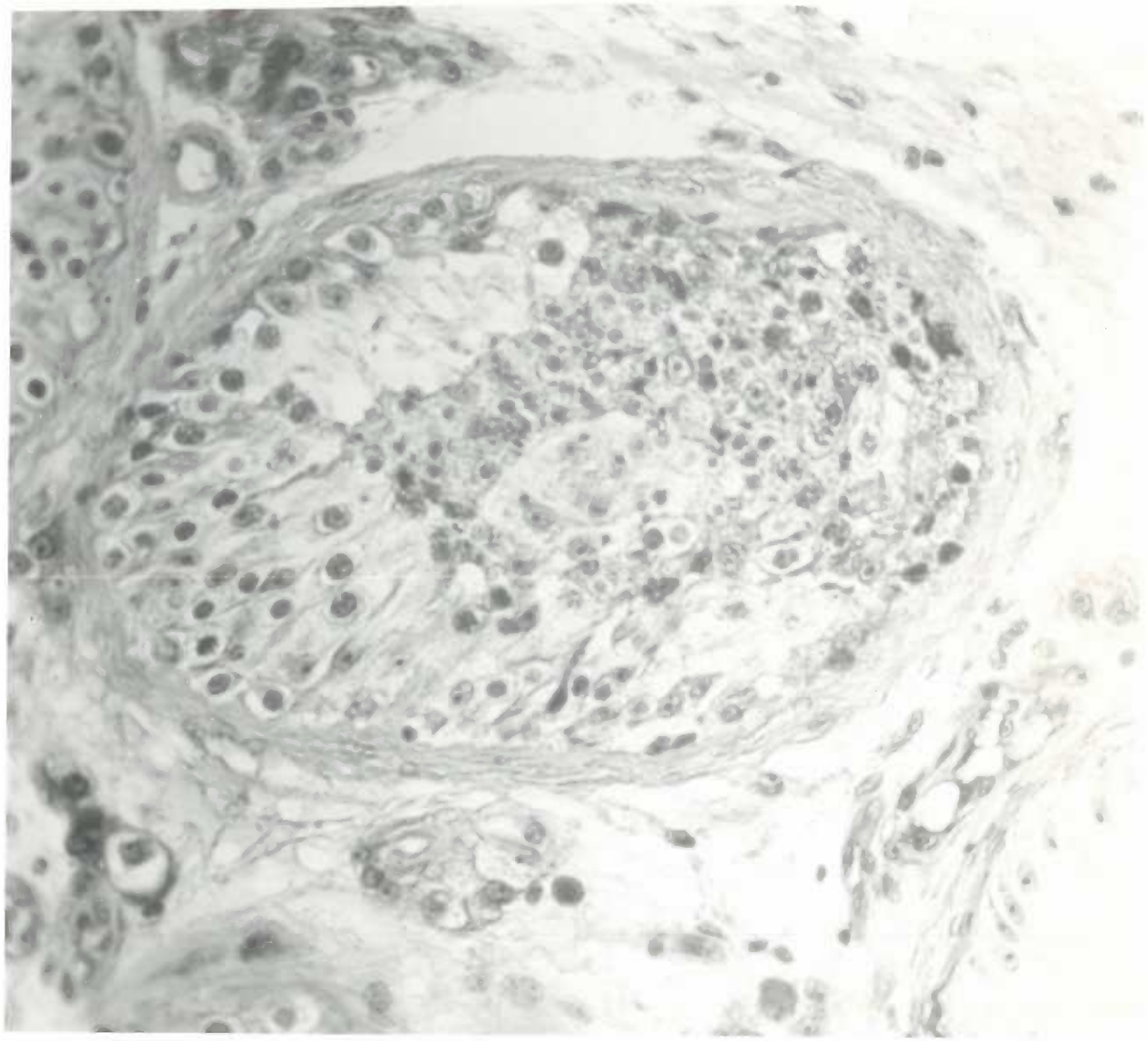


Figure 3

Figure 4

3+ Sclerosis without hyalinization

There is a severe thickening of the tunica propria, due to increase in both connective tissue cells and connective tissue cell layers about the tubules. No significant hyalinization is present. Spermatogenesis is very poor. Leydig cells show a relative increase in number and are normal in appearance. X 450. (KI 210R)

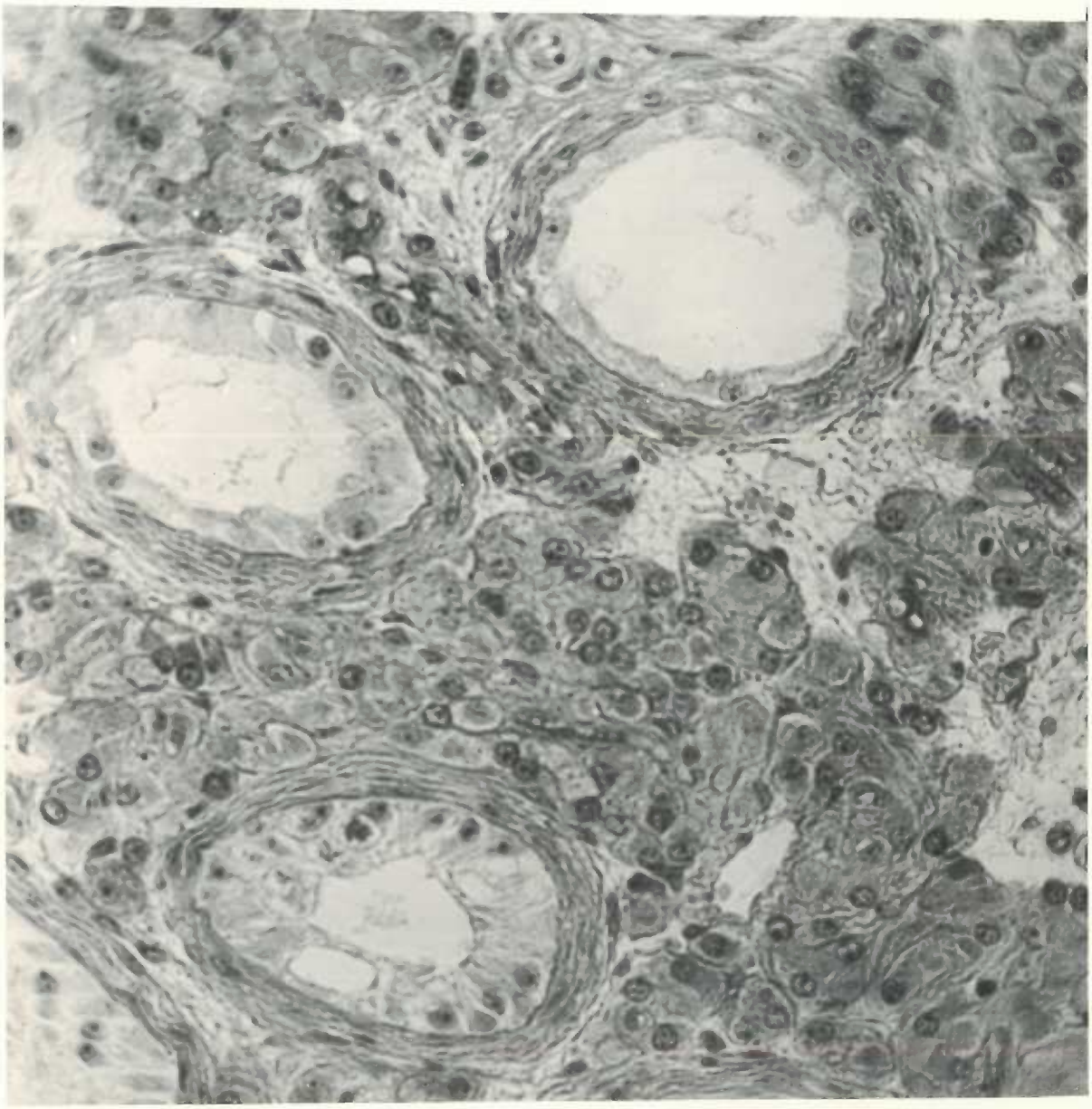


Figure 4

Figure 5

3+ Sclerosis with hyalinization

The greatly thickened connective tissue about the seminiferous tubules has become a homogeneous mass, due to hyalinization of the connective tissue. Spermatogenesis is poor, due to the severe impairment of blood supply. Leydig cells are occasional, yet appear in fair functional condition. X 450. (KI 236R)

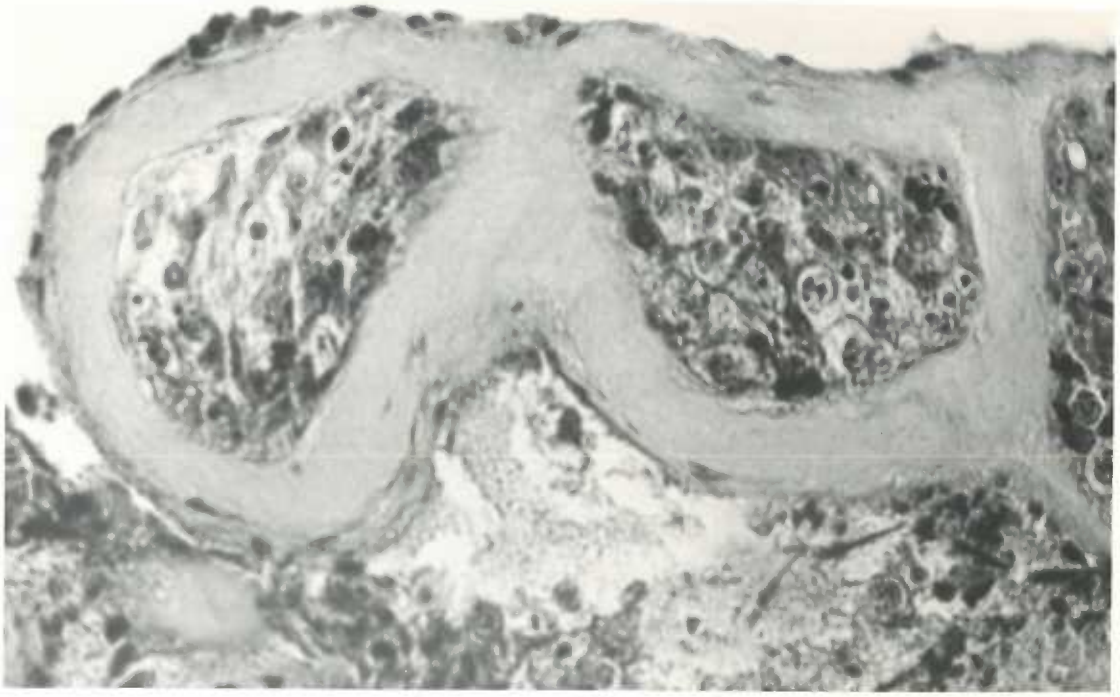


Figure 5

Figure 6

4+ Sclerosis (complete)
with hyalinization

The tubules contain no intraluminal elements, their outlines being represented by dense bands of hyaline tissue. Spermatogenesis is absent. Leydig cells are rated as "fair". X 450. (K1 277R)

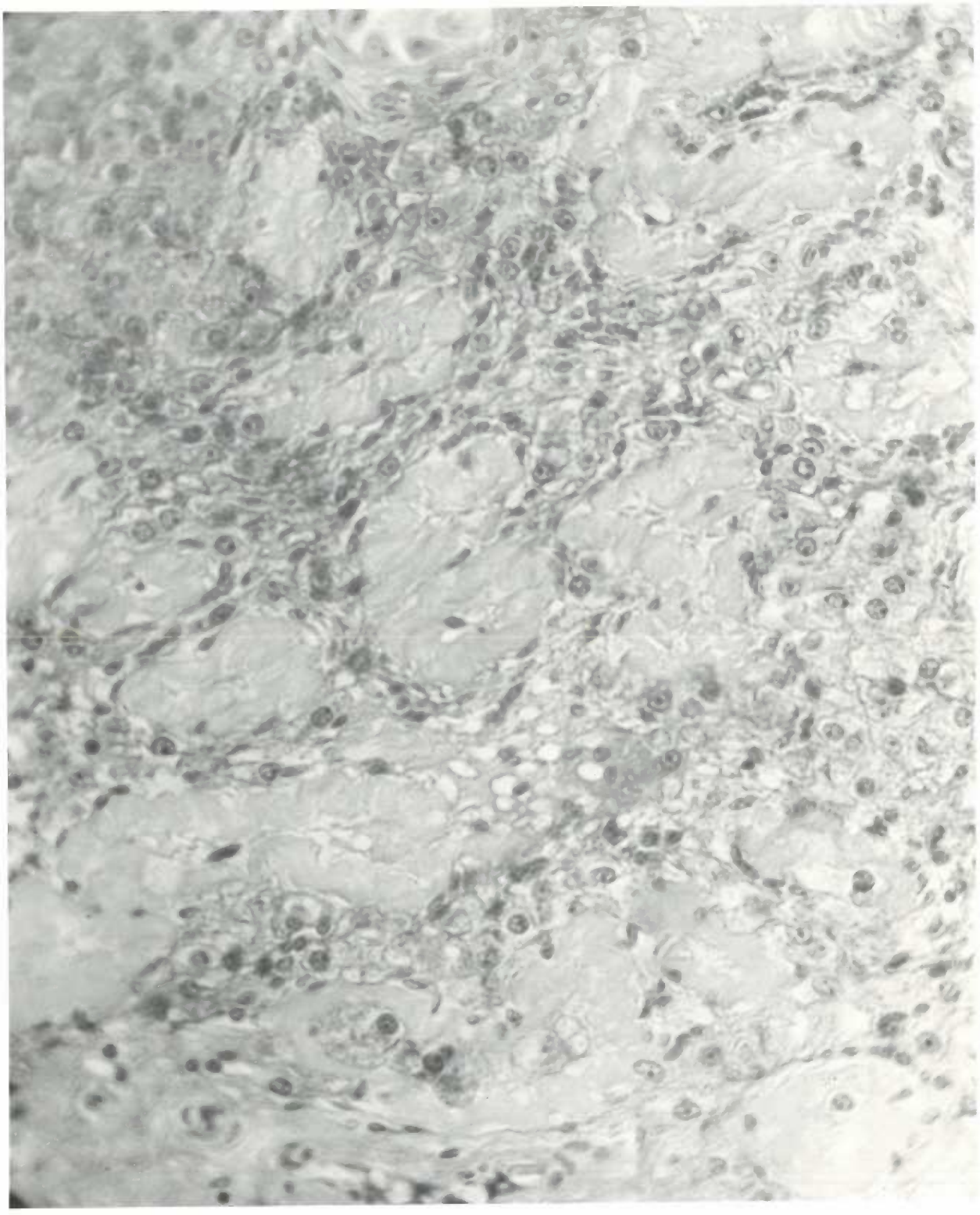


Figure 6

belonging to each category is estimated in the entire biopsy. In some instances, all tubules have the same degree of sclerosis, especially those that are normal (0-1+ sclerosis in all tubules) and those that are totally degenerated (4+ sclerosis in all tubules). In the majority of cases, no such uniformity is encountered, adjacent tubules often exhibiting widely varying degrees of sclerosis. Therefore the percentage of tubules in each category of sclerosis is judged for both testes, when they are similar, and recorded under the heading "% Sclerosis" in Table 1. When the testes of a patient are dissimilar, the rating for each testis is recorded separately in Table 1. However, in the overall consideration of testicular morphology for purposes of functional correlation, the condition of the two testes is averaged and the two treated as one functional unit (i.e. one organ).

Spermatogenesis

Classification of the Degree of Germinal Activity in Individual Seminiferous Tubules: The activity of the germinal elements was analyzed in each biopsy. It was soon discovered that no matter what the etiology, the degree of impairment, or the nature of the morphological involvement (i.e. sclerosis or no sclerosis, germinal stasis at one stage of maturation or another, or evidence of toxicity such as vacuolization of germinal cells), there was in each involved tubule the common denominator of sloughing of germinal elements and subsequent clogging of the lumina of the seminiferous tubules. This process of sloughing varied from none through various stages of minimal, moderate and severe to total desquamation of all spermatogenic cells, exposing the supporting cells of Sertoli.

The seminiferous tubules are judged as to their degree of spermatogenesis on the basis of the desquamation of germinal elements. Four degrees of germinal activity can be delineated--good, fair, poor and absent. The latter category is subdivided into a) tubules that are completely sclerosed, leaving neither spermatogenic elements nor Sertoli cells intact, and b) tubules that are completely denuded of germinal elements but in which Sertoli cells remain intact. The tubules involved in 4+ sclerosis are dealt with under "Sclerosis" in both the text and tables. Tubules representative of varying degrees of germinal failure are depicted in Figure 1 and Figures 7-11. These particular tubules are chosen because they demonstrate germinal failure occurring without accompanying Leydig cell failure and without accompanying thickening of the basement membrane and tunica propria beyond 0-1+ sclerosis.

Good spermatogenesis is synonymous with normal spermatogenesis. A tubule is considered to have good spermatogenesis when the basement membrane is lined with an orderly single row of spermatogonia and when there is a systematic progression in the stages of maturating germinal cells extending towards the lumen. These cell layers include primary spermatocytes, secondary spermatocytes, spermatids and spermatozoa. The lumen remains clear. Only a few Sertoli cells are recognizable as they are far outnumbered by the germinal elements. This description exactly fits the illustration of a normal testis in Figure 1.

Fair spermatogenesis includes those tubules in which all cells of the germinal series are identifiable, but less than normal numbers of some stages of maturation are present. Three types of evidence of

desquamation are usually present: 1) clogging of the lumen of the tubules with sloughed germinal cells, 2) disorderly arrangement of germinal elements--sloughing cells that normally remain in a peripheral location are found near or in the lumen; thus spermatogonia and primary spermatocytes may be seen in association with spermatozoa and spermatids in the luminal portion of the tubule, and 3) thinning in numbers of the sloughing cells in their normal position. In Figures 7 and 8, illustrating fair spermatogenesis, primary and secondary spermatocytes are less than normal in numbers in their usual positions but exist probably in greater than normal numbers for the tubules as a whole. Sloughing has usually not proceeded to the point of exposing the Sertoli cells to any appreciable extent in those tubules graded "fair".

Poor spermatogenesis includes all degrees of sloughing from "fair" spermatogenesis to the stage where no germinal elements are present. In general, any tubule containing some germinal elements but in which sloughing has advanced far enough to expose appreciable numbers of Sertoli cells is considered poor spermatogenesis. The lumen is usually choked with sloughed spermatogenic cells, and the numbers of germinal cells remaining at their usual site is minimal. Figures 9 and 10 illustrate two different degrees of poor spermatogenesis.

Absent spermatogenesis--the Sertoli cell only stage is characterized by the complete absence of all germinal cells and the presence of intact Sertoli cells. The desquamation of spermatogenic cells has gone to completion, exposing the structural framework of the seminiferous tubule, the supporting cells of Sertoli, and leaving the tubular lumen free of sloughed forms, as illustrated in Figure 11.

Figure 7

Fair Spermatogenesis

Sloughing of all types of germ cells except spermatogonia is occurring. Some spermatocytes remain in their normal position but note their relative paucity. In the lumen and the area adjacent to it, all types of cells except spermatogonia are recognizable but they are completely disorganized. Sertoli cells (recognized by the dark nucleolus) are recognized with the same frequency as in the normal testis. Sclerosis is absent. Leydig cells are normal and well granulated. X 450. (Fl 303L)

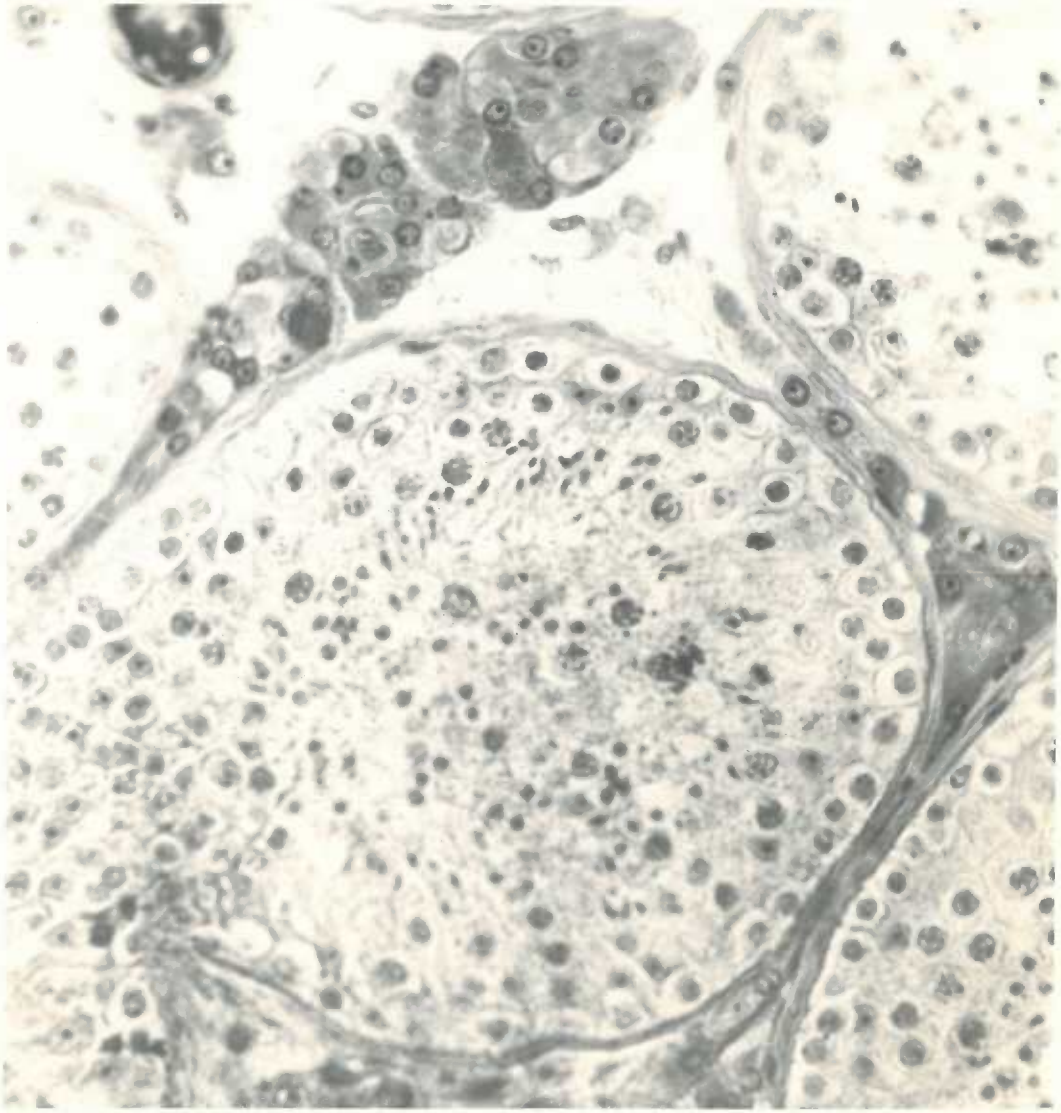


Figure 7

Figure 8

Fair Spermatogenesis

Sloughing has progressed to include most of the spermatocytes. Marked disorganization is noted beyond the basal primary spermatocyte layer. Sclerosis 1+. Leydig cells normal. X 460. (Kl 356)

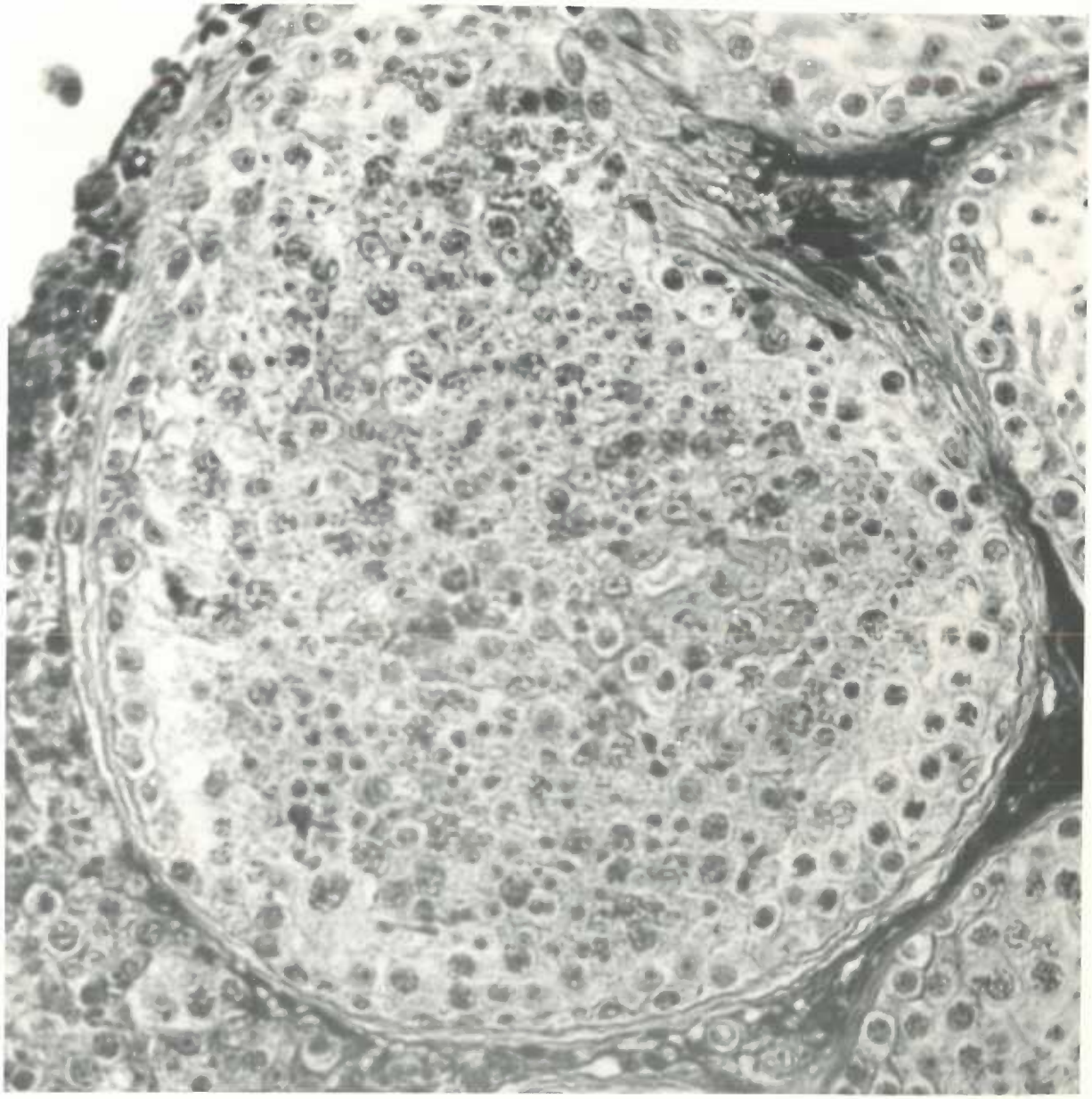


Figure 8

Figure 9

Poor Spermatogenesis

The spermatogenic elements have sloughed sufficiently to expose the Sertoli cells. The lumen is filled with sloughed cells. Spermatogonia and a few spermatocytes are the only spermatogenic cells remaining in situ in the upper tubule. Spermatogonia are sloughing in the lower left tubule. Sclerosis is 1+. Leydig cells are normal in number and appearance. X 450. (KL-~~194~~)

advanced
KL 194

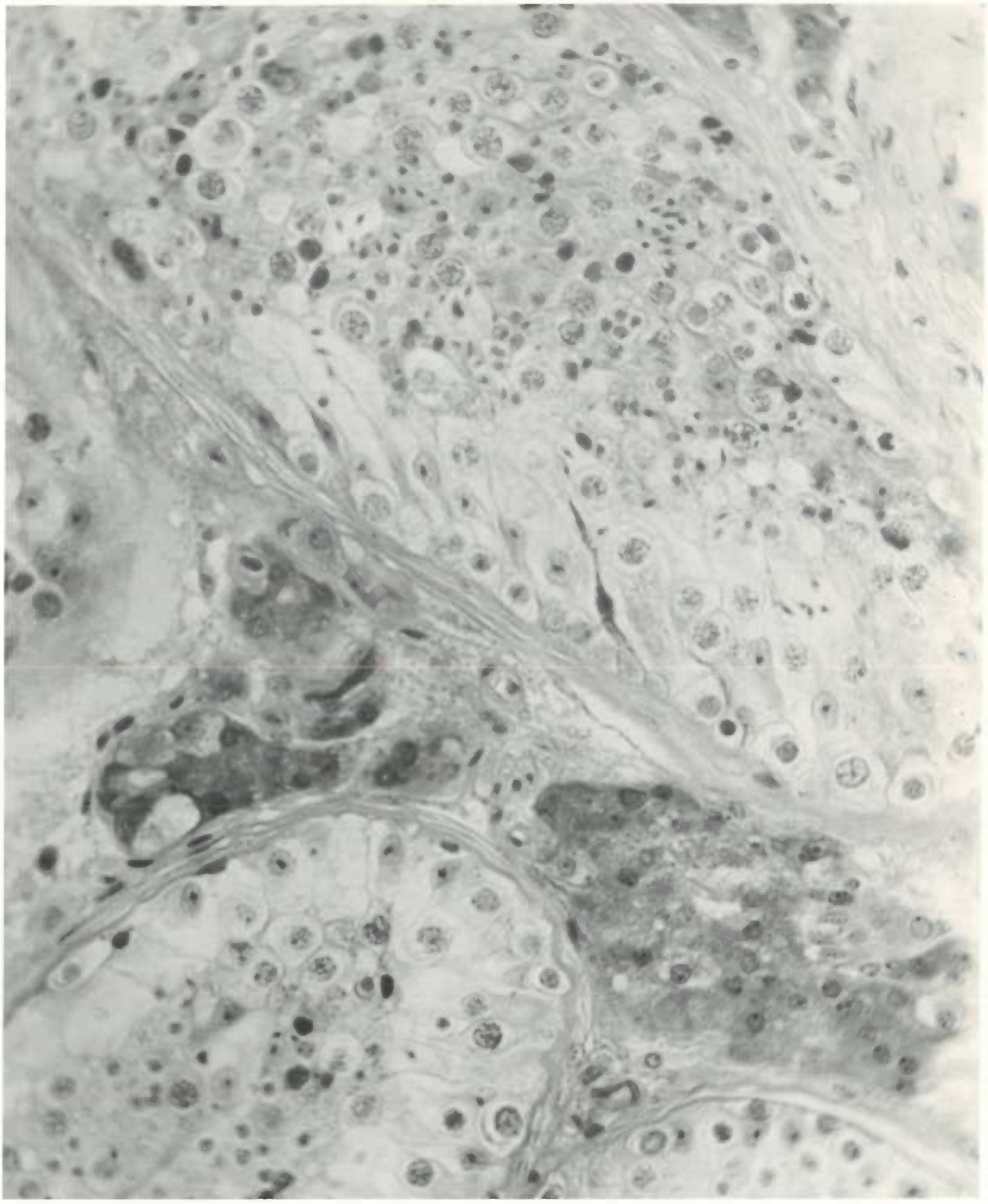


Figure 9

Figure 10

Poor Spermatogenesis

Germinal sloughing has proceeded almost to completion revealing many supporting cells of Sertoli. Only a few spermatogonia remain in situ. The tubule is plugged with degenerating cells. Sclerosis is 1+. Leydig cells are normal. X 450. (KL 307R)

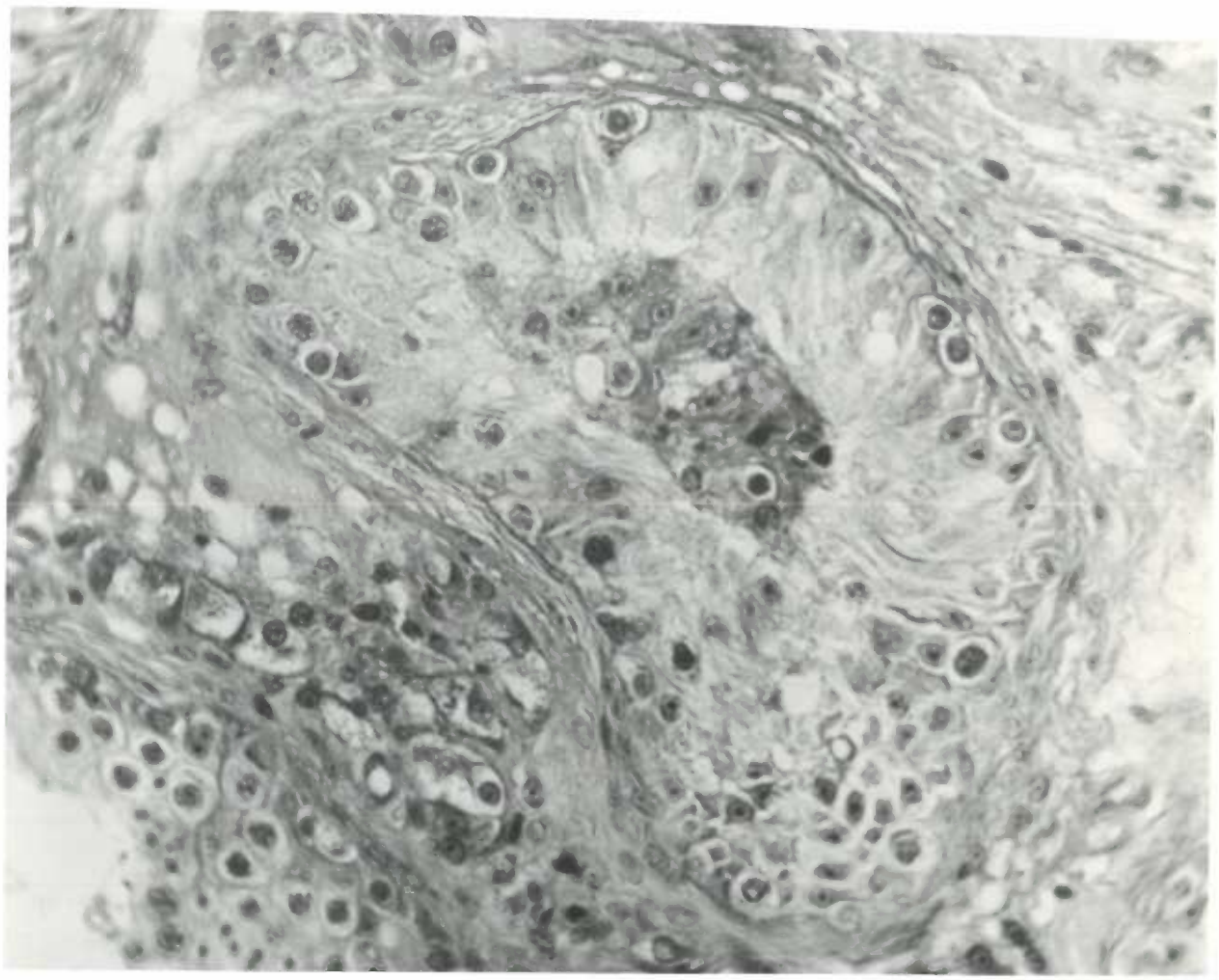


Figure 10

Figure 11

Sertoli Cells Only

The process of sloughing of the spermatogonic cells has gone to completion again leaving the lumen of the tubule clear and leaving behind only the structural framework of Sertoli cells. Sclerosis is 1+. Leydig cells are normal in number and appearance. X 450. (Kl 256)

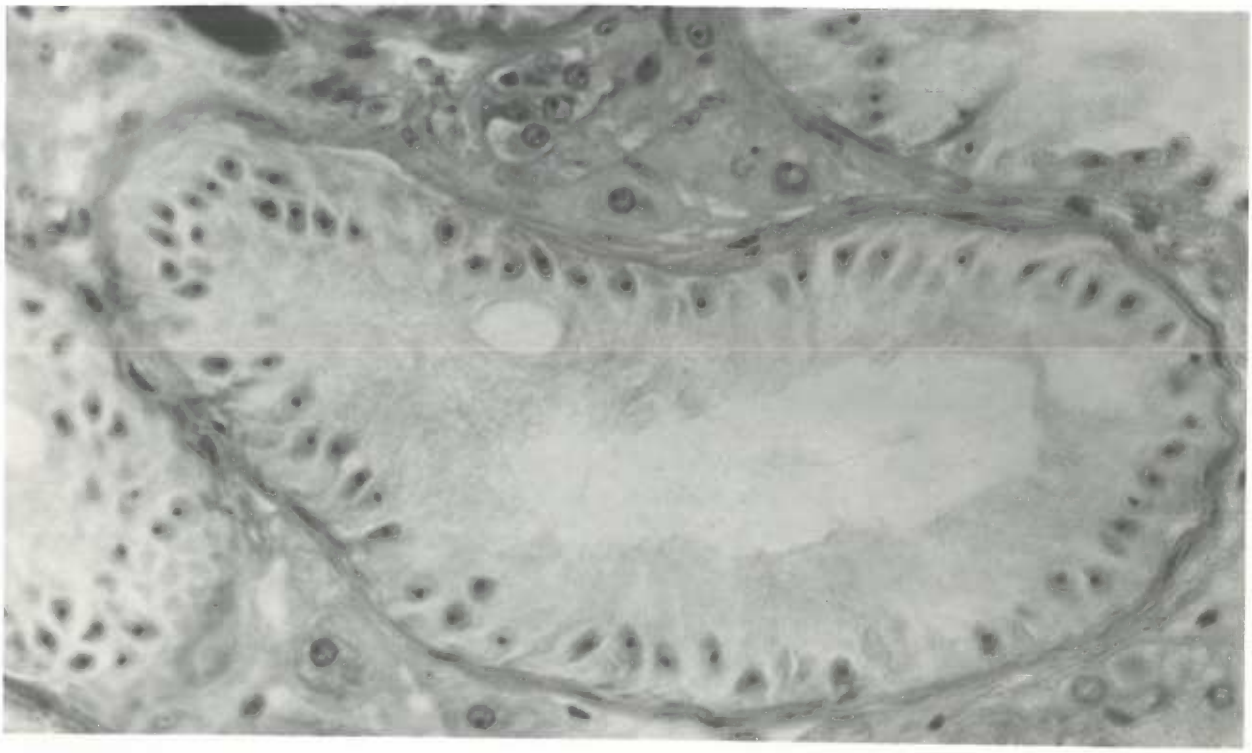


Figure 11

In making comparisons between Figures 1-11, it should be noted that the magnification in each instance is identical, i.e. X 450.

Classification of Testicular Biopsy According to Degree of Spermatogenesis: After placing individual seminiferous tubules in various categories based upon germinal activity, the relative numbers of tubules belonging in each category is estimated. As a general proposition, each biopsy, except the most nearly normal and those in which spermatogenesis is completely absent, contain tubules in several of the categories defined above and listed in Table 1 for each patient. Note that 4+ sclerosis is included as a category in calculating the percentage of spermatogenesis.

Spermatogenic Cells

Each biopsy is judged as to relative numbers of each of the germinal cell types, i.e. spermatogonia, spermatocytes, spermatids and spermatozoa. It is found that increases in relative and absolute numbers of cells occur in certain stages — for example, it is not uncommon to find increases in numbers of spermatogonia and spermatids associated with decreases in the number of cells of other stages of spermatogenesis. Normal for any cell type is graded as 2+, and increases above normal are graded as 3+ and 4+, whereas decreases below normal are rated as + or - (for absent). The rating of each biopsy is given in Table 1.

Leydig Cells

The interstitial cells of Leydig are rated as good, fair and poor, according to size and granulation of cytoplasm and size of nuclei. Good Leydig cells are to be seen in each figure except Figures 5 and 6, in which they are fair.

Urinary Gonadotrophin Titers

Quantitative determinations of gonadotrophin excretion in the urine of each patient were made. Ordinarily, the figure arrived at on Table 1 represents the average ovarian weights of four immature animals, each receiving the extract of a 12-hour urine aliquot. The assay figures of only 12-hour aliquots of urine were included, although in many instances with high titers, various lesser aliquots of urine were assayed simultaneously.

The ovarian weights of the 427 assay animals, in response to injection of 12-hour urine concentrates, varied from 5.4 to 149.5 mg. The ovaries of uninjected control rats average 13.5 mg. Ovarian weights of more than 40 mg. are considered to represent elevated gonadotrophin titers.

RESULTS

Sclerosis

The degree and amount of sclerosis of the seminiferous tubules was correlated with the urinary gonadotrophin titers. When more than 30% of all tubules of both testes are involved in 3+ or 4+ sclerosis, a rise in gonadotrophins occurs. Of the 115 patients, 40 exhibit 3+ to 4+ sclerosis in over 30% of the tubules. Of these, 39 have elevations of gonadotrophins above the 40 mg. ovary level. In the remaining one (KL 98), we suspect an error was made in urine collection. Thus, the correlation between marked degrees of sclerosis and elevation in gonadotrophins is excellent. However, 72 patients in the series have gonadotrophins elevated above the 40 mg. ovarian weight level, so 32 that do not have marked sclerosis are in this category. Many of the

32 have no significant degree of sclerosis. This means that some factor other than sclerosis must be involved in causing the rise in gonadotrophins. This factor is not androgen production, since androgen activity is judged to be normal in over half of the 40 men with severe sclerosis.

Spermatogenesis

The next logical correlation was to establish the relationship between the activity of the germinal cells and the level of urinary gonadotrophins. The first cases analyzed were 30 men having complete absence of all germinal elements. Two main types of cases were encountered: 1) cases having complete (4+) sclerosis and no Sertoli cells (3 cases) and 2) cases that have Sertoli cells only and no sclerosis (4 cases). All variations between these two extremes (23 cases) are tabulated in Chart 2. It should be noted that only the per cent of tubules having complete (4+) sclerosis are tabulated. Urinary gonadotrophins are elevated in each of the 30 instances, irrespective of the number of tubules sclerosed or the number of tubules having only Sertoli cells -- the common denominator is complete absence of active spermatogenesis.

It was next sought to determine whether a correlation existed between the degree of failure of spermatogenesis and urinary gonadotrophins. For this purpose, each of the 115 patients was rated as to the degree of germinal activity. The degree of germinal activity was assigned an arbitrary number as follows:

Good spermatogenesis -- 1

Fair spermatogenesis -- 2

Poor spermatogenesis -- 3

% Tubules Sertoli Cells Only	% Tubules Complete Sclerosis	% Tubules Spermatogenesis	Urinary Gonadotrophins
100	0	0	High
100	0	0	High
100	0	0	High
100	0	0	High
95	5	0	High
95	5	0	High
95	5	0	High
95	5	0	High
90	10	0	High
90	10	0	High
80	20	0	High
70	30	0	High
50	50	0	High
50	50	0	High
35	65	0	High
30	70	0	High
30	70	0	High
30	70	0	High
20	80	0	High
20	80	0	High
20	80	0	High
20	80	0	High
18	82	0	High
10	90	0	High
10	90	0	High
10	90	0	High
5	95	0	High
0	100	0	High
0	100	0	High
0	100	0	High

Chart 2

Sertoli cells only — 4

Complete sclerosis — 4

By multiplying the category number by the percentage of tubules in that category and adding the resultant products, a figure is reached which indicates the relative spermatogenic activity for the testis. If all tubules show good spermatogenesis, the rating is 100. When all tubules are completely sclerosed or show Sertoli cells only, then 100% x 4 gives 400, the figure which indicates complete absence of spermatogenesis. Using these numbers, a scatter graph (Chart 3) was constructed, plotting spermatogenesis (good 100, to absent 400) against the level of gonadotrophin excretion. The black squares represent the averages of the figures for each 50 units of spermatogenesis, i.e., 100 to 150, 150 to 200, etc.

It becomes readily apparent that a correlation is found between the degree of spermatogenic activity and the levels of urinary gonadotrophin excretion. As spermatogenic activity decreases, an increase in urinary gonadotrophin titers is noted.

It was previously noted that some degree of correlation existed between the severity of tubular sclerosis and elevation in gonadotrophins. This can be explained by the direct correlation that was established between the severity of the sclerosis and the impairment in spermatogenesis. 1+ sclerosis is compatible with normal spermatogenesis. Whenever sclerosis reaches 2+ or more, spermatogenesis is fair, poor or absent. The greater the degree of sclerosis beyond 2+, the greater the impairment in spermatogenesis. Thus:

In 2+ sclerosis, spermatogenesis is fair, poor or absent;

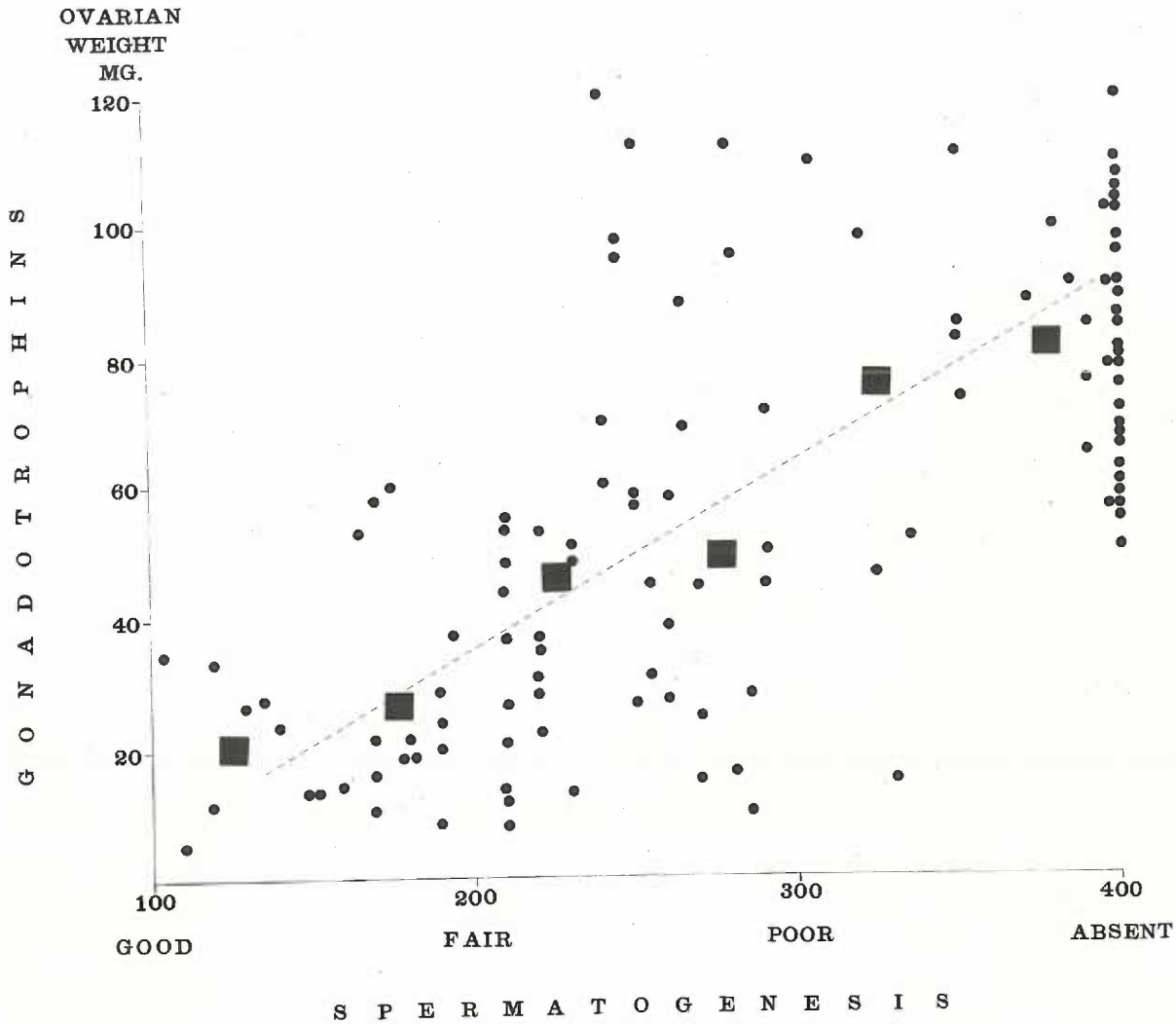

OVARIAN
WEIGHT
MG.
120
100
80
60
40
20
GONADOTROPHINS
100
200
300
400
GOOD
FAIR
POOR
ABSENT
SPERMATOGENESIS

Chart 3

in 3+ sclerosis, spermatogenesis is poor or absent;

in 4+ sclerosis, spermatogenesis is absent.

Since elevation in gonadotrophins follows the degree of impairment in spermatogenesis, and since sclerosis is accompanied by progressive impairment in spermatogenesis, it follows that gonadotrophins should be roughly proportional to the degree of sclerosis.

Spermatogenic Cells

Each of the testes was analyzed for the relative numbers of each of the spermatogenic elements. No correlation could be found between the specific types of spermatogenic cells present and the urinary gonadotrophin excretion. Further, no crucial stage of spermatogenesis was found beyond which gonadotrophins remained normal, and before which the gonadotrophins were consistently elevated.

Leydig Cells

The three categories of Leydig cells were correlated with the clinical evidence of androgenic function. The classification is based upon appearance of the cells as well as the relative numbers of cells observed. The three categories are classed as follows:

"Good" Leydig cells include those which are conventionally regarded as normal Leydig cells because of the size of the cell and nucleus, and the large numbers of secretory granules, when occurring in usual numbers.

"Fair" Leydig cells include normal-appearing Leydig cells when occurring in less than normal numbers, or small, dark staining, polyhedral interstitial cells with decreased cytoplasm and smaller nuclei, when numerous.

"Poor" Leydig cells indicate a marked reduction in number (or absence) of recognizable Leydig cells. These interstitial cells present could not be called either normal or small Leydig cells because they lacked the characteristic size, shape and granulation. On the other hand, they had nuclei characteristic of the cell of Leydig, so are not to be regarded as mesenchymal cells.

The correlation is best illustrated in the following summary:

Leydig Cell Classification	Total Number of Patients	Number of Patients having Normal Androgen Function	Number of Patients having Androgen Deficiency
Good	50	48	2
Fair	26	26	0
Poor	39	19	20

It is evident that normal androgen secretion is associated with both "good" and "fair" Leydig cells, and it may be concluded that forms of interstitial cells having less than the usual amount of cytoplasm, vacuoles and granules contained by conventional, mature Leydig cells are capable of secreting adequate amounts of androgen.

It is also evident that androgen deficiency is usually associated with Leydig cells in the "poor" category. However, the reverse does not hold since only 50% of patients in whom Leydig cells were classed as "poor" had androgen deficiency.

The degree of elevation of gonadotrophins in these cases tended to follow the germinal activity, which was disturbed in each of the 22 with overt androgenic deficiency--hence, gonadotrophins were elevated. However, no consistent pattern could be established between Leydig cell appearance and number and the gonadotrophin excretion.

Seminal Fluid

The number of spermatozoa per cc. tends to vary directly with the degree of germinal failure; however, so many individual variations are encountered that significance can be attached only to this general trend. The sperm count for a given patient is found to be largely without significance in predicting the degree of morphological change in the testes or the elevation in gonadotrophins.

Determination of motility of spermatozoa, total volume of the ejaculate, and morphological appearance of the spermatozoa is of relatively minor importance in establishing germinal failure. These tend to be poorer in general as total sperm counts decrease. No helpful correlation could be established between these observations and testicular morphology or gonadotrophin excretion.

DISCUSSION

The data presented bear upon each of the three hypotheses concerning the testis-pituitary relationship.

Advocates of the androgenic inhibition hypothesis contend that under physiologic circumstances, the secretion of gonadotrophin is kept in abeyance by circulating androgen. This hypothesis is held to be untenable by most workers because replacement doses of androgen, when given to hypogonadal or castrated men, restore all known androgen-controlled characteristics to normal without affecting gonadotrophin secretion or excretion.(1,2,6)

The present series includes 72 patients with elevated gonadotrophins. The majority had normal amounts of androgen in the circulation, and intact Leydig cells. This is incompatible with the androgen inhibition hypothesis.

Advocates of the inhibin hypothesis contend that the testis elaborates a non-androgenic water-soluble substance which keeps pituitary secretion in abeyance under physiological circumstances. This hypothesis is held to be untenable by most workers because no such substance has been isolated, and no such substance can be detected in testicular extracts with any regularity.

There is no direct evidence that pituitary content, secretion or urinary excretion of gonadotrophins has been altered by administration of "inhibin". In general, those extracts which have been most potent inhibitors of prostate or seminal vesicle development have been most crude and definitely toxic to the assay animal.(11)

It has been contended that Leydig cells produce "inhibin". In our series of cases, elevation in gonadotrophins is associated in the majority of patients with normal Leydig cell morphology and androgenic function. This is incompatible with the concept that Leydig cells normally produce "inhibin".

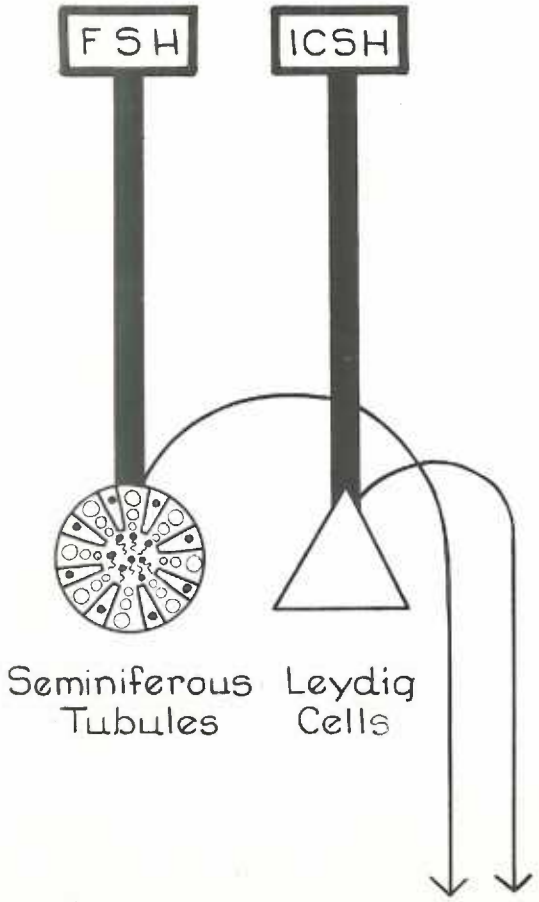
It has been contended that Sertoli cells produce "inhibin". In our series of cases, elevation in gonadotrophin occurs in a significant number of patients with intact Sertoli cells. This is incompatible with the concept that Sertoli cells produce "inhibin".

These same arguments would hold for Leydig cell or Sertoli cell production of any other inhibitor, e.g. estrogen.

It may be predicted that those workers that hold to the "inhibin" hypothesis will retreat to claiming germinal cells produce "inhibin". This is not disproven by the present data.

Advocates of the inactivation hypothesis contend that during active spermatogenesis gonadotrophins are inactivated. When spermatogenesis fails, the gonadotrophins are not inactivated and spill over in the urine in increased amounts. In Chart 2 are shown the data from patients having varying numbers of tubules showing complete sclerosis, and varying numbers of tubules containing only Sertoli cells; the two constant factors are a complete lack of spermatogenesis and uniformly high urinary gonadotrophin excretion. Thus it seems that it is not the degree of sclerosis nor the number of functional Sertoli cells, but the absence of spermatogenesis which causes the increased gonadotrophin excretion. Chart 4 illustrates this concept. In a patient with normal gonadotrophins, spermatogenesis is actively occurring and urinary gonadotrophins are at a normal level. In the case with only Sertoli cells, spermatogenesis is absent, and consequently there is an increased excretion of gonadotrophins in the urine. In both instances, the Leydig cells are present and normal in number and function, and in neither case is there a significant degree of sclerosis. The only variable in the testis, then, is the absence of spermatogenesis. In Chart 3 the titers of urinary gonadotrophins of all 115 cases are plotted against the relative activity of spermatogenesis. The black squares indicate the average figures. It can be seen that the averages follow a straight line curve--as spermatogenesis decreases, the urinary gonadotrophins increase. At the one end, where spermatogenesis was good in all tubules, the urinary gonadotrophin excretion was normal, whereas at the other end of the line, where spermatogenesis was entirely absent, the urinary gonadotrophin excretion was uniformly elevated. These findings are consonant with the hypothesis that during active gonadal

NORMAL



SERTOLI CELL ONLY

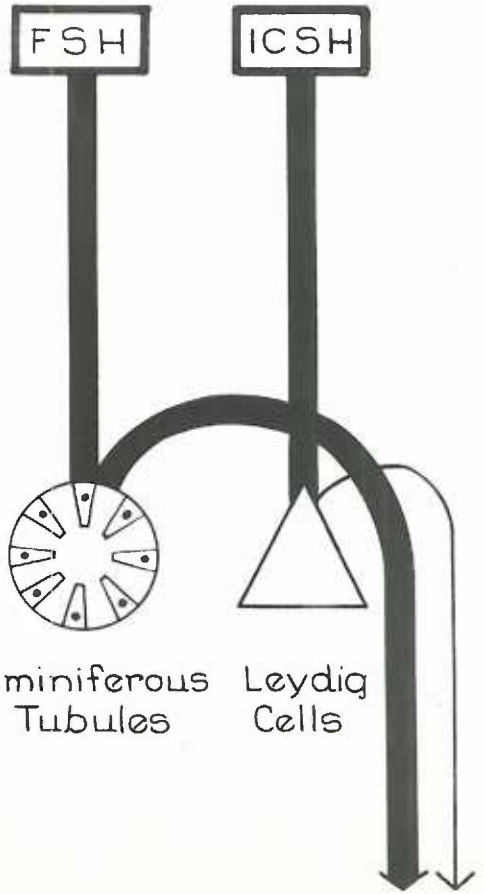


Chart 4

function, gonadotrophins are inactivated.

The inverse correlation between the degree of sclerosis and spermatogenesis is most likely due to interference of metabolic exchange between the seminiferous tubules (which have no intratubular vascular supply), and the blood vessels. All nutrient exchange between blood stream and germinal elements must pass the tunica propria and the basement membrane. The interposition of additional layers must necessarily interfere with passage of nutrients to the spermatogenic cells causing their eventual demise.

By correlating morphological appearance of Leydig cells with urinary gonadotrophin titers it was noted that small darkly stained polyhedral cells containing nuclei characteristic of Leydig cells are evidently producing adequate amounts of androgen. This confirms the concepts of Hooker,[12,13] Oslund[14] and Sand and Okkels.[15]

Oslund found that Leydig cell development may precede, accompany or follow evidences of androgen secretion in animals with seasonal breeding habits. In mature men Sand and Okkels found too much variation in Leydig cells to establish a normal pattern.

Hooker found that during sexual maturation in the bull, androgen is elaborated for many months before large, plump, well-granulated, vacuolated mature Leydig cells develop. The interstitial cell appearance in the bull during puberty but before mature Leydig cells develop are not unlike those in our "fair" category and even resembles some rated as "poor".

SUMMARY AND CONCLUSIONS

It is concluded that the physiological regulator of urinary gonadotrophin excretion is the inactivation of circulating gonadotrophins by the testis during the stimulation of active spermatogenesis. Ancillary mechanisms for the control of pituitary gonadotrophin secretion are recognized. They include the suppression of pituitary gonadotrophin secretion by greater than physiological amounts of estrogens and androgens.

There was found to be a direct correlation between the degree of germinal failure and elevation in urinary gonadotrophin excretion in 115 hypogonadal men. In the absence of germinal cells, gonadotrophin titers were invariably elevated even in the presence of normal numbers of normal appearing Leydig and Sertoli cells.

Interstitial cells, other than mature normal Leydig cells, are capable of secreting androgen.

Table 1

Pt.	Age	SEMINIFEROUS TUBULES: % Sclerosis 0-1+	2+	3+	4+	% Spermatogenesis Good	Fair	Poor	S.C.	Spermatogenic Cells: spnia	cytes	tids	sperm	LEYDIG CELLS	Sperm count m/cc.	Urin. Gonadotrophin No. Assays	Ave. Ovarian Wt. in mg.
K1 182	27	100	-	-	-	-	100	-	-	++++	+	++++	+	Good	30.0	5	21.1
K1 168	32	30	5	5	60	-	10	30	-	++	++	+	+	Poor	occ.	3	112.0
K1 185	26	90	-	5	5	85	5	5	-	++	++	+++	+	Good	35.0	4	32.2
K1 181	36	-	-	10	90	-	5	-	5	+++	++	+	-	Poor	2.0	4	75.8
K1 180	21	100	-	-	-	-	95	5	-	++	+++	+	+	Good	0.5	4	37.9
K1 184	31	45	25	25	5	5	35	50	5	+++	+	+	+	Fair	3.0	2	69.0
K1 183R	32	90	-	5	5	-	-	95	-	+++	+	+	-	Good	70.0	2	59.3
183L		90	-	5	5	20	70	5	-	++	+++	+++	+	Good			
K1 186	31	50	50	-	-	-	30	70	-	++	+	+	-	Good	12.0	4	45.1
K1 218L	29	25	50	25	-	75	25	-	-	++	++	++	+	Good	100.0	4	53.9
218R		10	50	40	-	30	35	35	-	++	+++	++	+	Fair			
K1 190	32	10	60	20	10	30	20	50	-	+	+++	+	++	Poor	60.0	6	27.0
K1 188	29	10	60	20	10	50	20	30	-	++	+++	+++	+	Poor	15.0	2	23.5
K1 189	22	20	70	10	-	30	60	20	-	++	++++	+	+	Poor	6.0	4	8.9
K1 195	29	70	20	10	-	20	60	20	-	++	+	+++	+	Fair	45.0	4	8.5

Table 1 (cont'd)

Pt.	Age	SEMINIFEROUS TUBULES: % Sclerosis 0-1+	2+	3+	4+	% Spermatogenesis: Good	Fair	Poor	S.C.	Spermatogenic Cells: Spermatogonia	Spermatocytes	Spermatids	Spermatozoa	LEYDIG CELLS	Sperm Count m/cc.	Urin. Gonadotrophin No. Assays	Ave. Ovarian Wt. in mg.
K1 163	29	90	10	-	-	20	50	30	-	++	++	++	++	Fair	110.0	10	55.4
K1 167	29	70	20	10	-	10	60	30	-	++	+	+++	+	Good	8.0	4	29.1
K1 191	23	90	10	-	-	90	10	-	-	++	++	++	++	Good	213.0	2	5.4
K1 192L	32	-	95	5	-	60	30	10	-	++	++	+	+	Fair	15.0	4	46.8
192R		60	30	10	-	10	45	45	-	++	++	+++	+	Fair			
K1 193L	29	-	-	5	95	-	-	-	5	-	-	-	-	Good	14.0	3	53.2
193R		30	10	10	50	40	5	5	-	++	++	++	+	Good			
K1 196	31	90	10	-	-	80	20	-	-	++	++	++	+	Good	30.0	3	11.6
K1 197L	32	20	80	-	-	-	30	70	-	+	+	+	++	Fair	5.0	4	98.5
197R		20	70	10	-	-	10	30	60	+	++	++	+	Fair			
K1 198	38	-	10	10	80	-	10	10	-	+	++	+	+	Fair	0.5	4	88.3
K1 199	24	5	5	5	85	-	5	5	5	+	+	+	+	Good	0.0	4	92.4
K1 200	28	20	70	10	-	10	80	10	-	+	++	++	++	Poor	45.0	6	20.3
K1 201	27	80	15	5	-	10	80	10	-	++	++	++	+	Poor	3.0	4	13.7
K1 202	27	-	-	-	100	-	-	-	-	-	-	-	-	Good	0.0	4	85.5

Table 1 (cont'd)

Pt.	Age	SEMINIFEROUS TUBULES: % Sclerosis 0-1+	2+	3+	4+	% Spermatogenesis Good	Fair	Poor	S.C.	Spermatogenic Cells: gonia	cytes	tide	sperm	LEYDIG CELLS	Sperm Count m/cc.	Urin. Gonadotrophin No. Assays	Ave. Ovarian Wt. in mg.
K1 303	30	10	70	20	-	10	50	40	-	++	+++	+	+	Poor	Occ.	4	48.3
K1 206	31	95	5	-	-	75	15	10	-	++	++	++	+	Good	0.0	4	26.7
K1 209L	36	90	10	-	-	60	10	10	-	++	++	++	+	Good	~~38.0~~ 19.0	7	60.3
K1 209R		90	10	-	-	30	40	30	-	++	+++	++	+	Fair			
K1 210L	29	90	5	5	-	-	5	-	95	+	+	+	+	Good	0.0	3	73.0
210R		80	10	10	-	-	40	10	50	+	+	+	+	Good			
K1 211	36	20	30	20	30	-	50	20	-	++	+++	+	+	Fair	~~8.0~~ 11.5	4	112.8
K1 212L	40	90	10	-	-	80	20	-	-	++	++	++	++	Good	112.0	3	39.2
212R		-	-	-	100	-	-	-	-	-	-	-	-	None			
K1 216	41	70	30	-	-	10	80	10	-	+++	++	+++	+	Fair	21.0	3	37.2
K1 217	34	10	50	30	10	-	45	45	-	++	+	+	+	Fair	5.6	3	87.5
K1 221	32	90	5	5	-	80	20	-	-	++	++	++	++	Good	Occ.	3	32.5
K1 222	25	90	10	-	-	-	10	90	-	+	+	+	+	Fair	20.0	4	45.3
K1 223	39	80	10	10	-	20	80	-	-	++	+++	+	+	Good	30.0	9	22.3
K1 224	29	70	10	10	10	20	50	30	-	++	+++	++	+	Fair	23.8	1	19.0

Table 1 (cont'd)

Pt.	Age	SEMINIFEROUS TUBULES: % Sclerosis 0-1+	2+	3+	4+	% Spermatogenesis Good	Fair	Poor	S.C.	Spermatogenic Cells: gonia	cytes	tids	sperm	LEYDIG CELLS	Sperm Count m/cc.	Urin. Gonadotrophin No. Assays	Ave. Ovarian Wt. in mg.
K1 226L	29	70	30	-	-	-	30	10	60	++	++	+	+++	Fair	5.0	3	96.5
226R		90	10	-	-	60	30	5	5	++	++	++	++	Good			
K1 227	32	80	20	-	-	5	-	35	60	+	+	+	+	Poor	2.7	3	85.1
K1 230	27	20	70	10	-	-	20	80	-	+	+	+	+	Poor	17.4	4	16.6
K1 231	35	60	30	5	5	5	40	50	-	++	+	+	+	Good	2-3/drop. ~~0.0~~	4	~~44.8~~ 55 ?
K1 232	38	80	20	-	-	50	40	10	-	++	++	+++	++	Fair	23.0	4	13.8
K1 233	33	10	45	20	25	30	20	25	-	+	++	+++	+	Good	8.0	4	95.1
K1 234	36	10	80	10	-	10	70	20	-	+++	+	+++	+	Fair	5.1	2	~~36.5~~ 35
K1 239	38	80	20	-	-	60	40	-	-	++	++	+	+	Good	18.0	3	~~34.4~~ 87
K1 240L	36	10	70	10	10	-	60	30	-	++	+	+	+	Poor	10.0	3	46.4
240R		-	-	-	100	-	-	-	-	-	-	-	-	None			
K1 241	31	30	40	10	20	10	60	10	-	++	+	+	+	Good	23.0	4	145.2
K1 245	23	20	70	10	-	20	50	30	-	++	++	+++	++	Good	42.6	4	13.4
K1 246	27	100	-	-	-	95	5	-	-	++	++	++	++	Good	0.0	3	35.2
K1 248	30	10	80	10	-	10	60	30	-	++	+	+++	+	Fair	0.0	4	34.5

9 Ht with error → error

Table 1 (cont'd)

Pt.	Age	SEMINIFEROUS TUBULES: % Sclerosis 0-1+	2+	3+	4+	% Spermatogenesis: Good	Fair	Poor	S.C.	Spermatogenic Cells: gonia	cytes	tids	sperm	LEYDIG CELLS	Sperm Count m/cc.	Urin. Gonadotrophin No. Assays	Ave. Ovarian Wt. in mg.
KL 253	59	10	60	30	-	20	50	30	-	++	++	+	+	Poor	200.0	~~4~~ 6	~~43.7~~ 550
KL 254	26	20	30	10	60	-	-	20	30	+	+	-	+	Poor	0.0	2	99.8
KL 255L	32	-	40	10	50	-	20	30	-	++	+	+	+	Poor	0.0	4	72.1
255R		-	60	30	10	-	40	50	-	++	+	+	+	Poor			
KL 256	24	50	40	10	-	-	-	-	100	-	-	-	-	Good	0.0	7	17.7
KL 258	24	80	20	-	-	-	-	-	100	-	-	-	-	Good	0.0	2	106.7
KL 259	28	10	70	10	10	10	40	40	-	+	++	+++	+	Poor	0.0	4	113.2
KL 263	35	40	40	10	10	-	50	40	-	++	++	+	+	Poor	Occ.	4.	26.9
KL 264	65	-	80	10	10	-	40	50	-	++	+	+	+	Fair	100.5	4	25.4
KL 265	35	-	50	40	10	-	40	50	-	+	+	+	+	Poor	46.5	4	15.2
KL 267	37	50	40	10	-	50	50	-	-	++	++	++	++	Good	38.0	4	13.2
KL 274L	40	-	70	30	-	20	50	30	-	++	++	+	+	Fair	0.0	6	109.7
274R		-	-	-	100	-	-	-	-	-	-	-	-	Poor			
KL 275	25	20	45	25	10	-	-	-	90	-	-	-	-	Fair	0.0	3	67.0
KL 277	20	-	5	-	95	-	-	-	5	-	-	-	-	Good	0.0	1	62.2

out Varect.

out

out

45 mg is more likely correct

B

Table 1 (cont'd)

Pt.	Age	SEMINIFEROUS TUBULES: % Sclerosis 0-1+	2+	3+	4+	% Spermatogenesis Good	Fair	Poor	S.C.	Spermatogenic Cells: gonia	cytes	tids	sperm	LEYDIG CELLS	Sperm Count m/cc.	Urin. Gonadotrophin No. Assays	Ave. Ovarian Wt. in mg.
K1 278	29	80	20	-	-	-	-	100	-	+++	-	-	-	Good	17.5	4	50.4
K1 279	26	90	10	-	-	20	80	-	-	++	++++	++	+	Good	7.0	4	18.8
K1 281	34	-	10	30	60	-	-	-	40	-	-	-	-	Fair	0.0	4	149.5
K1 282	25	60	20	10	10	-	-	-	90	-	-	-	-	Fair	0.0	4	57.6
K1 283L	28	90	10	-	-	50	40	10	-	++	++	++	++	Good	0.2	4	53.7
283R		20	60	10	10	10	30	50	-	++	+	+	+	Good			
K1 286L	29	80	20	-	-	60	30	10	-	+++	++	+++	+	Fair	0.0	4	15.7
286R		60	30	10	-	30	50	20	-	++	++	++	+	Poor			
K1 293L	24	30	60	10	-	5	5	-	90	++	++	++	++	Fair	Occ.	4	14.5
293R		10	70	15	5	-	20	70	5	+	++	+	+	Poor			
K1 294L	38	20	70	10	-	-	80	20	-	++	+	+	++	Poor	71.5	4	57.8
294R		5	70	20	5	-	25	70	-	+	+	+	+	Poor			
K1 296L	53	-	60	20	20	-	30	50	-	+	+	+	+	Poor	300.0	4	31.0
296R		20	70	10	-	10	70	20	-	++	+	+	++	Fair			
K1 298	27	90	10	-	-	10	90	-	-	++	++	+++	++	Fair	30.0	4	29.3

Table 1 (cont'd)

Pt.	Age	SEMINIFEROUS TUBULES: % Sclerosis 0-1+	2+	3+	4+	% Spermatogenesis Good	Fair	Poor	S.C.	Spermatogenic Cells: spnia	sptes	tids	sperm	LEYDIG CELLS	Sperm Count m/cc.	Urin. Gonadotrophin No. Assays	Ave. Ovarian Wt. in mg.
K1 303	34	5	60	5	30	-	-	-	70	-	-	-	-	Good	Occ.	4	102.8
K1 303L	31	60	40	-	-	50	40	10	-	+++	++	++	++	Fair	17.0	4	57.9
303R		70	30	-	-	30	60	10	-	+++	++	+++	+	Fair			
K1 307L	28	10	60	20	10	30	30	10	20	++	+	+	+	Fair	Occ.	4	95.8
307R		30	60	10	10	10	30	10	40	++	++	+	+	Good			
K1 310	35	50	40	10	-	-	40	60	-	++	+	+	+	Poor	3.0	4	58.0
K1 311	31	60	30	10	-	60	30	10	-	++	++	+	+	Good	50.0	4	16.8
K1 318	27	20	70	10	-	-	70	30	-	++	++	+	+	Good	7.0	7	50.9
K1 319	29	40	50	10	-	-	80	20	-	+++	+	+++	+	Poor	10.0	4	22.7
K1 328L	41	10	60	20	10	-	50	40	-	+	++	++	+	Poor	7.0	4	10.3
328R		90	10	-	-	90	10	-	-	++	++	++	++	Good			
K1 330	26	20	50	20	10	10	60	20	-	++	+	+	+	Poor	29.0	4	14.4
K1 332	33	40	40	20	-	-	80	20	-	++	++	+	+	Good	0.0	4	49.9
K1 335L	30	50	20	10	20	-	-	80	-	+	+	+	-	Fair	Occ.	4.	26.5
335R		80	20	-	-	-	50	50	-	++	+	+	-	Fair			

Table 1 (cont'd)

Pt.	Age	SEMINIFEROUS TUBULES: % Sclerosis 0-1+	2+	3+	4+	% Spermatogenesis: Good	Fair	Poor	S.C.	Spermatogenic Cells: gonia	cytes	tids	sperm	LEYDIG CELLS	Sperm Count m/cc.	Urin. Gonadotrophin No. Assays	Ave. Ovarian Wt. in mg.
K1 336	20	70	20	10	-	10	60	30	-	++	+	+++	+	Fair	9.5	4	30.5
K1 337	41	60	20	10	10	20	50	20	-	++	++	+++	+	Good	16.0	4	55.0
K1 338L	44	-	-	-	100	-	-	-	-	-	-	-	-	Fair	0.0	4	63.2
338R		10	30	20	40	-	40	20	-	+	++	+	+	Poor			
K1 339	30	80	20	-	-	40	50	10	-	++	++	++	+	Good	17.0	4	10.5
K1 343L	31	30	50	10	10	-	80	-	10	++	++	+	+	Good	19.0	3	59.7
343R		10	60	10	20	10	60	10	-	++	++	+	+	Poor			
K1 352	29	70	10	20	-	10	40	50	-	++	+++	+	++	Good	6.5	2	70.0
K1 353	31	80	20	-	-	50	30	20	-	++	++	+	+	Fair	15.4	4	32.4
K1 1	21	15	20	-	65	-	-	-	35	-	-	-	-	Good	0.0	9	75.0
K1 6	22	-	5	10	85	-	-	-	15	-	-	-	-	Good	0.0	3	104.0
K1 9	32	35	35	20	10	-	-	-	90	-	-	-	-	Good	0.0	4	55.0
K1 28	22	35	35	-	30	-	-	-	70	-	-	-	-	Good	0.0	2	81.0
K1 35	19	15	15	10	60	-	-	10	30	+	+	-	-	Poor	0.0	3	85.0
K1 39	27	10	10	-	80	-	-	-	80 50	-	-	-	-	Good	0.0	4	73.0

Table 1 (cont'd)

Pt.	Age	SEMINIFEROUS TUBULES: % Sclerosis 0-1+	2+	3+	4+	% Spermatogenesis: Good	Fair	Poor	S. C.	Spermatogenic Cells: spnia	cytes	tids	sperm	LEYDIG CELLS	Sperm Count m/cc.	Urin Gonadotrophin: No. Assays	Ave. Ovarian Wt. in mg.
K1 42	19	40	40	-	20	-	-	-	80	-	-	-	-	Poor	0.0	4	103.0
K1 44	19	15	5	-	80	-	-	-	20	-	-	-	-	Poor	0.0	1	56.0
K1 58	69	-	5	25	70	-	-	-	30	-	-	-	-	Poor	0.0	2	61.0
K1 62	19	15	15	-	70	-	-	-	30	-	-	-	-	Good	0.0	4	88.0
K1 81	18	-	10	-	90	-	-	-	10	-	-	-	-	Good	0.0	9	66.0
K1 83	20	25	10	15	50	-	-	-	50	-	-	-	-	Fair	0.0	1	56.0
K1 98	35	50	50	-	-	-	-	-	100	-	-	-	-	Good	0.0	3	80.0
K1 105	56	-	-	2	98	-	-	-	2	—	-	-	-	Poor	0.0	2	105.0
K1 111	25	5	-	5	90	-	-	-	10	-	-	-	-	Poor	0.0	5	98.0
K1 127	27	5	5	10	80	-	-	-	20	-	-	-	-	Poor	0.0	2	50.0
K1 147	18	10	-	-	90	-	-	1	9	+	-	-	-	Poor	0.0	3	78.0
K1 166	28	95	-	5	-	-	-	-	100	-	-	-	-	Good	0.0	1	68.0
K1 166a	18	30	30	-	50	-	-	10	40	+	-	-	-	Poor	0.0	2	65.0
K1 170	14	15	15	-	70	-	-	-	30	-	-	-	-	Poor	0.0	4	78.5
K1 177	31	40	25	35	5	-	-	-	95	-	-	-	-	Fair	0.0	3	85.3

Table 1 (cont'd)

Pt.	Age	SEMINIFEROUS TUBULES % Sclerosis 0-1+	2+	3+	4+	% Spermatogenesis Good	Fair	Poor	S.C.	Spermatogenic Cells Spermatogonia	Spermatocytes	Spermatids	Spermatozoa	LEYDIG CELLS	Sperm Count m/cc.	Urin. Gonadotrophin No. Assays	Ave. Ovarian Wt. in mg.
Kl el	26	80	10	5	5	-	-	-	95	-	-	-	-	Fair	0.0	4	94.6
Kl Sc	22	-	-	-	100	-	-	-	-	-	-	-	-	Poor	0.0	4	90.0
Kl Di	25	-	-	-	100	-	-	-	-	-	-	-	-	Poor	0.0	9	96.0

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