

# A Practical Approach to Testicular Biopsy Interpretation for Male Infertility

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• **Context.**—The combination of testicular biopsy and clinical evaluation for male infertility is becoming progressively more important because new technologies allow men previously considered infertile to father children. Although most general pathologists are experienced with normal, neoplastic, and cryptorchid testicular specimens, the testicular biopsy for infertility requires understanding of a different set of diagnostic categories not otherwise commonly encountered.

**Objective.**—To highlight a standardized nomenclature for germ cell abnormalities allowing for effective commu-

nication with the urologist and maximal clinical benefit from the biopsy.

**Data Sources.**—Previously published consensus statements, review articles, peer-reviewed research publications, and abstracts.

**Conclusions.**—A practical approach to evaluating testicular biopsies for fertility and the clinical implications for each abnormality are herein outlined.

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Infertility is not an uncommon problem in Western societies with approximately 15% of couples experiencing some difficulties with intended conception. In almost a quarter of these cases, male infertility is the primary problem and is a contributory element in an additional 30% to 40%. Although a basic male infertility evaluation requires a comprehensive history and physical along with semen analysis, a testicular biopsy can provide valuable information to the urologist by further categorizing men with azoospermia for purposes of prognosis and treatment.<sup>1</sup> The testicular biopsy can help predict the chances of finding sperm on microdissection of the testicles. In a group of 135 men, sperm were found in 51% of men with Sertoli-cell-only pattern, 83% in men with maturation arrest, and 100% of men with hypospermatogenesis.<sup>2</sup>

Knowledge of the specific nature of testicular pathology is of primary importance because other clinical parameters, such as follicle-stimulating hormone plasma levels and testicular volume, do not reliably discriminate between different testicular alterations. Most pathologists are comfortable with the identification of normal spermatogenesis that suggests an obstructive etiology. Unfortunately, due to the comparative lack of clinical cases and the absence of supporting literature, many are unable to confidently interpret the variety of pathologies found in men with nonobstructive azoospermia. An accurate pathologic diagnosis plays a critical role in the diagnosis and treatment of men who face reproductive challenges.

The causes of male infertility are most easily divided into 3 major categories: pretesticular, testicular, and posttesticular. The pretesticular causes of infertility may be defined as extragonadal endocrine disorders, such as those originating in the hypothalamus, pituitary, or adrenals, which have an adverse effect on spermatogenesis through aberrant hormonal stimulation or suppression. The testicular causes of infertility are primary defects of the testes. These may be congenital or occur secondarily to environmental insults or other disease processes. The posttesticular causes of infertility consist primarily of obstructions of the ducts leading away from the testes. Individuals in this category may be candidates for surgical reconstruction of the ducts or cystic fibrosis screening. The increasing use of these categorizations permits a rational classification of the testicular lesions responsible for infertility and provides an intelligent basis for the institution of corrective measures or the withholding of therapy in cases in which the biopsy indicates a hopeless prognosis for fertility.

For men with a zero sperm count (azoospermia), testicular biopsy is done to determine if a blockage is present or if primary testicular failure is the cause. With many azoospermic men, in vitro fertilization/intracytoplasmic sperm injection has become the major reproductive treatment option if testicular sperm can be retrieved. For obstructed patients with normal spermatogenesis, testicular sperm retrieval is relatively simple. A repeat testicular biopsy or aspiration can procure sperm with high success rates because sperm production is unaffected. For patients with nonobstructive azoospermia, the presence of sperm within the testicle is not guaranteed. These men may choose to have a more comprehensive procedure called microdissection testicular sperm extraction to look for sperm. Described initially in 1999, microdissection testicular sperm extraction involves the use of intraoperative microscopy to carefully explore all

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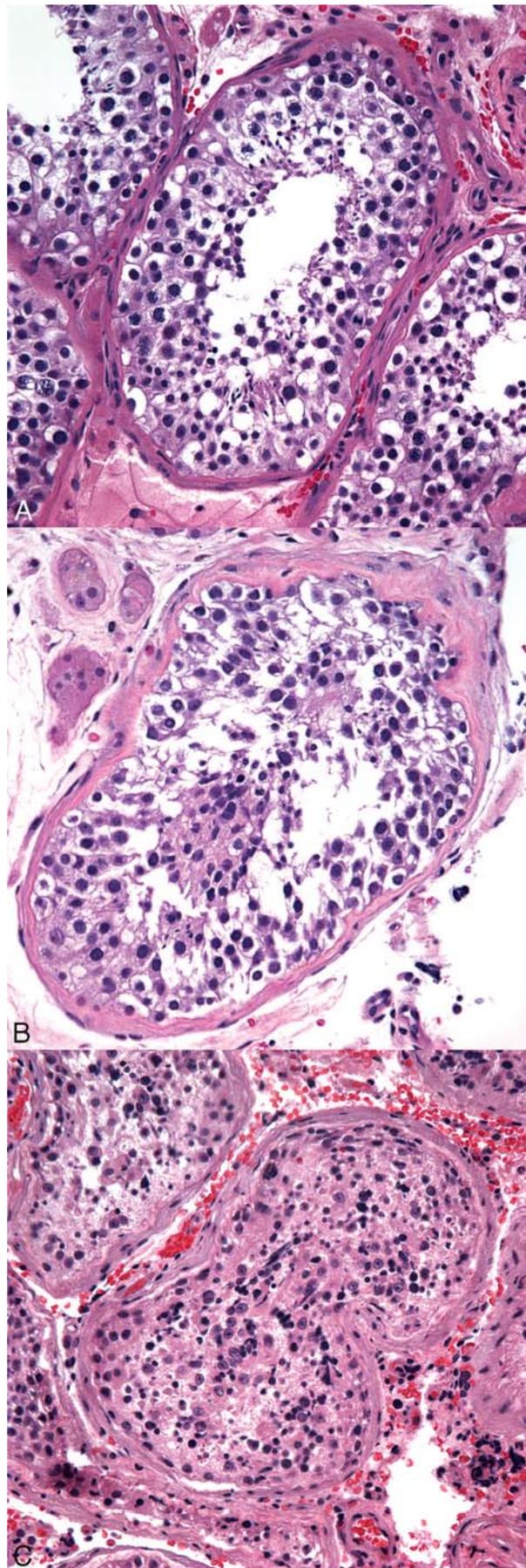
the lobules of a testicle to look for isolated islands of sperm production that can be used for in vitro fertilization/intracytoplasmic sperm injection. A properly interpreted diagnostic testicular biopsy is critical because it helps with preoperative counseling. Based on the histopathology, patients can be educated about chances of successful sperm retrieval with microdissection testicular sperm extraction.

The value of testicular biopsy is diminished as a result of lack of familiarity with the reporting of such specimens by pathologists. This article outlines a clear and systematic approach to testicular biopsy and attempts to familiarize the pathologist with uniform reporting terminology that is clinically useful.

#### INDICATIONS FOR TESTICULAR BIOPSY

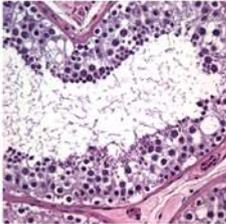
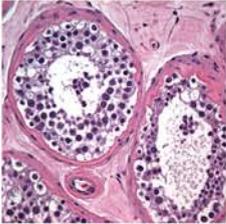
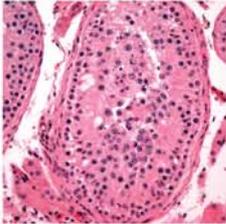
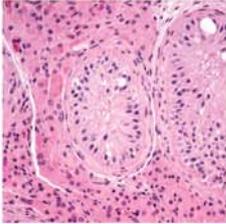
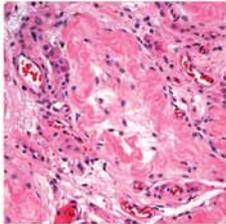
Testicular biopsy is generally reserved for men with azoospermia, or absence of sperm from the ejaculate, a finding identified in about 5% to 10% of men evaluated for infertility and diagnosed when 2 sequential sperm counts yield less than 20 million sperm per milliliter of seminal fluid. It is not the only cause of male infertility; it may be related to numerous other factors, including defects in sperm motility, function, or karyotype. Instead, it represents the final outcome of a variety of testiculopathies, ranging from normal spermatogenesis with seminal tract obstruction or absence of vas deferens (obstructive azoospermia) to a variety of problems with the spermatogenic process itself (nonobstructive azoospermia). Evaluation of men with azoospermia incorporates with semen analyses a complete history and physical exam, genetic studies, and a hormonal profile. Unfortunately, these tests are not always conclusive. Consequently, a testicular biopsy, when properly interpreted, can be the cornerstone upon which a male fertility specialist can formulate a treatment plan for these men.

The indications for testicular biopsy have expanded during the last several decades. Previously azoospermic men with serum follicle-stimulating hormone concentrations greater than 2 to 3 times normal were designated as having severe testicular failure not amenable to conventional therapy, and a diagnostic testicular biopsy was considered unnecessary. However, beginning in the mid 1990s, intracytoplasmic sperm injection using sperm harvested through testicular microdissection has become a viable treatment option for many of these individuals. This technique is unique from conventional in vitro fertilization in that it requires only a single, viable spermatozoon per oocyte. Therefore, many men who previously were not in vitro fertilization candidates are now eligible for testicular biopsy. Still, the pivotal role of the biopsy remains that of differentiating azoospermia

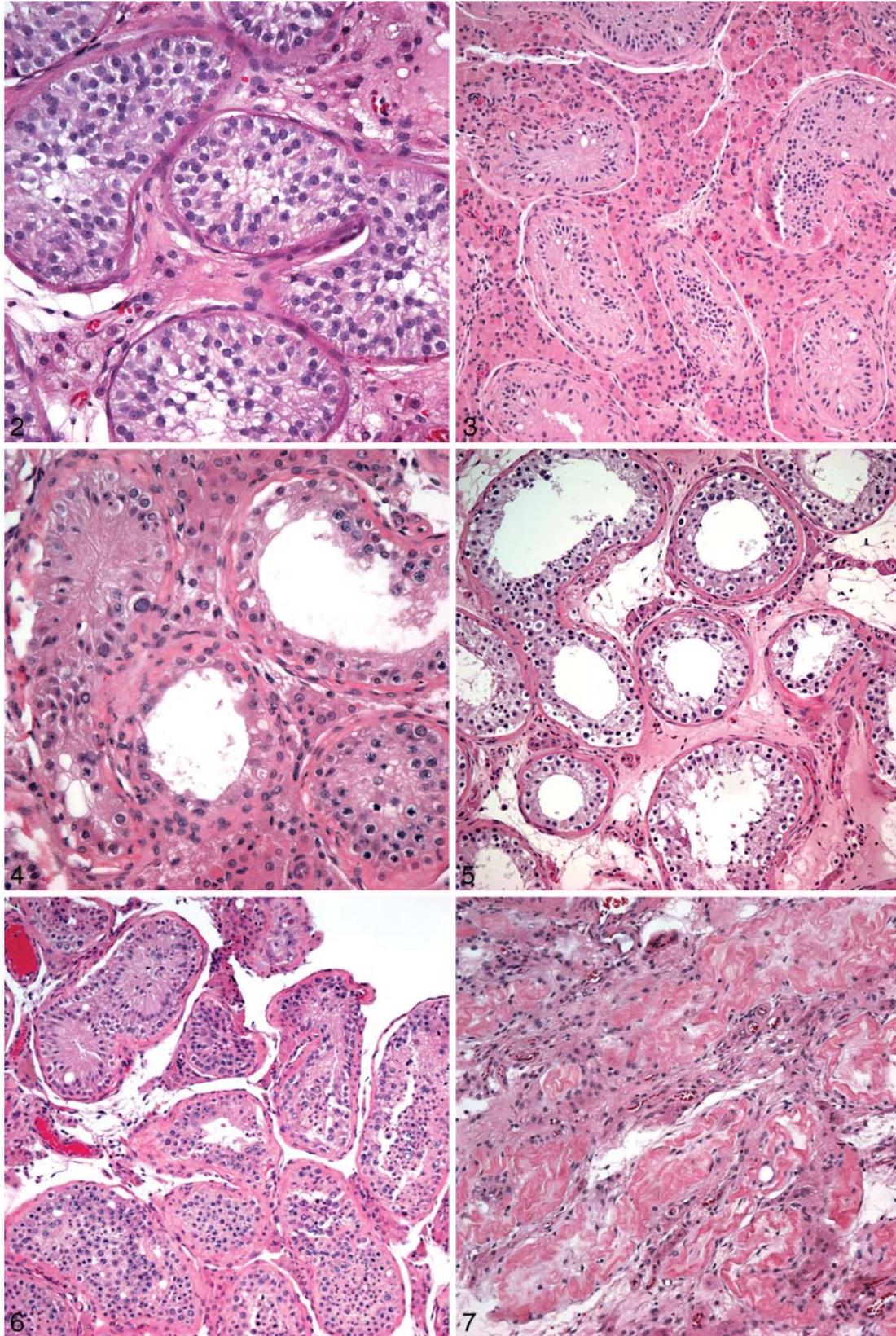


**Figure 1.** Tissue-handling artifacts in normal spermatogenesis. A, Tissue fixed in Bouin solution shows minimal artifact and is amenable to interpretation. B, Formalin-fixed tissue results in marked shrinkage artifact and poor cellular morphology with luminal sloughing of cells. C, Seminiferous tubules with crush artifact acquired during specimen handling yields irregular tubular outlines, obliteration of the lumen, and obscured cytology with angular, hyperchromatic nuclei shrouding mature spermatids (hematoxylin-eosin, original magnification  $\times 400$  [A, B, and C]).

**Table 1. Classification of human spermatogenesis**

Diagnostic Classification	Histology (H&E, ×400)	Histologic Findings	Clinical Implications
Normal testicular biopsy		Complete spermatogenesis in the entire biopsy and the presence of normal inter-tubular tissue.	Usually associated with posttesticular causes of azoospermia and carries an excellent reproductive prognosis.
Hypospermatogenesis		All stages of spermatogenesis present but reduced to a varying degree. This includes the mixed pattern with some tubules showing Sertoli cells only or hyaline sclerosis with other tubules containing complete spermatogenesis.	In a series of 39 patients with hypospermatogenesis on testicular biopsy, MicroTESE was successful in retrieving sperm in 79% of these men. <sup>8</sup>
Maturation arrest		Complete arrest at a particular stage, most often at the spermatogonial or primary spermatocyte stage. If rare spermatids are present focally, the lesion is best classified as severe hypospermatogenesis, rather than arrest.	In a series of 61 patients with maturation-arrest on testicular biopsy, testicular exploration can successfully identify sperm in these men. For men with pure early MA (maturation up to the level of the primary spermatocyte), the retrieval rate was 14.3%. For men with late MA (maturation from the secondary spermatocyte to immature spermatids), the retrieval rate was 46.1%. The retrieval rate for men with a mixed pattern (early and late MA or SCO with MA), the retrieval rates ranged from 26.7% to 47.5%. <sup>9,10</sup>
SCO		Tubules contain only Sertoli cells, and there is complete absence of germ cells.	In a series of 373 patients with SCO on testicular biopsy, MicroTESE was successful in retrieving sperm in 45% of these men. Pregnancy rates with IVF/ICSI were approximately 50%. <sup>11</sup>
Seminiferous tubule hyalinization		Thickening of the peritubular membranes due to fibrosis and basement membrane-like material, with absence of intratubular germ cells and Sertoli cells.	The reproductive prognosis of patients with uniform seminiferous tubule hyalinization is very poor.

Abbreviations: H&E, hematoxylin-eosin; IVF/ICSI, in vitro fertilization/intracytoplasmic sperm injection; MA, maturation arrest; MicroTESE, microdissection testicular sperm extraction; SCO, Sertoli-cell-only.



**Figure 2.** Immature testis. The immature tubules contain juvenile Sertoli cells that have smaller, haphazardly distributed nucleoli. Spermatogonia are not prominent, and no germ cell maturation is observed. Only scattered Leydig cells are present in the interstitium (hematoxylin-eosin, original magnification  $\times 200$ ).

due to ductal obstruction from ablative testicular pathology. Biopsy is not warranted for cases in which the cause of azoospermia can be elucidated on clinical grounds, such as Klinefelter syndrome or prepubertal gonadotropin insufficiency.

A small yet distinct subset of men with nonobstructive azoospermia demonstrate uniform maturation with normal testicular volume and normal follicle-stimulating hormone levels. These patients form a clinically definable group with nonobstructive azoospermia that have different treatment outcomes. They have a higher incidence of chromosomal abnormalities and Y chromosome microdeletions compared with other men with nonobstructive azoospermia. Despite having normal follicle-stimulating hormone level and typically normal testicular volume, sperm retrieval may be difficult and the chance of successful pregnancy is limited.<sup>3</sup>

### SPECIMEN HANDLING AND ARTIFACTS

Ideally, a 3 × 3 × 3-mm aggregate of tissue is recommended for processing. The surgeon should drop the tissue directly from the scissors into a fixative receptacle, thereby avoiding tissue compression. A fixative such as Bouin or acetic acid–zinc formalin rather than plain buffered formalin is recommended because the latter results in shrinkage artifact and luminal sloughing of cells, obscuring the cell lineages under evaluation (Figure 1, A through C). At least 5 sections of the tissue, at 4 to 5 μm, should be stained with hematoxylin-eosin or the periodic acid–Schiff reaction to be used for evaluation. Bilateral biopsies may prove useful because approximately a quarter of biopsies show variations in histologic pattern between testes.<sup>4</sup>

### NORMAL GERM CELL DEVELOPMENT AND HISTOLOGY

The active component of the each testis consists of several hundred seminiferous tubules measuring up to 70 cm in length. It is within these tubules that the process of spermatogenesis occurs, and in the normal testis, all stages of differentiation are present simultaneously. Because all stages of spermatogenesis do occur simultaneously, normal spermatogenesis does not yield mature spermatids in every tubular cross section in a testicular biopsy. Various more immature stages are normally

appreciated and should not be misinterpreted as a maturation abnormality.

Defining the outline of the tubule is a fine basement membrane surrounded by collagen and elastin fibers. Outside the tubules lies the interstitial tissue occupied by fibroblasts, mast cells, macrophages, nerves, and lymphatic vessels. During puberty, Leydig cells, which secrete testosterone, mature within this space. The Leydig cells are found singly or in small clusters and are easily recognized by their prominent granular eosinophilic cytoplasm. They may normally contain small lipid droplets, lipofuscin pigment, or eosinophilic rodlike inclusions in the cytoplasm, termed Reinke crystals.

The Sertoli cell, an intratubular elongated pyramidal cell with its base adherent to the tubular basal lamina, functions to support spermatogenesis. The cellular outlines of Sertoli cells appear poorly delimited, a feature related ultrastructurally to their numerous lateral processes that envelop the spermatogenic cells. The nucleus of a mature Sertoli cell contains a prominent centrally located nucleolus, a useful feature for quickly differentiating them from germ cells. In pathologic states, Sertoli cells may assume a more immature (prepubertal) appearance with a less prominent nucleolus.

The pathologist must be able to recognize the individual germ cell types, which proceed through spermatogenesis in an orderly fashion. The process begins with the spermatogonium, which resides next to the basal lamina of the seminiferous tubules. It is a relatively small cell (approximately 12 μm) with pale-staining nuclear chromatin. At sexual maturity, the spermatogonium divides and either develops into a type A spermatogonia, remaining an undifferentiated stem cell, or differentiates through mitotic cycles into a type B spermatogonia. This latter cell gives rise to the primary spermatocyte, which quickly undergoes its first meiotic division and passes through 4 prophase stages, leptotene, zygotene, pachytene, and diplotene, before undergoing meiotic metaphase. The 4 prophase stages require approximately 3 weeks; thus, numerous primary spermatocytes are present in the cross sections of tubules in a typical biopsy. The primary spermatocyte is the largest of the germ cells in the tubule, and the various stages are distinguished based on the degree of chromosome coiling.

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**Figure 3.** Sertoli-cell-only syndrome. The tubules have a reduced diameter, no germ cells, and large mature Sertoli cells. There is a prominence of Leydig cells in the interstitium in this biopsy from an adult patient with Klinefelter syndrome, although this is not a specific finding (hematoxylin-eosin, original magnification ×100).

**Figure 4.** Maturation arrest. Sections show a variation in tubular and luminal diameter. Note the absence of mature spermatids, while primary spermatocytes continue to be prominent (hematoxylin-eosin, original magnification ×400).

**Figure 5.** Hypospermatogenesis. Sections show variably reduced tubular and luminal diameters and an overall reduction in germ cell elements but all can be identified, including rare mature spermatids. High-power examination may be necessary to note the presence of mature spermatids, the nuclei of which appear dark and angulated. These findings are commonly seen in conjunction with sclerotic tubules and/or tubules containing only Sertoli cells (hematoxylin-eosin, original magnification ×200).

**Figure 6.** Focal Sertoli cell prominent tubule in normal background. Sections show a Sertoli-cell-only tubule (upper right) in a background of otherwise normal spermatogenesis, consider a mixed pattern of hypospermatogenesis. Such a biopsy should be categorized as hypospermatogenesis, but comments should also be made concerning the appearance of tubules with Sertoli cells only and an approximate percentage supplied (hematoxylin-eosin, original magnification ×200).

**Figure 7.** Atrophy and fibrosis. The atrophic tubules have a thickened, convoluted basement membrane with a hyalinized appearance surrounding a lumen largely obliterated by fibrous tissue. This is the end stage of a large number of processes causing tubular injury (hematoxylin-eosin, original magnification ×200).

**Table 2. Etiologies of the Sertoli-Cell-Only Syndrome**

Idiopathic (most cases)
Klinefelter syndrome (47,XXY)
Exposure to chemicals/toxins
Hormonal therapy for prostate cancer
Viral orchitis
Radiation
Congenital (microdeletions of the Y chromosome)

After the meiotic division, a smaller secondary spermatocyte is formed. These cells are occasionally visible but typically far fewer in number due to the short time interval of this stage. They quickly undergo a second meiotic division resulting in spermatids, which are only 7 to 8  $\mu\text{m}$  in size. Spermatids are recognizable not only by their smaller size but also by their dark, condensed chromatin and juxtaluminal position within the tubule. Further differentiation including development of a flagellum, continued loss of cytoplasm, and nuclear elongation result in the formation of a mature spermatozoon, the final end product released into the lumen.<sup>5</sup>

### GERM CELL ABNORMALITIES

The current European Association of Urology recommendations for the reporting of a testicular biopsy include (1) absence of seminiferous tubules (seminiferous tubule hyalinization), (2) presence of Sertoli cells only (Sertoli-cell-only syndrome), (3) maturation arrest—incomplete spermatogenesis, not beyond the spermatocyte stage, and (4) hypospermatogenesis—all cell types up to spermatozoa are present, but there is a distinct decline in the number of reproducing spermatogonia. The etiology of most of these patterns cannot be determined from histology alone because they each reflect a common manifestation of separate disorders that may be more or less clear from clinical findings. This classification is summarized in Table 1.

### SERTOLI-CELL-ONLY SYNDROME

Sertoli-cell-only syndrome (also referred to as germ cell aplasia) applies to a testicle in which germ cells at any stage of maturation are absent, but the tubular architecture is not effaced by fibrosis and supporting cells continue to be present. The picture superficially resembles the prepubertal testis (Figure 2). The etiology is unknown in most cases (Table 2). To optimize its clinical value, the term Sertoli-cell-only syndrome should strictly be applied to the pattern wherein no germ cells are seen in any tubular profile (Figure 3). In most cases, the tunica propria and tubular basement membranes do not show significant hyalinization, and the tubules are normal or only minimally decreased in diameter. The interstitium contains variable numbers of Leydig cells.

### MATURATION ARREST

This term (alternatively termed germ cell arrest or spermatogenic arrest) should be applied when there is complete interruption of spermatogenesis uniformly in all tubules (Figure 4). The arrest is most frequently observed at primary spermatocyte level but can occur at earlier or later levels. There should be homogenous spermatocyte maturation arrest in all the tubules obtained in the biopsy. This is relatively rare in biopsied tissue, so some apply a less strict definition and refer to cases with focal spermatid

**Table 3. Etiologies of Hypospermatogenesis**

Hyperprolactinemia	Cirrhosis
Diabetes mellitus	Alcohol abuse
Undescended testes	Cyclophosphamide
Varicocele	Methotrexate
Infectious orchitis	Pesticide toxicity
Irradiation	

maturation as “incomplete” maturation. These cases, however, are best classified as hypospermatogenesis with a heterogeneous pattern, a topic detailed in a subsequent section.

Spermatogenic arrest can occur at spermatogonial level in case of gonadotropin insufficiency or after germ cell damage due to chemotherapy or radiotherapy. Impairment of chromosome pairing during meiosis is the usual etiologic factor underlying maturation arrest at the spermatocyte stage.<sup>6</sup> Reversible arrest at the primary spermatocyte level can be due to heat, infections, or hormonal and nutritional factors, while irreversible arrest at the primary spermatocyte or spermatid level is most often related to chromosomes anomalies either in somatic cells or in germ cells with subsequent impairment of meiosis.<sup>7,8</sup>

### HYOSPERMATOGENESIS

The finding of a mature spermatid in any tubule profile indicates completion of spermatogenesis and is a defining component of hypospermatogenesis, a disorder in which full maturation occurs, but the total number of germ cells is decreased. The pattern can be uniform across tubules (Figure 5), but more often there is variability between tubules including some with extensive sclerosis or a Sertoli-cell-only pattern (Figure 6). It is important to remember that spermatogenesis does not appear complete in every tubular cross section in a biopsy even in a completely normal testis. Other clues to hypospermatogenesis include an increased number of small-caliber tubules, and, due to the associated disruptions in the architecture of germ cell maturation, earlier stages of germ cell development may be shed into the lumen.

A wide number of causes induce the nonspecific change of irregular hypospermatogenesis, including diabetes mellitus and the presence of a varicocele. Additional etiologies are outlined in Table 3.

### SEMINIFEROUS TUBULE HYALINIZATION

Also known as the “end-stage testis” or “tubular sclerosis,” these biopsies are characterized by extensive intratubular and peritubular hyalinization with an absence of germ cells. Normal tubules are not prominent. This pattern is distinct from the mixed patterns described later by its more extensive hyalinization, which includes all tubules within the biopsy. Sertoli cells are commonly absent as well, although Leydig cells may persist in the tubular interstitium (Figure 7). In testis brought to biopsy, these findings may be the result of ischemia or remote infection, although in many cases an underlying cause cannot be determined. The pattern may also be seen in adults with Klinefelter syndrome, although these patients do not commonly undergo biopsy. The outlook for patient fertility with extensive tubular sclerosis is poor.

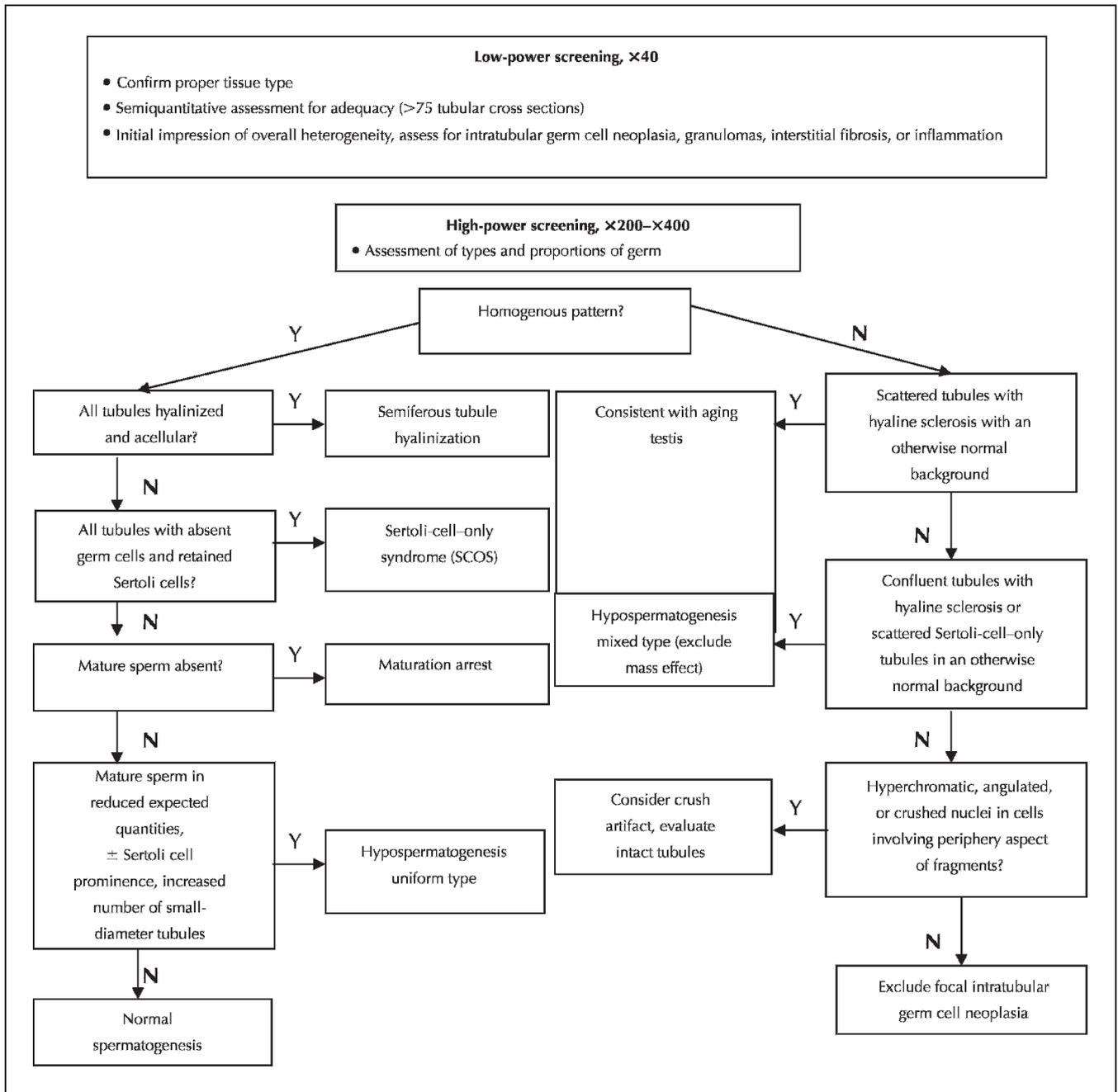


Figure 8. Diagnostic algorithm for testicular biopsy interpretation for infertility.

### MIXED PATTERNS

It is more common to see mixed patterns of testicular pathology than pure examples. Commonly included are Sertoli-cell-only syndrome or hyalinized tubules in a background of seminiferous tubules showing normal or decreased maturation. As previously noted, these findings should be categorized as hypospermatogenesis with a percentage estimate given for each component. A heterogeneous pattern precludes the diagnosis of maturation arrest, which is uniform across all tubules. A mixed pattern of hyalinized and Sertoli-cell-only tubules with some tubules consisting of immature or prepubertal Sertoli cells has been proposed as a characteristic of

Klinefelter syndrome, but similar patterns can be seen in germ cell aplasia or varicocele, so the diagnosis of Klinefelter syndrome should not be made on the basis of testicular biopsy.

A decline in testicular function occurs normally with the aging process, matched by involutional changes in the testicular parenchyma, including hypospermatogenesis, peritubular fibrosis, and hyalinization of tubules commonly resulting in a pattern resembling that of mixed primary testicular pathology. Although a few sclerosed tubules may still be compatible with a normal aging testis, larger or contiguous areas of sclerosis are distinctly pathologic. Abnormal sperm maturation, sloughing of germ cells in the tubular lumen, degeneration of germ cell

elements, and Sertoli cell lipid accumulation and cytoplasmic vacuolization are frequent.

### SYSTEMATIC APPROACH TO TESTICULAR BIOPSY INTERPRETATION

Initially, the low-power impression should yield the degree of uniformity of the histologic features (Figure 8). If heterogeneity is found, an estimate of the proportion of tissue with a certain pattern can be given. At this power it is possible to confirm whether the testis appears immature or mature, a feature that may be commented on. Tubular diameter should also be examined, although it is rarely necessary to measure. A decrease in tubular diameter is associated with damage to the tubular epithelium, which may be further evaluated at higher power.<sup>5</sup> Low-power examination is also useful to assess for the presence or absence of interstitial edema, fibrosis, granulomas, or inflammation, which may be associated with secondary injury to the testis from varicocele or orchitis. Tubules should also be evaluated for the presence of intratubular dysplasia as a matter of course. Lastly, the intertubular tissue should be examined at high magnification for the presence or accumulation of Leydig cells.

Higher power examination provides an assessment of the types and proportions of germ cells in the tubules. Evaluation for maturation arrest requires evaluating whether spermatogenesis proceeds to full spermatid differentiation across the tubules. It is most useful to work backward, evaluating for the presence of elongated spermatids across tubules. If they are absent, then working backward through spermatocytes to spermatogonia should allow one to note at which level differentiation appears to arrest. Germ cell arrest should only be diagnosed if there is no maturation beyond an immature stage in all tubules present within the biopsy. If there is lack of differentiation in some but not all tubules, the quantity of mature forms should be noted and a comment reflecting the heterogeneous pattern should be made along with an interpretation of hypospermatogenesis. A prominence of Sertoli cells, with a relative overall decrease in germ cell quantity, is often seen with hypospermatogenesis as well and is the primary diagnostic feature when the disorder is uniform. When the disorder is heterogeneous, a mixed pattern of tubules in which full maturation occurs, along with adjacent tubules containing only Sertoli cells or hyaline sclerosis, can be a clue to diagnosis.

The term Sertoli-cell-only syndrome should be reserved for those cases in which all the tubules in the biopsy show absence of germ cells; if some tubules contain only Sertoli cells but other tubules contain advanced spermatids, the overall diagnosis is hypospermatogenesis with a mixed pattern. If the tubular basement membranes are thickened and wrinkled, along with absent germ cell development and shrunken lumens, the diagnosis of tubular hyalinization is obvious.

Important elements to comment on include the severity of the testicular abnormality, if present, and whether the finding is homogeneous or heterogeneous, such as "mild to moderate hypospermatogenesis with a heterogeneous reduction in mature spermatids identified; mature spermatids focally identified." The clinical interpretation of this example clearly implies that harvesting sperm for intracytoplasmic sperm injection has a high likelihood of success. A diagnosis of "maturation arrest identified, with only primary spermatocytes present in all tubular profiles" implies a far less favorable outlook for spermatid recovery. Exact recovery rates for this latter condition are highly disparate due to variation in the application of the term maturation arrest, with many cases including those with a mixed phenotype (ie, some tubules with arrest and others with mature sperm).

### CONCLUSION

Testicular biopsy is usually an office-based procedure involving removal of a small piece of tissue from the testis while the man is under light anesthesia (conscious sedation). The tissue is assessed microscopically to determine the presence of sperm and whether the sperm production process is normal. An accurate biopsy interpretation is critical in determining both reproductive prognosis and therapeutic considerations for men with azoospermia. The use of standardized nomenclature for diagnosis as outlined herein enhances the clinical benefit of the testicular biopsy.

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