

## **Male Infertility**

Infertility is defined as the inability to conceive after 1 year of unprotected sexual intercourse. Infertility affects approximately 15% of couples. Roughly 40% of cases involve a male contribution or factor, 40% involve a female factor, and the remainder involve both sexes.

### **DIAGNOSIS OF MALE INFERTILITY**

#### **HISTORY**

It should note the duration of infertility, earlier pregnancies with present or past partners, and whether there was previous difficulty with conception.

A sexual history should be addressed. Most men (80%) do not know how to precisely time intercourse to achieve a pregnancy. Since sperm reside within the cervical mucus and crypts for 1–2 days, an appropriate frequency of intercourse is every 2 days. Lubricants can influence sperm motility and should be avoided. If needed, acceptable lubricants include vegetable, safflower, and peanut oils.

A general medical and surgical history is also important. Any generalized insult such as a fever, viremia, or other acute infection can decrease testis function and semen quality. The effects of such insults are not noted in the semen until 2 months after the event, because spermatogenesis requires at least 60 days to complete. Surgical procedures on the bladder, retroperitoneum, or pelvis can also lead to infertility, by causing either retrograde ejaculation of sperm into the bladder or anejaculation (aspermia), in which the muscular function within the entire repro-

ductive tract is inhibited. Hernia surgery can also result in vas deferens obstruction in 1% of cases; this incidence may be rising because of the recent increased use of highly inflammatory mesh patches.

Childhood diseases may also affect fertility. A history of mumps can be significant if it occurs postpubertally. After age 11, unilateral orchitis occurs in 30% of mumps infections and bilateral orchitis in 10%. Mumps orchitis is thought to cause pressure necrosis of testis tissue from viral edema. Marked testis atrophy is usually obvious later in life. Cryptorchidism is also associated with decreased sperm production. This is true for both unilateral and bilateral cases. Longitudinal studies of affected boys have shown that abnormally low sperm counts can be found in 30% of men with unilateral cryptorchidism and 50% of men with bilateral undescended testes.

Differences in fertility have not been as easy to demonstrate, but it appears that boys with unilateral cryptorchidism have a slightly higher risk of infertility. However, only 50% of men with a history of bilateral undescended testes are fertile. It is important to remember that orchidopexy performed for this problem does not improve semen quality later in life.

Exposure and medication histories are very relevant to fertility. Decreased sperm counts have been demonstrated in workers exposed to specific pesticides, which may alter normal testosterone/estrogen hormonal balance. Ionizing radiation is also a well-described exposure risk, with temporary reductions in sperm production seen at doses as low as 10 cGy. Several medications and ingestants such as tobacco, cocaine, and marijuana have all been implicated as gonadotoxins. The effects of these agents are usually reversible on withdrawal. Androgenic steroids, often taken by bodybuilders to increase muscle mass and development, act as contraceptives with respect to fertility. Excess testosterone inhibits the pituitary-gonadal

hormone axis. The routine use of hot tubs or saunas should be discouraged, as these activities can elevate intratesticular temperature and impair sperm production.

The family and developmental histories may also provide clues about infertility. A family history of cystic fibrosis (CF), a condition associated with congenital absence of the vas deferens (CAVD), or intersex conditions is important. The existence of siblings with fertility problems may suggest that a Y chromosome microdeletion or a cytogenetic (karyotype) abnormality is present in the family. A history of delayed onset of puberty could suggest Kallmann or Klinefelter syndrome. A history of recurrent respiratory tract infections may suggest a ciliary defect characteristic of the immotile cilia syndromes. It is important to remember that reproductive technologies enable most men afflicted with such conditions to become fathers and therefore allow for the perpetuation of genetic abnormalities that may not be normally sustained.

### *Components of the Infertility History.*

#### **Medical history**

Fevers

Systemic illness—diabetes, cancer, infection

Genetic diseases—cystic fibrosis, Klinefelter syndrome

#### **Surgical history**

Orchidopexy, cryptorchidism Herniorraphy

Trauma, torsion

Pelvic, bladder, or retroperitoneal surgery

Transurethral resection for prostatism

Pubertal onset

### **Fertility history**

Previous pregnancies (present and with other partners)

Duration of infertility

Previous infertility treatments Female evaluation

### **Sexual history**

Erections

Timing and frequency

Lubricants

### **Family history**

Cryptorchidism

Midline defects (Kartagener syndrome)

Hypospadias

Exposure to diethylstilbestrol

Other rare syndromes—prune belly, etc.

### **Medication history**

Nitrofurantoin Cimetidine Sulfasalazine Spironolactone Alpha blockers

### **Social history**

Ethanol Smoking/tobacco Cocaine

Anabolic steroids

### **Occupational history**

Exposure to ionizing radiation

Chronic heat exposure (saunas)

Aniline dyes

Pesticides

Heavy metals (lead)

### **Medications Associated with Impaired Ejaculation.**

Antihypertensive agents

Alpha-adrenergic blockers (Prazosin, Phentolamine)

Thiazides

Antipsychotic agents

Mellaril (thioridazine)

Haldol (haloperidol)

Librium

Antidepressants

Imipramine

Amitriptyline

## PHYSICAL EXAMINATION

A complete examination of the infertile male is important to identify general health issues associated with infertility. For example, the patient should be adequately virilized; signs of decreased body hair or gynecomastia may suggest androgen deficiency.

The scrotal contents should be carefully palpated with the patient standing. As it is often psychologically uncomfortable for young men to be examined, one helpful hint is to make the examination as efficient and matter of fact as possible. Two features should be noted about the testis: size and consistency. Size is assessed by measuring the long axis and width; as an alternative, an orchidometer can be placed next to the testis for volume determination.

Standard values of testis size have been reported for normal men and include a mean testis length of 4.6 cm (range 3.6–5.5 cm), a mean width of 2.6 cm (range 2.1–3.2 cm), and a mean volume of 18.6 mL ( $\pm$  4.6 mL). Consistency is more difficult to assess but can be described as firm (normal) or soft (abnormal). A smaller or softer than normal testis usually indicates impaired spermatogenesis.

The peritesticular area should also be examined. Irregularities of the epididymis, located posterior-lateral to the testis, include induration, tenderness, or cysts. The presence or absence of the scrotal vas deferens is critical to observe, as 2% of infertile men may present with CAVD.

Engorgement of the pampiniform plexus of veins in the scrotum is indicative of a varicocele. Asymmetry of the spermatic cords is the usual initial observation, followed by the feeling of a “bag of worms” when retrograde blood flow through the pampiniform veins occurs with a Valsalva maneuver. Varicoceles are usually found on the left side (90%) and are commonly associated with atrophy of the left testis. A discrepancy in testis size between the right and left sides should alert the clinician to this possibility.

Prostate or penile abnormalities should also be noted. Penile abnormalities such as hypospadias, abnormal curvature, or phimosis could result in inadequate delivery of semen to the upper vaginal vault during intercourse. Prostatic infection may be detected by the finding of a boggy, tender prostate on rectal examination. Prostate cancer, often suspected with unusual firmness or a nodule within the prostate, can occasionally be diagnosed in infertile men. Enlarged seminal vesicles, indicative of ejaculatory duct obstruction, may also be palpable on rectal examination.

## LABORATORY

## *Urinalysis*

A urinalysis is a simple test that can be performed during the initial office visit. It may indicate the presence of infection, hematuria, glucosuria, or renal disease, and as such may suggest anatomic or medical problems within the urinary tract.

## *Semen Analysis*

An abnormal semen analysis simply suggests the likelihood of decreased fertility. Studies have established that there are certain limits of adequacy below which it may be difficult to initiate a pregnancy. These semen analysis values were identified by the World Health Organization (1999) and are considered the minimum criteria for “normal” semen quality. It is statistically more difficult to achieve a pregnancy if a semen parameter falls below any of those listed. Of these semen variables, the count and motility appear to correlate best with fertility.

### A. SEMEN COLLECTION

Semen quality can vary widely in a normal individual from day to day, and semen analysis results are dependent on collection technique. For example, the period of sexual abstinence before sample collection is a large source of variability. With each day of abstinence (up to 1 week), semen volume can rise by up to 0.4 mL, and sperm concentration can increase by 10–15 million/mL. Sperm motility tends to fall when the abstinence period is longer than 5 days. For this reason, it is recommended that semen be collected after 48–72 hours of sexual abstinence.

To establish a baseline of semen quality, at least 2 semen samples are needed. Semen should be collected by self-stimulation, by coitus interruptus (less ideal), or with a special, nonspermicidal condom into a clean glass or plastic container. Because sperm motility decreases after



ejaculation, the specimen should be analyzed within 1 hour of procurement. During transit, the specimen should be kept at body temperature.

## B. PHYSICAL CHARACTERISTICS AND MEASURED VARIABLES

Fresh semen is a coagulum that liquefies 15–30 minutes after ejaculation. Ejaculate volume should be at least 1.5 mL, as smaller volumes may not sufficiently buffer against vaginal acidity. Low ejaculate volume may indicate retrograde ejaculation, ejaculatory duct obstruction, incomplete collection, or androgen deficiency. Sperm concentration should be >20 million sperm/mL. Sperm motility is assessed in 2 ways: the fraction of sperm that are moving and the quality of sperm movement (how fast, how straight they swim).

Sperm cytology or morphology is another measure of semen quality. By assessing the exact dimensions and shape characteristics of the sperm head, midpiece, and tail, sperm can be classified as “normal” or not. In the strictest classification system (Kruger morphology), only 14% of sperm in the ejaculate are normal looking. In fact, this number correlates with the success of egg fertilization in vitro and thus is ascribed real clinical significance. In addition, sperm morphology is a sensitive indicator of overall testicular health, because these characteristics are determined during spermatogenesis. The role of sperm morphology in the male infertility evaluation is to complement other information and to better estimate the chances of fertility.

### **Semen Analysis—Minimal Standards of Adequacy.**

Ejaculate volume      1.5–5.5 mL

Sperm concentration   >20 x 10<sup>6</sup> sperm/mL

Motility                      >50%

Forward progression   2 (scale 1–4)

Morphology               >30% WHO normal forms (>4% Kruger normal forms)

### **C.COMPUTER-ASSISTED SEMEN ANALYSIS**

In an effort to remove the subjective variables inherent in the manually performed semen analysis, computer-aided semen analyses (CASA) couple video technology with digitalization and microchip processing to categorize sperm features by algorithms. Although the technology is promising, when manual semen analyses are compared to CASA on identical specimens, CASA can overestimate sperm counts by 30% with high levels of contaminating cells such as immature sperm or leukocytes. In addition, at high sperm concentrations, motility can be underestimated with CASA. CASA has accepted value in the research setting and in some clinical laboratories.

### **D.SEMINAL FRUCTOSE AND POSTEJACULATE URINALYSIS**

Fructose is a carbohydrate derived from the seminal vesicles and is normally present in the ejaculate. If absent, the condition of seminal vesicle agenesis or obstruction may exist. Seminal fructose testing is indicated in men with low ejaculate volumes and no sperm. A postejaculate urinalysis is the microscopic inspection of the first voided urine after ejaculation for sperm. The presence of sperm in the urine is diagnostic of retrograde ejaculation. This test is indicated in diabetic patients with low semen volume and sperm counts; patients with a history of pelvic, bladder, or retroperitoneal surgery; and patients receiving medical therapy for prostatic enlargement. In general, the semen analyses of infertile men have patterns that may suggest a diagnosis .

#### *Hormone Assessment*

An evaluation of the pituitary-gonadal axis can provide valuable information on the state of sperm production. In turn, it can reveal problems with the pituitary axis that can cause infertility (hyperprolactinemia, gonadotropin deficiency, congenital adrenal hyperplasia). FSH and testosterone should be measured in infertile men with sperm densities of  $<10 \times 10^6$  sperm/mL. Testosterone is a measure of overall endocrine balance. FSH reflects more on the state of sperm production rather than endocrine balance. This combination of tests will detect virtually all (99%) endocrine abnormalities. Serum LH and prolactin levels may be obtained if testosterone and FSH are abnormal, to help pinpoint the endocrine defect. Thyroid hormone, liver function, and other organ-specific tests should be obtained if there is clinical evidence of active disease, as uncontrolled systemic illness can affect sperm production.

With relatively normal spermatogenesis, low levels of plasma LH and FSH have no clinical meaning; likewise, an isolated low LH with normal testosterone is not significant. The measurement of plasma estradiol should be reserved for those men who appear

underandrogenized or have gynecomastia in association with low, normal, or elevated testosterone levels.

In addition to low sperm concentration (<10 million/mL), other indications for hormonal evaluation of the infertile male are evidence of impaired sexual function (impotence, low libido) and findings suggestive of a specific endocrinopathy (eg, thyroid). On initial testing, approximately 10% of infertile men with have an abnormal hormone level, with clinically significant endocrinopathies occurring in 2% of men.

## ADJUNCTIVE TESTS

### *Semen Leukocyte Analysis*

White blood cells (leukocytes) are present in all ejaculates and play important roles in immune surveillance and clearance of abnormal sperm. Leukocytospermia or pyospermia, an increase in leukocytes in the ejaculate, is defined as  $>1 \times 10^6$  leukocytes/mL semen and is a significant cause of male subfertility. The prevalence of pyospermia ranges from 2.8% to 23% of infertile men. In general, neutrophils predominate among inflammatory cells. This condition is detected by a variety of diagnostic assays, including differential stains (eg, Papanicolaou), peroxidase stain that detects the peroxidase enzyme in neutrophils, and immunocytology.

### *Antisperm Antibody Test*

Autoimmune infertility may result when the bloodtestis barrier is broken and the body is exposed to sperm antigens. Trauma to the testis and vasectomy are 2 common ways in which this occurs, giving rise to antisperm antibodies (ASA). ASA may be associated with impaired sperm transport through the reproductive tract or impairment in egg fertilization. An assay for ASA should be obtained when

1. The semen analysis shows sperm agglutination or clumping.
2. Low sperm motility exists with history of testis injury or surgery.
3. There is confirmation that increased round cells are leukocytes.
4. There is unexplained infertility.

### *Sperm Chromatin Structure*

There is now evidence to suggest that the integrity of sperm DNA-chromatin packaging is important for male fertility. The structure of sperm chromatin (the DNA-associated proteins) can be measured by several methods, ASAs can be found in 3 locations: serum, seminal plasma, and sperm-bound. Among these, sperm-bound antibodies are the most relevant. The antibody classes that appear to be clinically relevant include immunoglobulin G (IgG) and IgA. IgG antibody is derived from local production and from transudation from the bloodstream (1%). IgA is thought to be purely locally derived.

### *Hypoosmotic Swelling Test*

The most clinically useful measure of sperm viability is cell motility. However, a lack of motility does not necessarily signify absent viability. Indeed, there are clinical conditions, such as immotile cilia syndrome and extracted testicular sperm, in which there may be immotile but otherwise presumably healthy sperm. Such sperm can now be used clinically for micromanipulation and in vitro fertilization (IVF). Cell viability can be evaluated noninvasively by using the physiologic principle of hypoosmotic swelling. Conceptually, viable cells with functional membranes should swell when placed in a hypoosmotic environment. Since sperm have tails, the swelling response is very obvious in that tail coiling accompanies head swelling. This sperm test is indicated in cases of complete absence of sperm motility.

### *Sperm Penetration Assay*

It is possible to measure the ability of human sperm to penetrate a specially prepared hamster egg in the laboratory setting. The hamster egg allows interspecies fertilization but no further development. This form of bioassay can give important information about the ability of sperm to undergo the capacitation process as well as penetrate and fertilize the egg. Infertile sperm would be expected to penetrate and fertilize a lower fraction of eggs than normal sperm. The indications for the diagnostic sperm penetration assay (SPA) are limited to situations in which functional information about sperm are needed, that is, to further evaluate couples with unexplained infertility and to help couples decide whether intrauterine insemination (IUI) (good SPA result) or IVF and micromanipulation (poor SPA result) is the appropriate next treatment. including the COMET and TUNNEL assays as well as by flow cytometry after acid treatment and staining of

sperm with acridine orange. These tests assess the degree of DNA fragmentation that occurs after chemically stressing the sperm DNA-chromatin complex, and can indirectly reflect the quality of sperm DNA-chromatin complex, and can indirectly reflect the quality of sperm DNA integrity. Abnormally fragmented sperm DNA rarely occurs in fertile men, but can be found in 5% of infertile men with normal semen analyses and 25% of infertile men with abnormal semen analyses. This test can detect infertility that is missed on a conventional semen analysis. Often reversible, causes of DNA fragmentation include tobacco use, medical disease, hyperthermia, air pollution, infections, and varicocele.

### *Chromosomal Studies*

Subtle genetic abnormalities can present as male infertility. It is estimated that between 2% and 15% of infertile men with azoospermia (no sperm count) or severe oligospermia (low sperm counts) will harbor a chromosomal abnormality on either the sex chromosomes or autosomes. A blood test for cytogenetic analysis (karyotype) can determine if such a genetic anomaly is present. Patients at risk for abnormal cytogenetic findings include men with small, atrophic testes, elevated FSH values, and azoospermia. Klinefelter syndrome (XXY) is the most frequently detected sex chromosomal abnormality among infertile men.

### *Cystic Fibrosis Mutation Testing*

A blood test is indicated for infertile men who present with CF or the much more subtle condition, CAVD. Similar genetic mutations are found in both patients, although the latter group is generally considered to have an atypical form of CF, in which the scrotal vas deferens is

nonpalpable. Approximately 80% of men without palpable vasa will harbor a CF gene mutation. Recent data also indicate that azoospermic men with idiopathic obstruction and men with a clinical triad of chronic sinusitis, bronchiectasis, and obstructive azoospermia (Young syndrome) may be at higher risk for CF gene mutations.

### *Y Chromosome Microdeletion Analysis*

As many as 7% of men with oligospermia and 15% of azoospermic men have small, underlying deletions in one or more gene regions on the long arm of the Y chromosome (Yq). Several regions of the Y chromosome have been implicated in spermatogenic failure, identified as AZFa, b, and c. Deletion of the DAZ (deleted in azoospermia) gene in the AZFc region is the most commonly observed microdeletion in infertile men. Fertility is possible in most men with these deletions with IVF and micromanipulation of sperm. A polymerase chain reaction-based blood test can examine the Y chromosome from peripheral leukocytes for these gene deletions and is recommended for men with low or no sperm counts and small, atrophic testes.

### *Radiologic Testing*

#### A. SCROTAL ULTRASOUND

High-frequency (7.5–10 mHz) ultrasound of the scrotum has become a mainstay in the evaluation of testicular and scrotal lesions. Scrotal ultrasound is indicated in men who have a hydrocele within the tunica vaginalis space, such that the testis is nonpalpable, to confirm that it



is normal. Any abnormality of the peritesticular region should also undergo a scrotal ultrasound to determine its characteristics or origin.

Recently, scrotal color Doppler ultrasonography has been used to investigate varicoceles. By combining measurements of bloodflow patterns and vein size, both physiologic and anatomic information can be obtained to confirm the diagnosis. Although diagnostic criteria that define a varicocele vary widely, a **pampiniform venous diameter of >3 mm is considered abnormal**. Retrograde blood flow through the veins with a Valsalva maneuver is also an important radiologic feature of a varicocele.

#### B. VENOGRAPHY

Venography is accepted as the most accurate way to diagnose varicoceles. Although found by palpation in approximately 30–40% of subfertile men, varicoceles can be detected by venography in 70% of patients. Renal and spermatic venography is fairly invasive and is usually performed through percutaneous cannulization of the internal jugular vein or common femoral vein. Venographically, a varicocele is defined by a Valsalva- induced retrograde flow, of contrast material from the renal vein into the scrotal pampiniform plexus. This test is expensive and technician dependent; at present its main indications are to guide simultaneous percutaneous varicocele embolization or to diagnose recurrent varicoceles after prior treatment.

#### C. TRANSRECTAL ULTRASOUND

High-frequency (5–7) mHz transrectal ultrasound (TRUS) offers superb imaging of the prostate, seminal vesicles, and ejaculatory ducts. Due to both accuracy and convenience, transrectal ultrasound has replaced surgical vasography in the diagnosis of obstructive lesions that cause infertility.

#### D. COMPUTED TOMOGRAPHY SCAN OR MAGNETIC RESONANCE IMAGING OF THE PELVIS

The imaging techniques of computed tomography (CT) and magnetic resonance imaging (MRI) can further define reproductive tract anatomy. However, since the advent of TRUS, these studies have relatively few indications. They include evaluation of a patient with a solitary right varicocele, a condition often associated with retroperitoneal pathology, and evaluation of the nonpalpable testis.

#### *Testis Biopsy & Vasography*

The testis biopsy is a useful adjunct in the infertility evaluation because it provides direct information regarding the state of spermatogenesis. Most commonly, the technique involves a small, open incision in the scrotal wall and testis tunica albuginea under local anesthesia. A small wedge of testis tissue is removed and examined histologically. Abnormalities of seminiferous tubule architecture and cellular composition are then categorized into several patterns. This procedure is most useful in the azoospermic patient, in which it is often difficult to distinguish between a failure of sperm production and obstruction within the reproductive tract ducts. A testis biopsy allows definitive delineation between these 2 conditions and can guide further treatment options in azoospermic men.

In obstructed patients defined by testis biopsy, formal investigation of the reproductive tract is warranted, beginning with a vasogram. A vasogram involves the injection of dye or contrast media into the vas deferens toward the bladder from the scrotum. In plain film radiographs, contrast material can delineate the proximal vas deferens, seminal vesicle, and ejaculatory duct anatomy and determine whether obstruction is present. Sampling of vasal fluid during the same procedure can also determine whether sperm exist within the scrotal vas deferens. Vasal sperm presence implies that there is no obstruction in the testis or epididymis. With this information, the site of obstruction can be accurately determined.

Whether biopsy is indicated for oligospermia is controversial. Rare cases of partial reproductive tract obstruction may exist and be diagnosed by biopsy, but the incidence of these disorders is low. While a unilateral testis biopsy is usually sufficient, the finding of 2 asymmetric testes warrants bilateral testis biopsies. This situation may reflect a unilateral unobstructed failing testis paired with a normal obstructed testis. Testis biopsies may also be indicated to identify patients at high risk for intratubular germ cell neoplasia. This premalignant condition exists in 5% of men with a contralateral germ cell tumor of the testis and is more prevalent in infertile than fertile men.

A relatively new indication for the testis biopsy is to determine whether men with atrophic, failing testes and elevated FSH levels actually have mature sperm that may be used for IVF and intracytoplasmic sperm injection (ICSI). A single testis biopsy can detect the presence of sperm in 30% of men with azoospermia, elevated FSH levels, and atrophic testes. Testicular sperm that are harvested by biopsy are now routinely used to help men with severe malefactor infertility to achieve fatherhood.

### *Fine-Needle Aspiration “Mapping” of Testes*

Although testicular sperm is used with IVF and ICSI to achieve pregnancies, there is a failure to obtain sperm in 25–50% of men with testis failure. When testis biopsies fail to retrieve sperm, IVF cycles are canceled at great emotional and financial cost. To minimize the chance of failed sperm retrieval, percutaneous fine-needle aspiration and “mapping” of the testis has been described. This technique can detect sperm in 60% of men with azoospermia due to testis failure and has confirmed that spermatogenesis can vary geographically in the failing testis.

Like a testis biopsy, fine-needle aspiration is performed under local anesthesia. Percutaneously aspirated seminiferous tubules from various locations in the testis are smeared on a slide, fixed, stained, and read by a cytologist for the presence of sperm. The information gained from this technique can fully inform patients of their chances of subsequent sperm retrieval for IVF and ICSI.

### *Semen Culture*

Seminal fluid that passes through the urethra is routinely contaminated with bacteria. This can make the interpretation of semen culture difficult. Thus, semen cultures should be obtained only in selected situations, given that 83% of all infertile men will have positive semen cultures and that the relationship between bacterial cultures and infertility is at best inconclusive. Semen cultures should be obtained when there are features suggestive of infection, including (1) a

history of genital tract infection, (2) abnormal expressed prostatic secretion, (3) the presence of more than 1000 pathogenic bacteria per milliliter of semen, and (4) the presence of  $>1 \times 10^6$  leukocytes/mL of semen (pyospermia).

## ■ CAUSES OF MALE INFERTILITY

The causes underlying male infertility are numerous but are conveniently grouped by effects at one or more of the following levels: pretesticular, testicular, and posttesticular.

### PRETESTICULAR

Conditions that cause infertility that act at the pretesticular level tend to be hormonal in nature.

#### *Hypothalamic Disease*

##### A. GONADOTROPIN DEFICIENCY

##### (KALLMANN SYNDROME)

Kallmann syndrome is a rare (1:50,000 persons) disorder that occurs in familial and sporadic forms. The X-linked form of the disease is a consequence of a single gene deletion (Xp22.3 region, termed KALIG-1). It may also be autosomally transmitted with sex limitation to males.

In either case, there is a disturbance of neuronal migration from the olfactory placode during

development. This neural region also contains precursors for the LH-releasing cells of the hypothalamus, which explains the 2 most common clinical deficits in the disorder: anosmia and absence of GnRH. Pituitary function is normal. The clinical features include anosmia, facial asymmetry, color blindness, renal anomalies, microphallus, and cryptorchidism. The hallmark of the syndrome is a delay in pubertal development. The differential diagnosis includes delayed puberty. Patients have severely atrophic testes (<2 cm) with biopsies showing germ cell arrest and Leydig cell hypoplasia. Hormone evaluation reveals low testosterone, low LH, and low FSH levels.

Virilization and fertility can be achieved when given FSH and LH are given to stimulate testis function.

#### B. ISOLATED LH DEFICIENCY “FERTILE EUNUCH”

This very rare condition is due to partial gonadotropin deficiency in which there is enough LH produced to stimulate intratesticular testosterone production and spermatogenesis but insufficient testosterone to promote virilization. Affected individuals have eunuchoid body proportions, variable virilization, and often gynecomastia. These men characteristically have normal testis size, but the ejaculate contains reduced numbers of sperm. Plasma FSH levels are normal, but serum LH and testosterone levels are low-normal.

#### C. ISOLATED FSH DEFICIENCY

In this rare condition, there is insufficient FSH production by the pituitary. Patients are normally virilized, as LH is present. Testicular size is normal, and LH and testosterone levels are normal. FSH levels are uniformly low and do not respond to stimulation with GnRH. Sperm counts range from azoospermia to severely low numbers (oligospermia).

#### D. CONGENITAL HYPOGONADOTROPIC SYNDROMES

Several syndromes are associated with secondary hypogonadism. Prader-Willi syndrome (1:20,000 persons) is characterized by genetic obesity, retardation, small hands and feet, and hypogonadism and is caused by a deficiency of hypothalamic GnRH. The single gene deletion associated with this condition is found on chromosome 15.

Similar to Kallmann syndrome, spermatogenesis can be induced with exogenous FSH and LH. Bardet-Biedl syndrome is another autosomal recessive form of hypogonadotropic hypogonadism that results from GnRH deficiency. It is characterized by retardation, retinitis pigmentosa, polydactyly, and hypogonadism. The presentation is similar to Kallmann syndrome except it includes genetic obesity. The hypogonadism can be treated with FSH and LH. Cerebellar ataxia can be associated with hypogonadotropic hypogonadism. This rare condition can result from consanguineous unions. Cerebellar involvement includes abnormalities of speech and gait. These patients can be eunuchoid-looking with atrophic testes. Hypothalamic-pituitary dysfunction due to pathologic changes in cerebral white matter is thought to be the reason for infertility.

### **Pituitary Disease**

#### A. PITUITARY INSUFFICIENCY

Pituitary insufficiency may result from tumors, infarcts, surgery, radiation, or infiltrative and granulomatous processes. In sickle cell anemia, pituitary and testicular microinfarcts from sickling of red blood cells are suspected of causing infertility. Men with sickle cell anemia have decreased testosterone and variable LH and FSH levels. Beta Thalassemia patients have mutations in the betaglobin gene that lead to an imbalance in alpha and beta globin composition of hemoglobin; these patients are mainly of Mediterranean or African origin. Infertility is also believed to result from the deposition of iron in the pituitary gland and testes. Similarly, hemochromatosis results in iron deposition within the liver, testis, and pituitary and is associated with testicular dysfunction in 80% of cases.

#### B. HYPERPROLACTINEMIA

Another form of hypogonadotropic hypogonadism is due to elevated circulating prolactin. If hyperprolactinemia occurs, secondary causes such as stress during the blood draw, systemic diseases, and medications should be ruled out. With these causes excluded, the most common and important cause of hyperprolactinemia is a prolactin-secreting pituitary adenoma. High-resolution CT scanning or MRI of the sella turcica has classically been used to distinguish between microadenoma (<10 mm) and macroadenoma (>10 mm) forms of tumor.

Stratification of disease based on radiologic diagnosis alone is misleading, as surgery for hyperprolactinemia almost always reveals a pituitary tumor. Elevated prolactin usually results in decreased FSH, LH, and testosterone levels and causes infertility. Associated symptoms include loss of libido, impotence, galactorrhea, and gynecomastia. Signs and symptoms of other pituitary hormone derangements (adrenocorticotrophic hormone, thyroid-stimulating hormone) should also be investigated.



## C. EXOGENOUS OR ENDOGENOUS HORMONES

1. Estrogens—An excess of sex steroids, either estrogens or androgens, can cause male infertility due to an imbalance in the testosterone-estrogen ratio. Hepatic cirrhosis increases endogenous estrogens because of augmented aromatase activity within the diseased liver. Likewise, excessive obesity may be associated with testosterone-estrogen imbalance owing to increased peripheral aromatase activity. Less commonly, adrenocortical tumors, Sertoli cell tumors, and interstitial testis tumors may produce estrogens. Excess estrogens mediate infertility by decreasing pituitary gonadotropin secretion and inducing secondary testis failure. Exposure to exogenous estrogens has been implicated as a reason for the controversial finding of decreased sperm concentrations in men over the last 50 years. Supporters of this claim suggest that men are overexposed to estrogenic compounds during fetal life, which results in compromised semen quality later. Postulated sources of exposure include anabolic estrogens in livestock, consumed plant estrogens, and environmental estrogenic chemicals like pesticides. This xenoestrogen exposure theory, however, remains unproved as a cause of impaired fertility.

2. Androgens—An excess of androgens can suppress pituitary gonadotropin secretion and lead to secondary testis failure. The use of exogenous androgenic steroids (anabolic steroids) by as many as 15% of high school athletes, 30% of college athletes, and 70% of professional athletes may result in temporary sterility due to this effect. Initial treatment is to discontinue the steroids and reevaluate semen quality every 3–6 months until spermatogenesis returns. The most common reason for excess endogenous androgens is congenital adrenal hyperplasia, in which the enzyme 21-hydroxylase is most commonly deficient. As a result, there is defective cortisol synthesis and excessive adrenocorticotropic hormone production, leading to abnormally high

production of androgenic steroids by the adrenal cortex. High androgen levels in prepubertal boys results in precocious puberty, with premature development of secondary sex characteristics and abnormal enlargement of the phallus. The testes are characteristically small because of central gonadotropin inhibition by androgens. In young girls, virilization and clitoral enlargement may be obvious. In cases of the classic 21-hydroxylase-deficient congenital adrenal hyperplasia that presents in childhood, normal sperm counts and fertility have been reported, even without glucocorticoid treatment. This disorder is one of the few intersex conditions associated with fertility. Other sources of endogenous androgens include hormonally active adrenocortical tumors or Leydig cell tumors of the testis.

3.      Glucocorticoids—Exposure to excess glucocorticoids either endogenously or exogenously can result in decreased spermatogenesis. Elevated plasma cortisone levels depress LH secretion and induce secondary testis failure.

Source of exogenous glucocorticoids include chronic therapy for ulcerative colitis, asthma, or rheumatoid arthritis. Cushing's syndrome is a common reason for excess endogenous glucocorticoids. Correction of the problem usually improves spermatogenesis.

4.      Hyper- and hypothyroidism—Abnormally high or low levels of serum thyroid hormone affect spermatogenesis at the level both the pituitary and testis. Thyroid balance is important for normal hypothalamic hormone secretion and for normal sex hormone-binding protein levels that govern the testosterone-estrogen ratio. Thyroid abnormalities are a rare cause (0.5%) of male infertility.

5.      Growth hormone—There is emerging evidence that growth hormone may play a role in male infertility. Some infertile men have deficient responses to growth hormone challenge tests

and may respond to growth hormone treatment with improvements in semen quality. Growth hormone is an anterior pituitary hormone that has receptors in the testis. It induces insulinlike growth factor-1, a growth factor important for spermatogenesis. The routine measurement of serum growth hormone is presently not indicated in the infertility evaluation.

## TESTICULAR

Unlike most pretesticular conditions, which are treatable with hormone manipulation, testicular effects are, at present, largely irreversible. If sperm are observed, however, assisted reproductive technology can provide biological children for affected men.

### *Chromosomal Causes*

Abnormalities in chromosomal constitution are well-recognized causes of male infertility. In a study of 1263 infertile couples, a 6.2% overall incidence of chromosomal abnormalities was detected. Among men whose sperm count was <10 million/mL, the incidence was 11%. In azoospermic men, 21% had significant chromosomal abnormalities. For this reason, cytogenetic analysis (karyotype) of autosomal and sex chromosomal anomalies should be considered in men with severe oligospermia and azoospermia.

### *Testicular Causes of Infertility.*

Chromosomal (Klinefelter syndrome [XXY], XX sex reversal, XYY syndrome)

Noonan syndrome (male Turner syndrome)

Myotonic dystrophy

Vanishing testis syndrome (bilateral anorchia)

Sertoli-cell-only syndrome (germ cell aplasia)

Y chromosome microdeletions (DAZ)

Gonadotoxins (radiation, drugs)

Systemic disease (renal failure, liver failure, sickle cell anemia)

Defective androgen activity

Testis injury (orchitis, torsion, trauma)

Cryptorchidism

Varicocele

Idiopathic

#### A. KLINEFELTER SYNDROME

Klinefelter syndrome is the most common genetic reason for azoospermia, accounting for 14% of cases (overall incidence 1:500 males). It has a classic triad: small, firm testes; gynecomastia; and azoospermia. This syndrome may present with delayed sexual maturation, increased height, decreased intelligence, varicosities, obesity, diabetes, leukemia, increased likelihood of extragonadal germ cell tumors, and breast cancer (20-fold higher than in normal males). In this

abnormality of chromosomal number, 90% of men carry an extra X chromosome (47, XXY) and 10% are mosaic, with a combination of XXY/XY chromosomes. Paternity with this syndrome is rare but more likely in the mosaic or milder form of the disease. The testes are usually <2 cm in length and always <3.5 cm; biopsies show sclerosis and hyalinization of the seminiferous tubules with normal numbers of Leydig cells. Hormones usually demonstrate decreased testosterone and frankly elevated LH and FSH levels. Serum estradiol levels are commonly elevated. Since testosterone tends to decrease with age, these men will require androgen replacement therapy both for virilization and for normal sexual function.

#### B. XX MALE SYNDROME

XX male syndrome is a structural and numerical chromosomal condition, a variant of Klinefelter syndrome, that presents as gynecomastia at puberty or as azoospermia in adults. Average height is below normal, and hypospadias is common. Male external and internal genitalia are otherwise normal. The incidence of mental deficiency is not increased. Hormone evaluation shows elevated FSH and LH and low or normal testosterone levels. Testis biopsy reveals absent spermatogenesis with fibrosis and Leydig cell clumping. The most obvious explanation is that sex determining ratio (SRY), or the testis-determining region, is translocated from the Y to the X chromosome. Thus, testis differentiation is present; however, the genes that control spermatogenesis on the Y chromosome are not similarly translocated, resulting in azoospermia.

#### C. XYY SYNDROME

The incidence of XYY syndrome is similar to that of Klinefelter, but the clinical presentation is more variable. Typically, men with 47, XYY are tall, and 2% exhibit aggressive or antisocial behavior. Hormone evaluation reveals elevated FSH and normal testosterone and LH levels.

Semen analyses show either oligospermia or azoospermia. Testis biopsies vary but usually demonstrate arrest of maturation or Sertoli-cell-only syndrome.

### *Other Syndromes*

#### A. NOONAN SYNDROME

Also called male Turner syndrome, Noonan syndrome is associated with clinical features similar to Turner syndrome (45, X). However, the karyotype is either normal (46, XY) or mosaic (X/XY). Typically, patients have dysmorphic features like webbed neck, short stature, lowset ears, wideset eyes, and cardiovascular abnormalities. At birth, 75% have cryptorchidism that limits fertility in adulthood. If testes are fully descended, then fertility is possible and likely. Associated FSH and LH levels depend on the degree of testicular function.

#### B. MYOTONIC DYSTROPHY

Myotonic dystrophy is the most common reason for adultonset muscular dystrophy. In addition to having myotonia, or delayed relaxation after muscle contraction, patients usually present with cataracts, muscle atrophy, and various endocrinopathies. Most men have testis atrophy, but fertility has been reported. Infertile men may have elevated FSH and LH with low or normal testosterone, and testis biopsies show seminiferous tubule damage in 75% of cases. Pubertal development is normal; testis damage seems to occur later in life.

#### C. VANISHING TESTIS SYNDROME

Also called bilateral anorchia, vanishing testis syndrome is rare, occurring in 1:20,000 males. Patients present with bilateral nonpalpable testes and sexual immaturity due to the lack of testicular androgens. The testes are lost due to fetal torsion, trauma, vascular injury, or infection.

In general, functioning testis tissue must have been present during weeks 14–16 of fetal life, since Wolffian duct growth and Müllerian duct inhibition occur along with appropriate growth of male external genitalia. Patients have eunuchoid body proportions but no gynecomastia. The karyotype is normal. Serum LH and FSH levels are elevated, and serum testosterone levels are extremely low. There is no treatment for this form of infertility; patients receive lifelong testosterone for normal virilization and sexual function.

#### D. SERTOLI-CELL-ONLY SYNDROME

Also referred to as germ cell aplasia, the hallmarks of Sertolicellonly syndrome are an azoospermic male with testes biopsies that show the presence of all testis cell types except for germinal epithelium. Several causes have been proposed, including genetic defects, congenital absence of germ cells, and androgen resistance. Clinically, these men have normal virilization with small testes of normal consistency. There is no gynecomastia. Testosterone and LH levels are normal, but FSH levels are usually (90%) elevated. The use of the word “syndrome” implies that no recognized insult has occurred, since gonadotoxins like ionizing radiation, chemotherapy, and mumps orchitis can also render the testes aplastic of germ cells. There is no known treatment for this condition. In some patients, extensive testis sampling with fine-needle aspiration mapping or multiple biopsies can reveal sperm that can be used for pregnancy with assisted reproductive technologies.

#### E. Y CHROMOSOME MICRODELETIONS

Approximately 7% of men with low sperm counts and 13% with azoospermia have a structural alteration in the long arm of the Y chromosome (Yq). The testis-determining region genes that control testis differentiation are intact, but there may be gross deletions in other regions that may

lead to defective spermatogenesis. The recent explosion in molecular genetics has allowed for sophisticated analysis of the Y chromosome. At present, 3 gene sites are being investigated as putative AZF (azoospermia factor) candidates: AZFa, b, and c. The most promising site is AZFc, which contains the DAZ gene region. The gene, of which there are at least 6 copies in this region, appears to encode a ribonucleic acid (RNA)-binding protein that regulate the meiotic pathway during germ cell production. Homologs of the DAZ gene are found in many other animals, including mouse and *Drosophila*. A quantitative polymerase chain reaction-based assay is used to test blood for these deletions. In the future, sperm DNA may also be tested as part of a semen analysis. Since men with these microdeletions can have sperm in the ejaculate, they are likely to pass them on to offspring if assisted reproductive technology is used.

### *Gonadotoxins*

#### A. RADIATION

The effects of radiotherapy on sperm production are well described. They are derived mainly from a series of remarkable experiments performed during the “atomic age” but only recently published. In a study of healthy prisoners in Oregon and Washington in the 1960s, Clifton and Bremner (1983) examined the effects of ionizing irradiation on semen quality and spermatogenesis. Before a vasectomy, each of 111 volunteers was exposed to different levels of radiation. There was a distinct dose-dependent, inverse relationship between irradiation and sperm count. A significant reduction in sperm count was observed at 15 cGy, and sperm counts were temporarily abolished at 50 cGy. Azoospermia was induced at 400 cGy, this persisted for at least 40 weeks. Despite these profound effects, sperm counts rebounded to preirradiation levels in most patients during recovery.



From examination of testis tissue after irradiation, it is observed that spermatogonia are the germ cells most sensitive to irradiation. Given the dramatic sensitivity of testis tissue to irradiation, recent studies have focused on the “scatter” to testes of men undergoing radiation therapy for cancer. In cases of abdominal radiation with gonadal shielding, the estimated mean unintended gonadal exposure is approximately 75 cGy. There does not appear to be an increase in congenital birth defects in offspring of irradiated men.

## B. DRUGS

Medications are usually tested for their potential as reproductive hazards before marketing. Despite this, it is wise to discontinue unnecessary medications that can be safely stopped during attempts to conceive. These can result in infertility by various mechanisms. Ketoconazole, spironolactone, and alcohol inhibit testosterone synthesis, whereas cimetidine is an androgen antagonist. Recreational drugs such as marijuana, heroin, and methadone are associated with lower testosterone levels. Certain pesticides, like dibromochloropropane, are likely to have estrogen-like activity.

Cancer chemotherapy is designed to kill rapidly dividing cells; an undesired outcome is the cytotoxic effect on normal tissues. Differentiating spermatogonia are the germinal cells most sensitive to cytotoxic chemotherapy. Alkylating agents such as cyclophosphamide, chlorambucil, and nitrogen mustard are the most toxic agents. The toxic effects of chemotherapeutic drugs vary according to dose and duration of treatment, type and stage of disease, age and health of the patient, and baseline testis function. Despite this toxicity, the mutagenic effects of chemotherapy agents do not appear to be significant enough to increase the chance of birth

defects or genetic diseases among offspring of treated men. However, patients should wait at least 6 months after chemotherapy ends before attempting to conceive.

### *Systemic Disease*

#### A. RENAL FAILURE

Uremia is associated with infertility, decreased libido, erectile dysfunction, and gynecomastia.

The cause of hypogonadism is controversial and probably multifactorial. Testosterone levels are decreased, and FSH and LH levels can be elevated. Serum prolactin levels are elevated in 25% of patients. It is likely that estrogen excess plays a role in hormone axis derangement. Medications and uremic neuropathy may play a role in uremic-related impotence and changes in libido. After successful renal transplantation, the hypogonadism usually improves.

#### B. LIVER CIRRHOSIS

Hypogonadism related to liver failure may have various contributing factors. The reason for organ failure is important. Hepatitis is associated with viremia, and associated fevers can affect spermatogenesis. Excessive alcohol intake inhibits testicular testosterone synthesis, independent of its liver effects. Liver failure and cirrhosis are associated with testicular atrophy, impotence, and gynecomastia. Levels of testosterone and its metabolic clearance are decreased; estrogen levels are increased owing to augmented conversion of androgens to estrogens by aromatases. Decreased testosterone levels are not accompanied by proportionate elevations in LH and FSH levels, suggesting that a central inhibition of the HPG axis may accompany liver failure.

#### C. SICKLE CELL DISEASE

As mentioned earlier, sickle cell disease can cause pituitary dysfunction, likely due to the sludging of erythrocytes and associated microinfarcts. This same mechanism may also occur in testis tissue and contribute to primary hypogonadism. As a result, spermatogenesis is decreased, accompanied by lower serum testosterone levels.

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### *Medications Associated with Infertility*

Calcium channel blockers

Allopurinol Cimetidine

Alpha blockers

Sulfasalazine

Nitrofurantoin

Valproic acid

Lithium

Spirolactone

Tricyclic antidepressants

Colchicine

## Antipsychotics

### *Defective Androgen Activity*

Peripheral resistance to androgens occurs with 2 basic defects: (1) a deficiency of androgen production through the absence of 5-alpha-reductase or (2) a deficiency in the androgen receptor.

In general, these conditions are a consequence of single gene deletions. Androgen insensitivity syndromes stem from aberrations in this pathway.

#### A. 5-ALPHA-REDUCTASE DEFICIENCY

5-Alpha-reductase deficiency results in normal development of the testes and Wolffian duct structures (internal genitalia) but ambiguous external genitalia. The ambiguity results from an inborn deficiency of the 5-alpha-reductase enzyme that converts testosterone to DHT in androgen-sensitive tissues like the prostate, seminal vesicle, and external genitalia. Thus far, 29 mutations have been described in the culprit enzyme. The diagnosis is made by measuring the ratio of testosterone metabolites in urine and confirmed by finding decreased 5-alpha-reductase in genital skin fibroblasts. Spermatogenesis has been described in descended testes; however, fertility has not been reported in these patients. The lack of fertility may be due largely to functional abnormalities of the external genitalia.

#### B. ANDROGEN RECEPTOR DEFICIENCY

Androgen receptor deficiency is an X-linked genetic condition marked by resistance to androgens. The androgen receptor, a nuclear protein, is absent or functionally altered such that testosterone or DHT cannot bind to it and activate target cell genes. Since androgens have no effect on tissues, both internal and external genitalia are affected. Fertility effects depend on the specific receptor abnormality. Some patients are 46, XY males with complete end-organ resistance to androgens. They have female external genitalia with intraabdominal testes. Testes show immature tubules and the risk of testis cancer is elevated: Tumors will develop in 10–30% of patients without orchiectomy. Fertility is absent. Patients with mild receptor defects may present as normal-appearing infertile men. Spermatogenesis may be present, although impaired. It is unclear exactly how common this occurs in infertile men.

### *Testis Injury*

#### A. ORCHITIS

Inflammation of testis tissue is most commonly due to bacterial infection, termed epididymo-orchitis. Viral infections also occur in the testis in the form of mumps orchitis. Orchitis is observed in approximately 30% of postpubertal males who contract parotitis. Testis atrophy is a significant and frequent result of viral orchitis but is less common with bacterial infections.

#### B. TORSION

Ischemic injury to the testis secondary to twisting of the testis on the spermatic cord pedicle is common in prepubertal and early postpubertal boys. When diagnosed and corrected surgically within 6 hours of occurrence, the testis can usually be saved. Torsion may result in inoculation of the immune system with testis antigens that may predispose to later immunological infertility. It

recognized that the “normal” contralateral mate of a torsed testis could also exhibit histologic abnormalities. It has not been clearly demonstrated whether this is related to the actual torsion or to an underlying abnormality in testes predisposed to torsion.

### C. TRAUMA

Because of the peculiar immunologic status of the testis in the body (ie, it is an immunologically privileged site), trauma to the testis can invoke an abnormal immune response in addition to atrophy resulting from injury. Both may contribute to infertility. Trauma to the testis that results in fracture of the testis tunica albuginea layer should be surgically explored and repaired to minimize exposure of testis tissue to the body.

### *Cryptorchidism*

The undescended testis is a common urologic problem, observed in 0.8% of boys at 1 year of age. It is considered a developmental defect and places the affected testis at higher risk of developing cancer. Although the newborn undescended testis is morphologically fairly normal, deterioration in germ cell numbers is often seen by 2 years of age. The contralateral, normally descended testis is also at increased risk of harboring germ cell abnormalities. Thus, males with either unilaterally or bilaterally undescended testes are at risk for infertility later in life.

Prophylactic orchidopexy is performed by 2 years of age to allow the testis to be palpated for cancer detection. It is unclear whether orchidopexy alters fertility potential in cryptorchidism.

## *Varicocele*

A varicocele is defined as dilated and tortuous veins within the pampiniform plexus of scrotal veins. It is the most surgically correctable cause of male subfertility. The varicocele is a disease of puberty and is only rarely detected in boys

<10 years of age. A left-sided varicocele is found in 15% of healthy young men. In contrast, the incidence of a left varicocele in subfertile men approaches 40%. Bilateral varicoceles are uncommon in healthy men (<10%) but are palpated in up to 20% of subfertile men. In general, varicoceles do not spontaneously regress. The cornerstone of varicocele diagnosis rests on an accurate physical examination.

Several anatomic features contribute to the predominance of left-sided varicoceles. The left internal spermatic vein is longer than the right; in addition, it usually joins the left renal vein at right angles. The right internal spermatic vein has a more oblique insertion into the inferior vena cava. This particular anatomy in the standing man may cause higher venous pressures to be transmitted to the left scrotal veins and result in retrograde reflux of blood into the pampiniform plexus.

Varicoceles are associated with testicular atrophy and varicocele correction can reverse atrophy in adolescents. There is indisputable evidence that the varicocele affects semen quality. In fact, a classic semen analysis pattern has been attributed to varicoceles in which low sperm count and motility is found in conjunction with abnormal sperm morphology. The finding of semen abnormalities constitutes the main indication for varicocele surgery in infertile men.

Precisely how a varicocele exerts an effect on the testicle remains unclear. Several theories have been postulated; it is likely that a combination of effects results in infertility. Pituitary-gonadal hormonal dysfunction, internal spermatic vein reflux of renal or adrenal metabolites, and an increase in hydrostatic pressure associated with venous reflux are also postulated effects of a varicocele. The most intriguing theory of how varicoceles affect testis function invokes an inhibition of spermatogenesis through the reflux of warm corporeal blood around the testis, with disruption of the normal countercurrent heat exchange balance and elevation of intratesticular temperature.

### *Idiopathic*

It has been estimated that at least 25–50% of male infertility has no identifiable cause. As our knowledge expands, it is likely that genetic and environmental factors will explain many of these cases. For example, based on findings from animal models, it is likely that X-chromosome gene mutations will play a significant role in human male infertility.

## POSTTESTICULAR

### *Posttesticular Causes of Infertility*

Reproductive tract obstruction

Congenital blockages

Congenital absence of the vas deferens (CAVD)



Young syndrome

Idiopathic epididymal obstruction

Polycystic kidney disease

Ejaculatory duct obstruction

Acquired blockages

Vasectomy

Groin surgery

Infection

Functional blockages

Sympathetic nerve injury

Pharmacologic

Disorders of sperm function or motility

Immotile cilia syndromes

Maturation defects

Immunologic infertility Infection

Disorders of coitus

Impotence

Hypospadias

Timing and frequency

### *Reproductive Tract Obstruction*

The posttesticular portion of the reproductive tract includes the epididymis, vas deferens, seminal vesicles, and associated ejaculatory apparatus.

#### A. CONGENITAL BLOCKAGES

1. Cystic fibrosis—CF is the most common autosomal recessive genetic disorder in the United States and is fatal. It is associated with fluid and electrolyte abnormalities (abnormal chloride–sweat test) and presents with chronic lung obstruction and infections, pancreatic insufficiency, and infertility. Interestingly, 99% of men with CF are missing parts of the epididymis. In addition, the vas deferens, seminal vesicles, and ejaculatory ducts are usually atrophic or absent, causing obstruction. Spermatogenesis is usually normal. CAVD accounts for 1–2% of infertility cases. On physical examination, no palpable vas deferens is observed on one or both sides. As in CF, the rest of the reproductive tract ducts may also be abnormal and unreconstructable. This disease is related to CF. Even though most of these men demonstrate no symptoms of CF, up to 80% of patients will harbor a detectable CF mutation. In addition, 15% of these men will have renal malformations, most commonly unilateral agenesis.

2. Young syndrome—Young syndrome presents with a triad of chronic sinusitis, bronchiectasis, and obstructive azoospermia. The obstruction is in the epididymis. The pathophysiology of the condition is unclear but may involve abnormal ciliary function or abnormal mucus quality. Reconstructive surgery is associated with lower success rates than that observed with other obstructed conditions.

3. Idiopathic epididymal obstruction—Idiopathic epididymal obstruction is a relatively uncommon condition found in otherwise healthy men. There is recent evidence linking this condition to CF in that one-third of men so obstructed may harbor CF gene mutations.

4. Adult polycystic kidney disease—Adult polycystic kidney disease is an autosomal dominant disorder associated with numerous cysts of the kidney, liver, spleen, pancreas, epididymis, seminal vesicle, and testis. Disease onset usually occurs in the twenties or thirties with symptoms of abdominal pain, hypertension, and renal failure. Infertility with this disease is usually secondary to obstructing cysts in the epididymis or seminal vesicle.

5. Blockage of the ejaculatory ducts—Blockage of the ejaculatory ducts, the delicate, paired, collagenous tubes that connect the vas deferens and seminal vesicles to the urethra, is termed ejaculatory duct obstruction. It is the cause of infertility in 5% of azoospermic men. Obstruction can be congenital and result from Müllerian duct (utricular) cysts, Wolffian duct (diverticular) cysts, or congenital atresia or is acquired from seminal vesicle calculi or postsurgical or inflammatory scar tissue. It presents as hematospermia, painful ejaculation, or infertility. The diagnosis is confirmed by finding a low-volume ejaculate and TRUS showing dilated seminal vesicles or dilated ejaculatory ducts.

## B. ACQUIRED BLOCKAGES

1. Vasectomy—Vasectomy is performed on 800,000 men per year in the United States for contraception. Subsequently, 5% of these men have the vasectomy reversed, most commonly because of remarriage.

2. Groin and hernia surgery—Groin and hernia surgery can result in inguinal vas deferens obstruction in 1% of cases. There has been concern that Marlex mesh used for hernia repairs may add to perivasal inflammation and increase the likelihood of vassal obstruction.
3. Bacterial infections—Bacterial infections (E. coli in men age, >35) or Chlamydia trachomatis in young men) may involve the epididymis, with scarring and obstruction.

### C. FUNCTIONAL BLOCKAGES

Besides physical obstruction, functional obstruction of the seminal vesicles may exist. Functional blockages may result from nerve injury or medications that impair the contractility of seminal vesicle or vasal musculature. A classic example of nerve injury affecting ejaculation is after retroperitoneal lymph node dissection for testis cancer. This can cause either retrograde ejaculation or complete anejaculation, depending on the degree of injury to postganglionic sympathetic fibers arising from the thoracolumbar spinal cord. These autonomic nerves overlie the inferior aorta and coalesce as the hypogastric plexus within the pelvis and control seminal emission. Multiple sclerosis and diabetes are other conditions that result in disordered ejaculation.

Evidence from animal models indicates that the seminal vesicles possess contractile properties similar to those of the urinary bladder, suggesting that seminal vesicle organ dysfunction may underlie some cases of ejaculatory duct “obstruction.” Medications implicated in this functional problem are those classically associated with ejaculatory impairment.

### *Disorders of Sperm Function or Motility*

## A. IMMOTILE CILIA SYNDROMES

Immotile cilia syndromes are a heterogeneous group of disorders (1:20,000 males) in which sperm motility is reduced or absent. The sperm defects are due to abnormalities in the motor apparatus or axoneme of sperm and other ciliated cells. Normally, 9 pairs of microtubules are organized around a central pair within the sperm tail and are connected by dynein arms (ATPase) that regulate microtubule and therefore sperm tail motion. Various defects in the dynein arms cause deficits in ciliary and sperm activity. Kartagener syndrome is a subset of this disorder (1:40,000 males) that presents with the triad of chronic sinusitis, bronchiectasis, and situs inversus. Most immotile cilia cases are diagnosed in childhood with respiratory and sinus difficulties. Cilia present in the retina and ear may also be defective and lead to retinitis pigmentosa and deafness in Usher's syndrome. Men with immotile cilia characteristically have nonmotile but viable sperm in normal numbers. Sperm nuclear material is thought to be unaffected. The diagnosis is made with electron microscopy of sperm.

## B. MATURATION DEFECTS

After vasectomy reversal, normal sperm counts but low motility is often observed. This is thought to be due to elevated epididymal intratubular pressure and epididymal dysfunction, a consequence of time after vasectomy-induced blockage. As a result, sperm may not gain the usual maturation and motility capacities during transit through the epididymis.

## C. IMMUNOLOGIC INFERTILITY

Autoimmune infertility has been implicated as a cause of infertility in 10% of infertile couples. The testis is a curious organ in that sperm are highly antigenic, yet normally coexist within the host; it is an immunologically privileged site, probably owing to the blood-testis barrier, which

consists of Sertoli cell tight junctions and locally down regulated cellular immunity.

Autoimmune infertility may result from an abnormal exposure to sperm antigens after, for example, vasectomy, testis torsion, or biopsy, which then incites a pathologic immune response.

Antibodies may disturb sperm transport or disrupt normal sperm-egg interaction. Antibodies may cause clumping or agglutination of sperm, which inhibits passage, or may block normal sperm binding to the oocyte. Many assays are available to detect (ASAs), but assays that detect sperm-bound, and not serum, antibodies are the most accurate.

#### D. INFECTION

Various products of activated leukocytes can exist in infected semen. A correlation exists between leukocytes in semen and the generation of superoxide anions, hydrogen peroxide, and hydroxyl radicals (reactive oxygen species), all of which can damage sperm membranes. Sperm are highly susceptible to the effects of oxidative stress because they possess little cytoplasm and therefore-little antioxidant activity. Damage to sperm from oxidative stress has been correlated to loss of function and damaged DNA. Although genital tract infection has been linked to infertility in epidemiologic studies, the correlation between individual organisms and infertility is unclear. Uncontrolled studies suggest that pregnancy rates may improve after treatment, but controlled studies do not confirm these findings.

#### *Disorders of Coitus*

##### A. IMPOTENCE

Sexual dysfunction stemming from low libido or impotence is a frequent cause of infertility.

The male hormonal evaluation can detect organic reasons for such problems. Most cases of

situational impotence, in which the stress of attempting to conceive results in poor erections, are treated with sexual counseling and oral phosphodiesterase inhibitors.

## B. HYPOSPADIAS

Anatomic problems like hypospadias can cause inappropriate placement of the seminal coagulum too distant from the cervix and result in infertility.

## C. TIMING AND FREQUENCY

Simple problems of coital timing and frequency can be corrected by a review of the couple's sexual habits. An appropriate frequency of intercourse is every 2 days, performed within the periovulatory period, the window of time surrounding ovulation when egg fertilization is possible. Charting of basal body temperature by the female partner allows for the calculation of that period for the next ovulatory cycle. Home kits that detect the LH surge in the urine before ovulation are also helpful. Couples should be counseled to avoid lubricants if at all possible. It is also wise to discontinue any unnecessary medications during attempts to conceive. Other coital toxins include heat exposure from regular saunas, hot saunas, hot tubs, or Jacuzzis and the use of cigarettes, cocaine, marijuana, and excessive alcohol.

## ■ TREATMENT OF MALE INFERTILITY

### SURGICAL TREATMENTS

## *Microsurgery in Urology*

The rise of microsurgery as a surgical discipline followed 3 advances. The first was refinements in optical magnification; the second, the development of more precise microsuture and microneedles; and the third, the ability to manufacture smaller and more refined surgical instruments. In urology, microsurgical techniques were first applied to renal transplantation and vasectomy reversal. Microsurgery in urology is one of the most challenging disciplines in the field.

## *Varicocele*

Although most men with varicoceles are fertile, the association of varicoceles with infertility is well established. Several treatment modalities, both surgical and nonsurgical, are available for varicoceles. These include incisional ligation of the veins through the retroperitoneal, inguinal, or subinguinal approaches; percutaneous embolization; and laparoscopy. The common goal of all treatments is to eliminate the retrograde reflux of venous blood through the internal spermatic veins. Treatments can be compared in terms of expected success rates (semen improvement and pregnancy), cost, and outcomes (pain pills, return to work or other activity), and their relative merits can be analyzed. Remember that if watchful waiting is chosen, a pregnancy rate of 16% can be expected. If IVF is chosen, a pregnancy rate of 35% can be expected. An overall complication rate of 1% is associated with the incisional approach, compared with a 4% complication rate for laparoscopy and 10–15% for radiologic occlusion. A significant problem with the radiologic approach is technical failure, meaning the inability to access and occlude the spermatic vein.



## *Vasovasostomy*

About 35,000 men per year undergo vasectomy reversal in the United States. The most common reason is remarriage and the desire for more children. Occasionally, an unfortunate individual will have lost a child and desire another. Infection, deformities, trauma, and previous surgery are less frequent indications for vasovasostomy or epididymovasostomy. A problem with duct obstruction is suspected in men with normal hormones and normal testis size and no sperm in the ejaculate.

There are several methods for performing a vasovasostomy. None has been proved superior to any other, except that magnification with an operating microscope results in better success rates.

Generally, either a single-layer anastomosis or a strict, 2 layer anastomosis is performed.

Although these procedures are technically different, the experience of the surgeon is the most important factor for success. Depending on these factors, 95% or more of patients may have a return of sperm after a vasovasostomy. If the vas fluid contains no sperm below the vasectomy site, a second problem may exist in the delicate tubules of the epididymis. The longer the time since vasectomy, the greater the “back-pressure” behind the blocked vas deferens. This may cause a blowout at some point in the single, 18-foot-long epididymal tubule, the weakest point in the system. A blowout results in blockage of the tubule as it heals. In this case, the vas must be connected to the epididymis above the blowout to allow sperm to travel through the reproductive tract. This is called an epididymovasostomy. After epididymovasostomy, approximately 60–65% of men will have sperm in the ejaculate. These rates, however, have improved remarkably during the last several years, with the evolution of surgical techniques and equipment.

The achievement of sperm in the ejaculate after vasovasostomy depends on the surgeon but pregnancy after surgery obviously involves a third party. It is rare that >67% of men who have

normal sperm counts after vasectomy reversal will impregnate a woman. Therefore, it is critical to understand the reproductive health of the female partner before embarking on the procedure. Other reasons that reproductive tract microsurgery fails are (1) the quality of preblockage semen may not have been normal; (2) ASAs develop in roughly 30% of men who have had vasectomies (high antibody levels may impair fertility); (3) postsurgical scar tissue can develop at the anastomotic site, causing another blockage; (4) when the vas deferens has been blocked for a long time, the epididymis is adversely affected and sperm maturation may be compromised.

### *Ejaculatory Duct Obstruction*

For over 20 years, transurethral resection of the ejaculatory ducts (TURED) has been used to relieve pain due to ejaculatory duct obstruction. Ejaculatory duct obstruction is suspected when the ejaculate volume is <2 mL and no sperm or fructose is present. Clinical suspicion can be confirmed by TRUS demonstration of dilated seminal vesicles or dilated ejaculatory ducts. Patients with ejaculatory duct obstruction sufficient to cause coital discomfort, recurrent hematospermia, or infertility should be considered for treatment.

Transurethral resection of the ejaculatory ducts is performed cystoscopically. A small resectoscope is inserted, and the verumontanum is resected in the midline. Since the area of resection is at the prostatic apex, near the external urethral sphincter and the rectum, careful positioning of the resectoscope is essential. Long-term relief of postcoital pain after TURED can be expected in 60% of patients.

Hematospermia has also been effectively treated with TURED, but this literature is anecdotal.

There is convincing evidence from several large studies of infertility patients that 65–70% of

men show significant improvement in semen quality after TURED and that a 30% pregnancy rate can be expected. The complication rate from TURED is approximately 20%. Most complications are self-limited and include hematospermia, hematuria, urinary tract infection, epididymitis, and a watery ejaculate. Rarely reported complications include retrograde ejaculation, rectal perforation, and urinary incontinence.

### *Electroejaculation*

A complete failure of emission and ejaculation occurs most commonly from spinal cord injury (10,000 cases/year in the United States) and as a result of deep pelvic or retroperitoneal surgery that injured the pelvic sympathetic nerves. With rectal probe electroejaculation, the pelvic sympathetic nerves undergo controlled stimulation, with contraction of the vas deferens, seminal vesicle, and prostate, such that a reflex ejaculation is induced. The semen is collected from the penis and the bladder as retrograde ejaculation is often associated with electroejaculation. Semen acquired in this way generally requires assisted reproductive technology for success.

In men with anejaculation after retroperitoneal surgery or spinal trauma, successful recovery of sperm with electroejaculation is possible in the vast majority of patients. Sperm motility tends to be lower than normal when obtained in this way, an effect independent of electrical or heat effects inherent to the procedure. In men with spinal cord injuries above the T5 level, it is often possible to induce a reflex ejaculation with high-frequency penile vibration, termed vibratory stimulation. With the use of handheld vibrators set to a frequency of 110 cycles/s at an amplitude of 3 mm, patients may be taught to perform the procedure and attempt to conceive at home with cervical insemination.

### *Sperm Aspiration*

Sperm aspiration techniques are indicated for men in whom the transport of sperm is not possible because the ductal system is absent or surgically unreconstructable. An example of this is vasal agenesis. Acquired forms of obstruction may also exist, the most common of which is failed vasectomy reversal. Aspiration procedures can involve microsurgery to collect sperm from the sperm reservoirs within the genital tract. At present, sperm are routinely aspirated from the vas deferens, epididymis, or testicle. It is important to realize that IVF is required to achieve a pregnancy with these procedures. Thus, success rates are intimately tied to a complex program of assisted reproduction for both partners. In cases of sperm aspiration from the testicle and epididymis, IVF along with ICSI is required. An obvious prerequisite for these procedures is ongoing sperm production. Although evaluated indirectly by hormone levels and testis volume, the most direct way to verify sperm production is with a testis biopsy.

#### A. VASAL ASPIRATION

After a scrotal incision and with an operating microscope, a vasotomy is made, and leaking sperm are aspirated into culture medium. Once enough sperm are obtained (>10–20 million), the vasotomy is closed with microscopic sutures. Vasal aspiration provides the most mature or fertilizable sperm, as they have already passed through the epididymis, where sperm maturation is completed.

#### B. EPIDIDYMAL SPERM ASPIRATION

Epididymal sperm aspiration is performed when the vas is not present or is scarred and unusable. Sperm are directly collected from a single, isolated epididymal tubule. After sperm are obtained, the epididymal tubule is closed with microscopic suture, and the sperm are processed.

Epididymal sperm are not as mature as vasal sperm; as a consequence, epididymal sperm require

ICSI to fertilize the egg. Egg fertilization rates of 65% and pregnancy rates of 50% are possible with epididymal sperm, but results vary among individuals because of differences in sperm and egg quality.

### C. TESTIS SPERM RETRIEVAL

The most recently developed aspiration technique is testicular sperm retrieval, begun in 1995. It is a breakthrough in that it demonstrates that sperm do not have to pass through the epididymis to fertilize the egg. Testicular sperm extraction is indicated for patients in whom there is an unreconstructable blockage in the epididymis, or in cases of severe testis failure, in which so few sperm are produced that they cannot reach the ejaculate. In this procedure, a small piece of testis tissue is taken in a manner similar to that of a regular testis biopsy. The testis tissue is specially treated in the laboratory to separate sperm from other cells. High egg fertilization rates (60–75%) and pregnancy rates (40–50%) are possible with testis sperm.

### *Orchidopexy*

An undescended testis occurs in 0.8% of male infants at 1 year of age. Although the most important reason for orchidopexy is to make testicles with a higher risk of cancer palpable, preservation of fertility is another debatable reason. Histologic studies of undescended testis show that significant decreases in spermatogonial numbers occur between birth and 2 years of age. Orchidopexy has been recommended within 2 years of age to potentially prevent this germ cell degeneration, although proof of this is lacking. Given that sperm can be retrieved from very atrophic testes and used with assisted reproduction, orchidopexy and not orchiectomy should be the primary goal in these cases.

Torsion of the testis is a urologic emergency. There are significant data from animal (but not human) studies to suggest that the unaffected, contralateral testis can become infertile after torsion of its mate. This has been termed sympathetic orchidopathy and is assumed to be immunologic in nature. It is the basis for the recommendation that the nonviable torsed testicle be removed at diagnosis. However, given the advances in assisted reproductive technologies, such recommendations should be reconsidered.

### *Pituitary Ablation*

Elevated serum prolactin levels stemming from a pituitary adenoma can be treated medically and surgically. If the adenoma is radiologically visible (macroadenoma), then transsphenoidal surgical ablation of the lesion is possible. If the adenoma is not visible (microadenoma), then medical therapy with the dopamine agonist bromocriptine or a derivative is indicated.

## NONSURGICAL TREATMENTS

### *Specific Therapy*

Specific therapy seeks to reverse known pathophysiologic effects to improve fertility. For the most part, they are cost-effective treatments.

#### A. PYOSPERMIA

The presence of elevated numbers of leukocytes in semen is termed pyospermia and has been associated with (1) subclinical genital tract infection, (2) elevated reactive oxygen species, and (3) poor sperm function and infertility. The treatment of pyospermia is controversial in the

absence of overt bacteriologic infection. It is important to evaluate the patient for sexually transmitted diseases, penile discharge, prostatitis, or epididymitis. An expressed prostatic secretion is examined for leukocytes, and urethral cultures are obtained for chlamydia and mycoplasma. The use of broadspectrum antibiotics such as doxycycline and trimethoprim-sulfamethoxazole has been shown to reduce seminal leukocyte concentrations, improve sperm function, and increase conception. Generally, the female partner is also treated.

In pyospermia with a documented prostatic source ( $>20$  leukocytes per high-power field in expressed prostatic secretion), frequent ejaculation (more than every 3 days) and doxycycline may result in a more durable resolution of pyospermia than either treatment alone. There is increasing evidence that the antioxidant vitamins (A, C, and E) as well as glutathione and other antioxidants may help scavenge reactive oxygen species within semen and improve sperm motility in pyospermic men.

## B. COITAL THERAPY

Simple counseling on issues of coital timing, frequency, and gonadotoxin avoidance can improve fertility. It is important to review the essentials of basal body temperature charting or home kits that detect the LH surge in the urine immediately, ( $<24$  hours) before ovulation. Since sperm reside in the cervical mucus for 48 hours and are released continuously, it is not necessary that coitus and ovulation occur at the exact same time, a fact that can reduce the stress associated with infertility. Coitus every other day around ovulation is the best recommendation. Coital lubricants should be avoided if possible. If necessary, vegetable oils, olive oil, and petroleum jelly are the safest.

Retrograde ejaculation results from a failure of the bladder neck to close during ejaculation. Diagnosed by the finding of sperm within the postejaculate bladder urine, it can be treated with a trial of sympathomimetic medications. Approximately 30% of men will respond to treatment with some degree of antegrade ejaculation. Begun several days before ejaculation, imipramine (25–50 mg twice a day), or Sudafed Plus (60 mg three times a day) have all been used with success. The side effects associated with these medications usually limit the efficacy of therapy. For medication failure, sperm harvesting techniques can be used with IUI to achieve a pregnancy. Premature ejaculation occurs when men ejaculate before the partner is ready. Sexual counseling combined with tricyclic antidepressants or serotonergic uptake inhibitors can be very effective.

### C. IMMUNOLOGIC INFERTILITY

ASA's are a complex problem underlying male infertility. Available treatment options include corticosteroid suppression, sperm washing, IUI, IVF, and ICSI. Steroid suppression is based on the concept that an overactive immune system can be weakened to reduce antibodies on sperm. Intrauterine insemination places more sperm nearer the ovulated egg to optimize the sperm-egg environment. Pregnancy rates with this technique generally fall in the 10–15%/cycle range. Assisted reproductive technology with IVF and ICSI is very effective in this scenario. In general, if >50% of sperm are bound with antibodies, then treatment should be offered. In addition, head-directed or midpiece-directed sperm antibodies appear more relevant than tail-directed antibodies. Since the presence of ASA is associated with obstruction in the genital tract, such lesions should be sought and corrected. There is renewed interest in the causes and possible treatments of this interesting problem, as several animal models exist that mimic the condition in humans.



#### D. MEDICAL THERAPY

Effective hormonal therapy can be offered to patients with diseases that predispose to infertility. Hormone therapy is effective when it is used as specific and not empiric treatment. Specific replacement therapy seeks to reverse well-established, pathophysiologic states. Empiric treatments attempt to overcome pathologic conditions that are ill-defined or have no proven treatment.

1. Hyperprolactinemia—Normal levels of prolactin in men help sustain high intratesticular testosterone levels and affect the growth and secretions of the accessory sex glands. Hyperprolactinemia abolishes gonadotropin pulsatility by interfering with episodic GnRH release. Visible lesions are generally treated with transsphenoidal surgery, and nonvisible lesions are treated with bromocriptine, 5–10 mg daily, to restore normal pituitary balance.
2. Hypothyroidism—Both elevated and depressed levels of thyroid hormone alter spermatogenesis. Replacement or removal of low or excessive thyroid hormone is effective treatment for infertility. As these diseases are clinically evident, routine thyroid screening is not recommended for infertility patients.
3. Congenital adrenal hyperplasia—Most commonly, the 21-hydroxylase enzyme is deficient, and defective cortisol production results. The testes fail to mature because of gonadotropin inhibition due to excessive androgens. The diagnosis is rare and classically presents as precocious puberty; careful laboratory evaluation is essential. In both sexes, the condition and the infertility associated with it are treated with corticosteroids.
4. Testosterone excess/deficiency—Patients with Kallmann syndrome lack GnRH that stimulates normal pituitary function. Infertility associated with this condition can be very

effectively treated with hCG, 1000–2000 U three times weekly, and recombinant FSH 75 IU twice weekly, to replace LH and FSH. It is also possible to give GnRH replacement in a pulsatile manner, 25–50 ng/kg every 2 hours, by a portable infusion pump. Individuals with fertile eunuch syndrome or isolated LH deficiency respond well to hCG therapy alone. One can expect to find sperm in the ejaculate beginning 9–12 months after therapy is started. Since injectable drug regimens are long, complex, and costly, it is good practice for men to cryopreserve motile sperm once achieved in the ejaculate. Anabolic steroids are a common and underdiagnosed reason for testicular failure in which excess exogenous testosterone and metabolites depress the pituitary-gonadal axis and spermatogenesis. Initially, the patient should discontinue the offending hormones to allow the return of normal homeostatic balance. Second-line therapy generally consists of “jump-starting” the testis with hCG and FSH as with Kallmann syndrome.

### *Empiric Medical Therapy*

In at least 25% of infertile men, no identifiable cause can be attributed to the problem. Because the pathophysiology is ill-defined, this is termed idiopathic infertility. There is a second group of men in whom a cause of infertility may be identified but no specific therapy is available. Both groups of men are candidates for empiric medical therapy. This form of therapy seeks to overcome pathologic conditions that are ill-defined or have no proven treatment. As a rule, it is important to establish a timeline of therapy and decide with the patient when empiric treatment is to be discontinued and other avenues pursued.

#### A. CLOMIPHENE CITRATE

Clomiphene citrate is a synthetic nonsteroidal drug that acts as an antiestrogen and competitively binds to estrogen receptors in the hypothalamus and pituitary. This blocks the action of the normally low levels of estrogen on the male hormone axis and results in increased secretion of GnRH, FSH, and LH. The enhanced output of these hormones increases testosterone production and sperm production. Its use in male infertility treatment is “off-label,” as it is only FDA-approved for the treatment of female infertility. Clomiphene therapy is given for idiopathic low sperm count in the setting of low-normal LH, FSH, and testosterone levels. It is less effective as a treatment for low motility. The dose is 12.5–50 mg/day either continuously or with a 5-day rest period each month. Serum gonadotropins and testosterone should be monitored at 3 weeks and the dose adjusted to keep the testosterone level within the normal range. Higher than normal testosterone levels may result in decreased semen quality. Therapy should be discontinued if no semen quality response is observed in 6 months. Although there have been over 30 published trials on clomiphene since 1964, only a few include control arms. In general, there are as many trials showing that clomiphene is equivalent to placebo as there are showing that it improves sperm density and pregnancy rates. Decreased sperm densities have also been observed on this therapy.

## B. ANTIOXIDANT THERAPY

There is evidence that up to 40% of infertile men have increased levels of reactive oxygen species in the reproductive tract. These species (OH, O<sub>2</sub> radicals, and hydrogen peroxide) can cause lipid peroxidation damage to sperm membranes. Treatment with scavengers of these radicals may protect sperm from oxidative damage: glutathione, 600 mg daily for 3–6 months, or vitamin E, 400–1200 U/ day. These agents may be useful in a subgroup of infertile men with

elevated levels of seminal reactive oxygen species. Non-FDA approved vitamin supplements abound as treatments for male infertility, but well-controlled trials demonstrating their efficacy are scarce.

### C. GROWTH HORMONE

There is emerging evidence that growth hormone-induced insulin-like growth factor-1 may be important for spermatogenesis. In recent European trials of growth hormone in infertile men, individuals with maturation arrest and azoospermia developed sperm counts. The use of growth hormone or its releasing factor may become a new and effective treatment for oligospermia.

## ASSISTED REPRODUCTIVE TECHNOLOGIES

If neither surgery nor medical therapy is appropriate for male infertility treatment, assisted reproductive techniques can be used to achieve a pregnancy.

### *Intrauterine Insemination*

IUI involves the placement of a washed pellet of ejaculated sperm within the female uterus, beyond the cervical barrier. The principal indication for IUI is for a cervical factor; if the cervix is bypassed, then pregnancies may ensue. IUI is also used for low sperm quality, for immunologic infertility, and in men with mechanical problems of sperm delivery (eg, hypospadias). There should be at least 5–40 million motile sperm in the ejaculate (volume  $\square$  concentration  $\square$  motility) to make this procedure worthwhile. Success rates vary widely and are directly related to female reproductive potential; given this, pregnancy rates of 8–16% per cycle have been reported with IUI as a treatment for male infertility. Success rates are improved if

ultrasound is used to document that follicles are enlarging and if urine testing is used to predict ovulation precisely.

### *In Vitro Fertilization and ICSI*

In vitro fertilization is a more complex technique than IUI and removes even more of the formidable obstacles to sperm in the female reproductive tract. It involves controlled ovarian stimulation and ultrasound-guided transvaginal egg retrieval from the ovaries before normal ovulation. Eggs are then fertilized in petri dishes with anywhere from 500,000 to 5 million motile sperm. This is excellent technology with which to bypass moderate to severe forms of male infertility in which low numbers of motile sperm are present. Most recently, a revolutionary addition to IVF has been described that is referred to as ICSI. The sperm requirement for egg fertilization has dropped from hundreds of thousands for IVF to 1 viable sperm for ICSI. This has led to the development of aggressive new surgical techniques to provide sperm for egg fertilization from men with apparent azoospermia (no ejaculated sperm). The availability of these techniques has pushed urologists to look beyond the ejaculate and into the male reproductive tract to find sperm for biologic pregnancies. At present, sources of sperm include the vas deferens, epididymis, and testicle. Two notes of concern are the following: (1) Since IVF and ICSI may eliminate many natural selection barriers that exist during natural fertilization, genetic defects that caused the infertility are expected to be passed on to offspring unabated. This has large ethical implications, especially with respect to X-linked diseases like Klinefelter syndrome that might be expected to resurface again in grandchildren of the affected but treatable infertile male. (2) Recent data show that offspring born to infertile couples with this technique have a fourfold higher incidence of sex chromosomal anomalies than do children who are naturally conceived. In addition to an elevated risk of certain birth defects, including hypospadias, in IVF-

ICSI offspring, there is concern that rare diseases such as Beckwith-Weideman syndrome, Angelman syndrome and other imprinting disorders are increased in children conceived with this technology.

### *Preimplantation Genetic Diagnosis*

Preimplantation genetic diagnosis is a specialized technique that enables the laboratory to precisely define the genetic normality of embryos. In patients with heritable, possibly life-threatening diseases, it is possible that offspring conceived with IVF and ICSI may have these diseases transmitted to them. This complex technique involves the removal of single cells from the early embryo while it is grown in petri dishes before transfer to the uterus. The genetic material from these “biopsied” cells can then be examined to determine whether the embryo carries an abnormal chromosome or gene. Through preimplantation genetic diagnosis, early human embryos that result from IVF and ICSI can be individually examined as they develop for the presence or absence of suspected genetic traits. Because of the realtime nature of the technique, decisions regarding embryo transfer are made within 24 hours and help ensure that lethal diseases are not transmitted to offspring. Remarkably, the removal of a few cells from the embryo is not detrimental to the survival and normal development of most embryos.

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