Endocrine

DIAGNOSIS AND MANAGEMENT

OF MALE INFERTILITY

Department of Internal Medicine

Grand Rounds

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James E. Griffin, M.D.

I. INTRODUCTION

Approximately 15% of couples attempting their first pregnancy are unsuccessful. Couples who have been unable to achieve a pregnancy after one year of unprotected intercourse are usually considered to have primary infertility. In approximately one-third of such cases a significant abnormality impairing fertility is thought to be in the man alone, and in an additional fifth of couples both the man and the woman have some abnormality. Thus in about half of infertile couples some abnormality in the male is in part responsible for the failure to conceive. Any man who has been unsuccessful in achieving fertility with a regularly menstruating woman after one year should be considered potentially subfertile.

Infertility in men may be an isolated problem with normal androgen production or one manifestation of an abnormality of testicular function that involves both Leydig cells and seminiferous tubules. In contrast, since sperm production is dependent on normal Leydig cell function, disorders that primarily affect androgen formation or action are usually associated with infertility. Therefore, it is essential to exclude the presence of subtle Leydig cell dysfunction in every man with infertility.

These rounds will review the normal regulation of testicular function and fertilization, consider the approach to the clinical assessment of the subfertile man, discuss the variety of possible causes of abnormal testicular function associated with infertility, and try to come to grips with management alternatives for this difficult problem. In considering the etiological factors in male infertility greater attention will be given to those etiologies that are potentially treatable. Two recent reviews of the overall subject are recommended (1,2).

1. Swerdloff RS, Overstreet JW, Sokol RZ, Rajfer J: Infertility in the male. Ann Intern Med 103:906-919, 1985.

2. Santen RJ, Swerdloff RS: Male Reproductive Dysfunction. Diagnosis and Management of Hypogonadism, Infertility, and Impotence. Marcel Dekker, New York, 1986.

II. REGULATION OF TESTICULAR FUNCTION

In the normal adult man approximately 2×10^8 sperm are produced each day. Normal spermatogenesis requires the coordinated effects of hormones from the hypothalamus, the anterior pituitary, and the Leydig cell coupled with normal Sertoli cell function (Fig. 1).

The preoptic area and the medial basal region of the hypothalamus contain important centers for control of gonadotropin secretion. Peptidergic neurons in this region secrete luteinizing hormone-releasing hormone (LHRH, also called gonadotropin-releasing hormone or GnRH). LHRH is transported to the pituitary by a portal vascular system and interacts with cell surface receptors on pituitary gonadotrophs to stimulate the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH). LH interacts with specific cell surface receptors on Leydig cells and functions to stimulate the conversion of cholesterol to testosterone. The seminiferous tubule is the primary site of action of FSH which binds to the basal aspect of the Sertoli cell (3). FSH may also influence Leydig cell maturation (4).

The secretion of LHRH is episodic resulting in the intermittent secretion of both immunoreactive and bioactive LH in 8 to 14 pulses per 24 hours in adult men (5). Pulsatile secretion of FSH also occurs but is of smaller amplitude, in part because of the longer half-life of FSH in the circulation. The rate of secretion of LH is controlled by the action of sex steroids on the hypothalamus and pituitary. Both testosterone and estradiol can inhibit LH secretion. Testosterone and its metabolites act on the central nervous system to slow the hypothalamic pulse generator and consequently decrease the frequency of LH pulsatile release (6). Testosterone can be converted to estradiol in the brain and pituitary, but the two hormones are thought to act independently. The fact that the testosterone metabolite dihydrotestosterone, which cannot be converted to estrogen, exerts negative feedback on LH secretion suggests that testosterone does not require conversion to estradiol to inhibit LH secretion. Testosterone also appears to have a negative feedback on LH secretion at the pituitary level. In normal men endogenous estrogens also act to restrain tonically the hypothalamic release of LHRH (7). Testicular hormones also exert negative feedback control on FSH secretion. Serum FSH levels increase selectively in proportion to the loss of germinal elements in the testis. A protein inhibitor of FSH in the testis, semen, and cultured Sertoli cells has been termed inhibin but has not been purified to homogeneity (8). The physiological importance of inhibin is not known. Testosterone and estradiol also have direct effects on FSH secretion, and decrease in the pulse frequency of LHRH release may effect a selective increase of FSH (9).

Figure 1

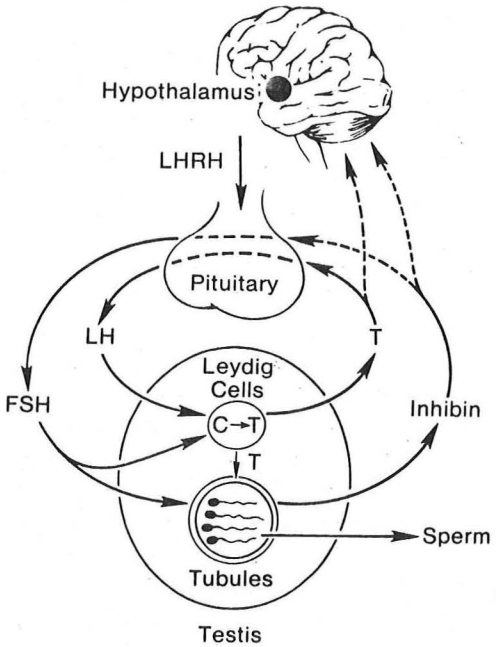
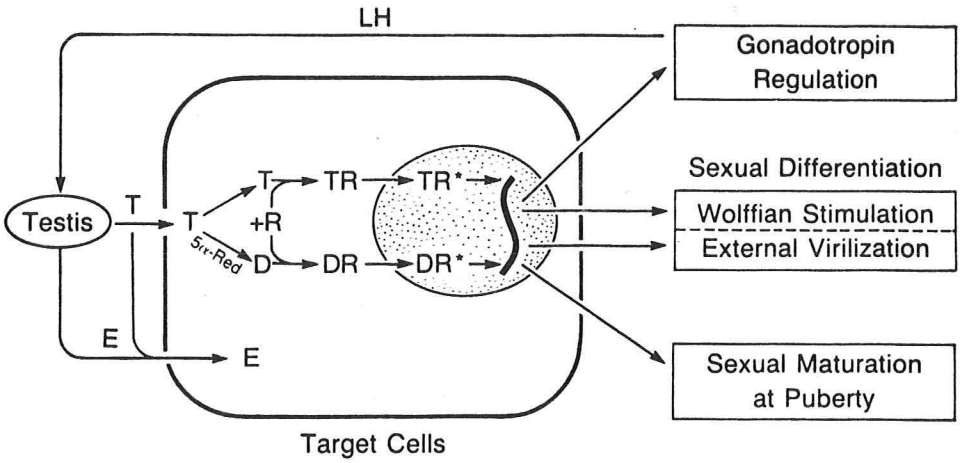


Figure 1 Hypothalamic-pituitary-testicular interrelationships. Schematic diagram to indicate feedback relationship of testosterone and inhibin produced by testes on gonadotropin secretion by hypothalamic-pituitary complex, and site of action of FSH and LH on testis. C = cholesterol; T = testosterone; FSH = follicle-stimulating hormone; LH = luteinizing hormone; LHRH = LH-releasing hormone. (From Griffin JE, Wilson JD. The Testis. In: Bondy PK, Rosenberg LE, eds. Metabolic Control and Disease. 8th ed. Philadelphia: W. B. Saunders, 1980: 1535–1578.)

Androgen action in target cells involves binding to specific high affinity receptor proteins, transformation of the hormone receptor complex to a state with increased affinity for chromatin sites, increased transcription of specific genes, and subsequent appearance of new messenger RNA and protein in the cytoplasm (Fig. 2). While testosterone is the major androgen secreted by the testes, in many target tissues the 5α-reductase enzyme effects local formation and accumulation of dihydrotestosterone as the principal target tissue androgen. Testosterone itself is thought to be responsible for gonadotropin regulation while dihydrotestosterone is thought to mediate most aspects of sexual maturation at puberty including spermatogenesis (10). Estrogens are both secreted directly by the testis and formed in extraglandular tissues. The mechanism by which estrogens act to augment or block androgen action are not fully understood. In the male breast estrogens oppose the action of androgens.

Figure 2



Mechanism of androgen action. T testosterone, D dihydrotestosterone, E 17β-estradiol, R androgen receptor, R, transformed androgen receptor, 5α-red = 5α-reductase, LH luteinizing hormone.*

Initiation of spermatogenesis requires both FSH and LH, and it is likely that both are necessary for quantitatively normal spermatogenesis (11). FSH acts predominantly on the spermatogenic tubule whereas LH influences spermatogenesis by its enhancement of testosterone synthesis in the adjacent Leydig cells (12). The spermatogenic tubule also contains androgen receptors (13). Androgens and FSH act to promote spermatogenesis at the level of the Sertoli cell rather than on spermatogonia (3).

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9. Gross KM, Matsumoto AM, Southworth MB, Bremner WJ: Evidence for decreased luteinizing hormone-releasing hormone pulse frequency in men with selective elevations of follicle-stimulating hormone. J Clin Endocrinol Metab 60:197-202, 1985.

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III. SPERM CAPACITATION AND FERTILIZATION

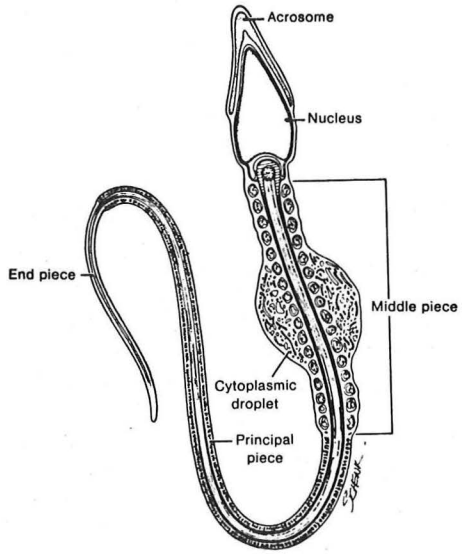
Fertility normally takes place within the fallopian tube. Spermatozoa usually require a period in the female reproductive tract before they can fertilize. This functional change, termed capacitation, is believed to consist of at least two components: 1) enhancement of rate of flagellar beat with acceleration of sperm movement, and 2) ability of sperm to undergo an acrosome reaction and consequently allow the underlying plasma membrane of the sperm to fuse with the ovum (14). The time required for optimal capacitation of normal sperm may vary from two to more than six hours (15). Whether capacitation is an absolute requirement in the human or serves only to enhance fertilizing capabilites has not been established.

The elements of the capacitation reaction that promote motility may involve a change in the intracellular concentration or metabolism of calcium or cAMP (16). The acrosome reaction appears to be more complex but also involves calcium. Neither the fallopian tube nor the egg itself appear to be essential

for this process. The acrosome reaction involves fragmentation and loss of the acrosome (Fig. 3) with release of a variety of hydrolytic enzymes and proteases allowing the sperm to penetrate the formidable vestments of the ovum and then to fuse with the ovum. The fact that the acrosome reaction is followed within a few hours by a loss of sperm motility suggests that variability in the timing of capacitation in a sperm population relative to the moment of insemination increases the chance of successful fertilization.

Understanding the mechanism of sperm penetration is largely based on studies of fertilization of human eggs in vitro, a situation that may not be identical to the phenomenon in vivo (17). Ovulated eggs are surrounded by layers of cumulus cells embedded in a matrix of hyaluronic acid. The mechanism by which spermatozoa tunnel through the cumulus is not known. Possibly, hyaluronidase is released by the degenerating acrosome, and the mechanical agitation of the flagellum may disperse cumulus cells (17). Under in vitro conditions, previous disposal of the cumulus with hyaluronidase is necessary to allow penetration of the zona pellucida and hence permit ferilization by sperm.

Figure 3



Spermatozoon

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IV. CLINICAL ASSESSMENT OF THE SUBFERTILE MAN

A. History and Physical Exam

The assessment of androgen status should include inquiry about defects of the urogenital tract at birth, sexual maturation at puberty, rate of beard growth, and current libido, sexual function, strength and energy. If Leydig cell failure occurs before puberty, sexual maturation will not occur. In contrast, the detection of Leydig cell failure beginning after puberty requires a high index of suspicion and, usually, appropriate laboratory assessment. Many men without hormonal abnormalities complain of decreased sexual function. In addition, even when Leydig cell function is impaired the rate of beard growth may not decrease for many months or even years.

The prepubertal testis measures about 2 cm in length and increases in size to a range of 3.5 to 5.5 cm in length in the normal adult. When damage to the seminiferous tubules occurs before puberty the testes are small and firm. Following postpubertal damage the testes are characteristically small and soft. However, considerable damage must occur before the overall size is decreased below the lower limits of normal. Because of the frequent occurrence of varicocele among infertile men and its possible causal role in infertility, its presence should be sought by careful palpation with the patient standing. Breast enlargement is the most consistent feature of feminizing states in men and may be an early sign of androgen deficiency.

B. Gonadotropins and Testosterone

Because of the pulsatile secretion of LH and the resultant pulsatile secretion of testosterone and the need to interpret the LH in light of the testosterone, it is usually appropriate to measure gonadotropins and testosterone on a pool formed by combining equal quantities of blood obtained from three or four samples at 15- to 20-minute intervals (5). The normal plasma immunoreactive LH and FSH values must be established for each laboratory based on the antibody and standard used. The normal range for plasma testosterone in adult men is 300 to 1000 ng/dl. Free testosterone concentrations can be estimated by equilibrium dialysis, but a more accurate assessment of available testosterone *in vivo* can be obtained by measuring the non-TeBG-bound fraction (18).

In certain circumstances the response of plasma LH to the administration of LHRH is measured to assess the functional integrity of the hypothalamic-pituitary-Leydig cell axis. When 100 µg of LHRH are given subcutaneously or intravenously to normal men, there is, on average, a four to fivefold increase in LH, with the peak level at 30 min. However, the range of response is broad, some normal men having less than a doubling of LH levels. In general, the peak LH following a single LHRH injection correlates with basal levels. In patients with primary testicular failure, measurement of basal LH is usually sufficient, and measurement of LHRH response adds little to the diagnosis. Men who have either pituitary disease or hypothalamic disease may have either a normal or abnormal LH response to an acute dose of LHRH. Therefore, a normal response is

of no diagnostic value, whereas a subnormal response is of value in determining that an abnormality exists, even though the site is not determined. Men with secondary hypogonadism and a subnormal response to an acute infusion of LHRH who develop a normal response to an acute dose after daily infusion of LHRH for a week usually have a hypothalamic cause of the hypogonadism (19).

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C. Seminal Fluid Examination

Routine evaluation of seminal fluid is largely dependent on tests that do not assess the functional capacity of sperm. Although methods to measure sperm penetration of bovine cervical mucus (20) and zona-free hamster ova (21) have been developed, they are not sufficiently standardized to permit general use. Seminal fluid should be obtained after masturbation into a clean glass or plastic container. The volume of the normal ejaculate is 2 to 6 ml. The specimen should be analyzed within an hour. Estimation of motility is made by examining a drop of undiluted seminal fluid and recording the percentage of motile forms. Normally 60% or more of the sperm should be motile with forward progression. Sperm density may be determined by diluting seminal fluid 20-fold with an appropriate solution (22) and estimating density in a hemocytometer or with the aid of an electronic particle counter. The normal value is usually considered to be greater than 20 million per ml with total sperm per ejaculate of greater than 60 million.

After the first two days, daily sperm output is relatively constant in normal men who ejaculate daily (23). The daily sperm output is calculated from the total sperm in the ejaculate divided by the number of days since the previous ejaculation. Counts in the first two days are variable and not closely related to the output thereafter due to differences in extragonadal sperm reserves. Random sampling of sperm density in men is also complicated by effects of toxic factors such as hot baths, acute febrile illnesses, and unknown medications. The net result is that it is difficult to define the minimally adequate ejaculate (24). Sherins and co-workers found that when 24 to 36 hours of sexual rest are specified and ejaculates examined at two-week intervals, average semen quality and sperm output are lower than is generally considered normal for fertile men (24). Ordinarily, three ejaculates are required to establish inadequacy of sperm number or cytology, and as many as six or more estimates may be necessary to establish a valid assessment if the initial ejaculates are of equivocal quality.

Seminal cytology is a useful index of fertility, and the seminal fluid smear is prepared in the same way as a blood smear but with special stains (22). Some abnormal spermatozoa are present in all semen. The best correlations between histological abnormalities and infertility occur when a single anomaly is found in a large percentage of the sample. It is generally believed that 60% or more of the spermatozoa should have a normal morphology (24). When it is available the details of sperm structure can be studied by electron microscopy. Such studies are useful in identifying the abnormalities in immotile sperm.

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23. Johnson, L: A re-evaluation of daily sperm output of men. Fertil Steril 37:811-816, 1982.

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D. Testicular Biopsy

Testicular biopsy is useful in some men with oligospermia and azoospermia, both as an aid in diagnosis and a guide to treatment. The most clear-cut indication is in that group of infertile men in whom the possibility of ductal obstruction is suggested by the finding of azoospermia and normal plasma FSH levels. The indications for testicular biopsy in infertile men are not so clear when the plasma FSH is elevated (usually implying an untreatable defect in spermatogenesis) or when oligospermia is present (implying that the excretory ducts are patent). The diagnosis of Klinefelter's syndrome secondary to chromosomal mosaicism that is limited to the testes can be established by tissue culture and karyotypic analysis of biopsy material.

V. ABNORMALITIES OF TESTICULAR FUNCTION CAUSING INFERTILITY

As mentioned above a useful distinction can be made between those disorders causing infertility in which underandrogenization is also a feature and those disorders causing infertility with normal virilization. The adult abnormalities of testicular function can be viewed as involving primarily the hypothalamic-pituitary system, the testes themselves, or sperm transport (Table 1). Some systemic disease effects, such as chronic liver disease, may occur at more than one level (e.g., hypothalamic-pituitary and testicular), and certain factors, such as hyperprolactinemia, radiation, cyclophosphamide administration, autoimmunity, paraplegia, and androgen resistance can cause either isolated infertility or a combined defect in testicular function in different individuals (Table 1).

Table 1 Abnormalities of Testicular Function Causing Infertility

	Infertility with Underandrogenization	Infertility with Normal Virilization
Hypothalamic-Pituitary	Panhypopituitarism	
	Hypogonadotropic hypogonadism	Isolated FSH deficiency
	Cushing's syndrome	Congenital adrenal hyperplasia
	Hyperprolactinemia	Hyperprolactinemia
	Hemochromatosis	Androgen administration
Testicular	Developmental and Structural Defects	
	Klinefelter's syndrome	Germinal cell aplasia
	XX male	Cryptorchidism
		Varicocele
		Immotile cilia syndrome
	Acquired Defects	
	Viral orchitis	Mycoplasma infection
	Trauma	
	Radiation	Radiation
	Drugs (spironolactone, alcohol, ketoconazole cyclophosphamide)	Drugs (cyclophosphamide, sulfasalazine)
		Environmental toxins
	Autoimmunity	Autoimmunity
	Granulomatous disease	
	Associated with Systemic Diseases	
	Renal failure	Febrile illness
	Liver disease	Celiac disease
	Sickle cell disease	
	Neurological diseases (myotonic dystrophy, paraplegia)	Neurological disease (paraplegia)
	Androgen Resistance	Androgen Resistance
Sperm Transport		Obstruction of epididymis or vas deferens (cystic fibrosis, diethylstilbestrol exposure)

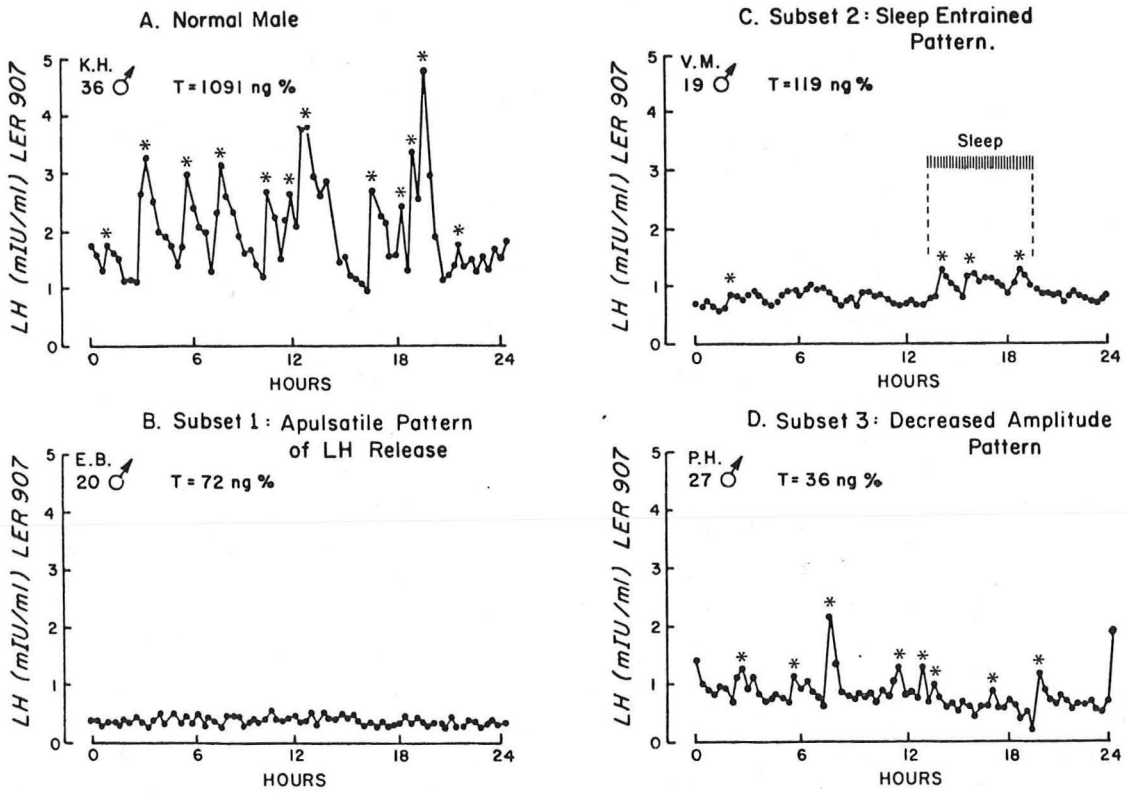
A. Infertility with Underandrogenization

Hypothalamic-Pituitary Disorders. Disorders of the hypothalamus and pituitary can impair gonadotropin secretion and decrease androgen production and

spermatogenesis either as an isolated defect (hypogonadotropic hypogonadism or Kallmann's syndrome) or as part of a more complex pituitary insufficiency.

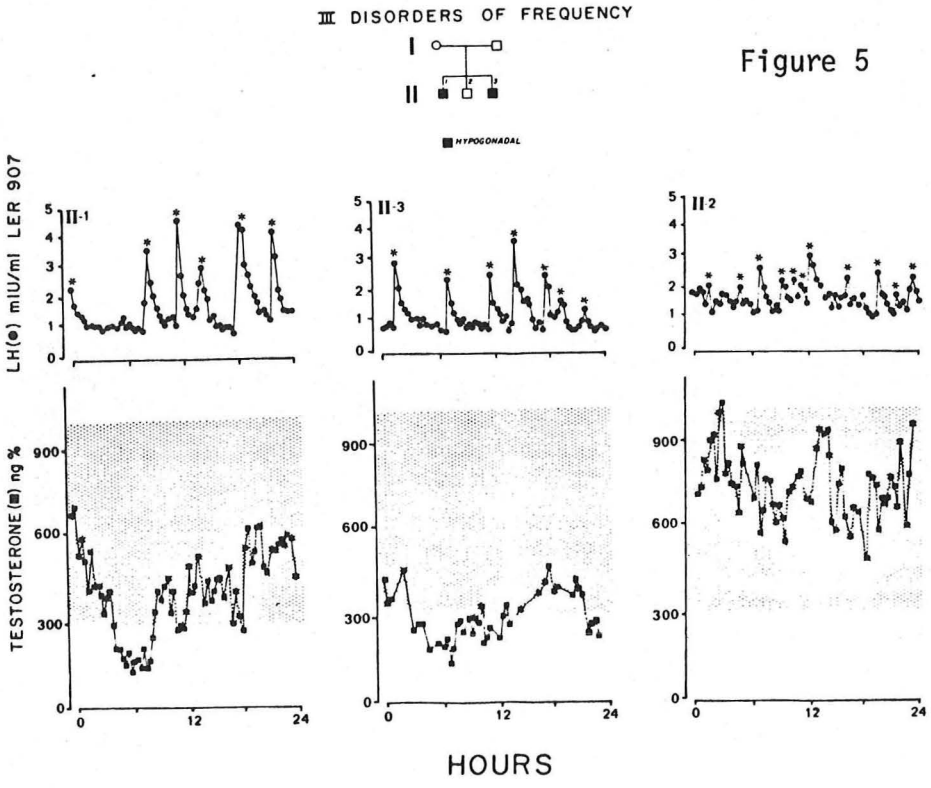
Since isolated gonadotropin deficiency is one of the few recognized causes of infertility that is readily treatable it will be considered in a little greater detail. [This is not meant to imply that hypogonadotropic hypogonadism is a common etiological disorder in men who present with infertility (see below).] Although most patients with hypogonadotropic hypogonadism have absent pubertal maturation, some undergo partial sexual maturation and develop partial testicular enlargement and do not come to medical attention until adulthood. In most centers isolated gonadotropin deficiency is second only to Klinefelter's syndrome as a cause of hypogonadism in men. The term Kallmann's syndrome is widely used to refer to both the sporadic and the familial forms with and without anosmia (25). Less severely affected individuals may have a negative family history (half of all subjects with the disorder) and only partial defects in FSH and/or LH secretion. The underlying defect is at the hypothalamic level with absence of or inadequate release of LHRH. Randomly obtained gonadotropin levels may be undetectable, low, or apparently normal in the face of a low testosterone level. The fact that the underlying defect is at the hypothalamic level was deduced by Boyar who reported that prolonged treatment of one patient with clomiphene corrected the defect in plasma LH (26). The validity of this thesis was established when LHRH became available; following short term administration of LHRH, plasma LH and FSH increase in about half of subjects. After repetitive infusion of LHRH for five days or longer, plasma gonadotropins rise to the normal range in virtually all Kallman patients but not in individuals with panhypopituitarism (19). The nature of the underlying abnormality (or abnormalities) has not been elucidated. It is assumed that the fundamental defect involves neurogenic control mechanisms that regulate LHRH release. Recently workers in Crowley's group have attempted to define some of the clinical heterogeneity in patients with hypogonadotropic hypogonadism by studying the patterns of LHRH secretion as inferred by frequent measurements of plasma LH (27). Men with idiopathic hypogonadotropic hypogonadism displayed several abnormal patterns of LHRH secretion (Fig. 4) (27). While the majority of men had an apulsatile pattern of LH release (Fig. 4B), other individuals demonstrated episodic LH secretion only during sleep (as in normal pubertal subjects) (Fig. 4C). In these latter subjects a history of early but arrested pubertal development was often obtained and testicular size was larger than in those subjects with an apulsatile pattern of LH release. In another family with idiopathic hypogonadotropic hypogonadism affected men consistently demonstrated a diminished LH pulse amplitude compared to normal men or their unaffected siblings (Fig. 4D). In yet another family a diminished frequency of LHRH pulsations was associated with a variably low to low normal testosterone in two affects subjects but not in their normal brother. These findings imply that maintenance of a physiological amplitude and frequency of endogenous LHRH secretion appear to be essential for normal reproductive function.

Figure 4



Patterns of GnRH secretion in the normal male and males with IHH. Detected LH pulsations are indicated by *asterisks*. A, A normal adult male pattern of LH secretion. Note the normal serum testosterone level and the high amplitude, regular pulsations occurring approximately at 2-h intervals; B, an apulsatile pattern of GnRH secretion in an IHH male. Note the low serum testosterone level and complete absence of detected pulsations; C, a sleep entrained or developmental arrest pattern of LH secretion in an IHH male. Note the relatively low amplitude LH pulsations clustered during the night-time hours (*hatched bars*); D, a disordered amplitude of the pattern of GnRH secretion in an IHH male. Note the low serum testosterone level in the presence of a nearly normal frequency of low amplitude LH pulsations. [Reproduced with permission from W. F. Crowley, Jr. *et al.*: *Recent Prog Horm Res* 41:473, 1985(34).]

Figure 5



A kindred of two hypogonadal brothers with gynecomastia (*left and center panels*) and their unaffected sibling. A 24-h pattern of LH secretion is shown in the *upper half* of the figure, with testosterone levels in the *lower half*. The normal range of serum testosterone is indicated by the *shaded area*. Gonadotropin pulsations are designated as in Fig. 2. Note the slowed frequency of GnRH secretion in the affected brothers and the frequent excursions of serum testosterone below the normal range when the LH interpulse interval lengthens. In contrast, the normal sibling demonstrates an ample frequency of his GnRH-induced LH pulsations and maintains his serum testosterone levels well within the normal range. [Reproduced with permission from W. F. Crowley, Jr., *et al.*: *Recent Prog Horm Res* 41:473, 1985(34).]

Destructive lesions of the pituitary, including infarction, pituitary macroadenomas, metastatic or suprasellar tumors, infections or granulomatous processes can result in panhypopituitarism and lead to a secondary testicular defect. Elevated plasma cortisol levels, as in Cushing's syndrome, can depress LH secretion independent of a space occupying lesion of the pituitary (28). The serum LH in these men, as in other instances of secondary testicular dysfunction, is usually in the normal range and only occasionally decreased. However, it is inappropriately low for the depressed serum testosterone. Even when Cushing's syndrome is associated with a pituitary adenoma, the hypogonadotropic hypogonadism appears to be secondary to the hypercortisolism, since treatments that lower cortisol levels without affecting the pituitary adenoma result in return of testosterone levels to normal (28).

Hyperprolactinemia may cause secondary testicular dysfunction whether due to a pituitary microadenoma or macroadenoma. Macroadenomas may give rise to hyperprolactinemia as a consequence of direct secretion by the tumor or of interference with transmission from the hypothalamus to the pituitary of the normal inhibitory influences that suppress prolactin secretion. Prolactin excess alone (without pituitary destruction) commonly causes underandrogenization and infertility, probably by impairing LHRH release (29).

The abnormalities of testicular function in hemochromatosis may in part result from the associated liver disease and iron deposition in the testes, but in most instances testicular dysfunction is secondary to hypogonadotropism (30).

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Testicular Disorders. Abnormalities of testicular function in the adult can be due to developmental and structural defects of the testes, acquired testicular defects, associated systemic disease, or androgen resistance.

Developmental and Structural Defects. Klinefelter's syndrome is the most common developmental defect of the testis, occurring in approximately one in 500

men (31). It was reviewed in detail by me in a prior rounds (31). The disorder is characterized by small firm testes, varying degrees of impaired sexual maturation, azoospermia, gynecomastia, and elevated gonadotropins (32). The underlying defect is the presence of an extra X chromosome in a male leading to the common karyotype 47,XXY (the classic form) or 46,XY/47,XXY (the mosaic form). The diagnosis is usually made after the time of expected puberty. Azoospermia and damage to the seminiferous tubules are consistent features of the 47,XXY variety. The small, firm testes are characteristically less than 2 cm in length. The 46,XY/47,XXY mosaicism is found in about 10% of patients based on chromosomal analysis of peripheral blood leukocytes. The true prevalence of this form of the disorder may be underestimated since chromosomal mosaicism can be present in the testes in individuals in whom the peripheral leukocyte karyotype is normal (33). The clinical manifestations of the mosaic form are usually less severe than in the 47,XXY variety, and the testes may be normal in size (33).

The XX male syndrome is probably most appropriately viewed as a rare variant of Klinefelter's syndrome (31, 34). The findings resemble those in classic Klinefelter's syndrome except for a decreased average height. The etiology of this disorder may be heterogeneous; some instances are probably due to transposition of fragments of the Y chromosome to other chromosomes.

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Acquired Defects. The most common cause of acquired testicular failure is viral orchitis due to mumps or other viruses. As many as a fourth of adult men who have mumps develop orchitis, most commonly unilateral (35). During the acute infection plasma LH and FSH levels are elevated and the plasma testosterone decreased. The testis may then return to normal size and function or undergo atrophy. Atrophy is usually apparent within one to six months after the orchitis subsides, but the full extent of the damage may not be evident until years later. Atrophy occurs in approximately one third of men who develop orchitis, and it is bilateral in about one tenth. The frequency with which mumps results in infertility is not known. After unilateral involvement sperm densities are initially less than 10 million/ml in half of men, but within one to two years semen analysis returns to normal in three-fourths (36). Less than one-third of men with bilateral orchitis have an eventual return of semen parameters to normal (36).

Trauma is second to viral orchitis as a cause of testicular atrophy in men. The exposed position of the testes in the scrotum make them particularly vulnerable to thermal and physical damage.

Both spermatogenesis and testosterone production are sensitive to radiation. The diminished secretion of testosterone resulting from radiation appears to be the result of decreased testicular blood flow (37). Although doses of radiation as low as 20 rads result in temporary increases of LH and FSH levels and damage to spermatogonia, permanent impairment of Leydig cell function is uncommon after low level radiation. However, one tenth of patients receiving approximately 800 rads of scattered radiation to the testes during childhood (38), and most boys receiving 2400 to 3000 rads of direct testicular radiation acute lymphoblastic leukemia (39) have permanently low testosterone levels.

Drugs can cause underandrogenization and infertility either by inhibition of testosterone synthesis, blockade of androgen action, or enhancement of estrogen levels. Certain drugs have multiple effects including inhibition of pituitary gonadotropin secretion and direct effects on sperm production. Spironolactone and cyproterone administered in high doses block testosterone biosynthesis. Plasma testosterone levels do not change appreciably during usual therapeutic regimens of spironolactone (40). The antifungal agent ketoconazole also blocks testosterone synthesis with doses greater than 400 mg per day resulting in sustained depression of testosterone levels (41). Independent of any effect on the liver ethanol ingestion inhibits testosterone synthesis and reduces testosterone levels both acutely and chronically (42, 43). The fact that the lower testosterone levels are not accompanied by appropriate elevations of plasma LH suggests that hypothalamic-pituitary function is also impaired by ethanol (42).

Antineoplastic and chemotherapeutic agents, especially cyclophosphamide, commonly induce infertility (see below). Combination chemotherapy for acute leukemia, Hodgkin's disease, and other malignancies may also impair Leydig cell function (44, 45). This may be associated with decreased serum testosterone and elevated LH or only an exaggerated response to LHRH in some instances. Gynecomastia is common in pubertal boys given chemotherapy. That this toxic effect on the Leydig cell is primarily due to alkylating agents, especially cyclophosphamide, is supported by the observation that pubertal boys given other regimens for acute lymphoblastic leukemia do not develop dysfunction of Leydig cells or seminiferous tubules (46). Treatment with alkylating agents during the prepubertal years does not interfere with testicular function in later life.

Plasma testosterone levels may be low in men taking large amounts of marijuana, heroin, or methadone (47, 48). In general, elevations of plasma LH do not occur, suggesting a hypothalamic-pituitary abnormality as well as a testicular defect. Elevated plasma estradiol levels and decreased plasma testosterone levels may occur in men taking digitalis preparations by an unclear mechanism. Drugs can interfere with gonadotropin production either as a direct effect as in medroxyprogesterone acetate administration or secondary to enhanced prolactin secretion (49).

Several drugs inhibit androgen action by competition at the level of the androgen receptor. In usual dosages spironolactone primarily acts by antagonizing androgen action at the receptor level to result in gynecomastia and

impotence (40). The most commonly administered drug known to be an androgen antagonist is cimetidine (50, 51). Gynecomastia occurs in a significant fraction of men given the drug, and decreased sperm density and elevated basal testosterone may occur in conjunction with a slight diminution of LH response to LHRH (50). Ranitidine appears to be a less potent antiandrogen (52).

Testicular insufficiency can occur as a portion of a generalized autoimmune disorder in which multiple primary endocrine gland deficiencies occur and in which circulating antibodies to the testis are present (53). The testis can be the site of granulomatous disease. Testicular atrophy occurs in about 10-20% of men with lepromatous leprosy (54) and less commonly in other granulomatous diseases.

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Associated with Systemic Diseases. Since chronic generalized wasting may occur with systemic diseases, it is often difficult to distinguish specific effects on the pituitary-testicular axis from nonspecific effects attributable to malnutrition.

About half of men with renal failure on dialysis evidence impairment in testosterone production and in spermatogenesis that can vary from a mild diminution in sperm production to total destruction of the germ cell population (55). Diminished testosterone levels are accompanied by elevated gonadotropins indicating a defect at the testis level. Although adequate dialysis results in increase in testosterone levels, the testosterone levels do not usually return to the normal range (55). Zinc deficiency may be a contributing factor, and

uremic men may be zinc deficient in spite of dialysis. In one study, oral zinc therapy led to a return of testosterone levels to normal with lowering LH and FSH levels and an improvement in libido and potency (56). Another potential mechanism for abnormalities in the hypothalamic-pituitary-testicular axis in renal failure is estrogen excess (57). In contrast to the lack of correction of testicular abnormalities in men with renal failure on maintenance hemodialysis, successful renal transplantation is associated with return of testosterone levels to normal, partial reduction of LH and FSH, and improvement in sperm density to greater than 10 million/ml (58).

Cirrhosis of the liver impairs testicular function independent of the direct toxic effects of ethanol. Half of men with cirrhosis have gynecomastia and testicular atrophy, and three-fourths are impotent (59). Plasma estradiol is usually elevated, and plasma testosterone is decreased. Studies of androgen-estrogen dynamics indicate that peripheral conversion of androgens, primarily androstenedione, to estrogens is increased about threefold, presumably because of decreased hepatic extraction of androgens (60). Basal plasma levels of LH and FSH are normal to moderately elevated (59). Dynamic testing of the pituitary-testicular axis in men with cirrhosis suggests a defect at the level of the testis, but the modest elevations of basal LH and FSH levels and the lack of hyperresponsiveness to LHRH suggests that the hypothalamic-pituitary axis does not respond appropriately to the diminished testosterone levels. The reason for the impaired testosterone production and the lack of appropriate response to the hypothalamic pituitary system is uncertain. Presumably elevated estrogen levels could be responsible for both defects. Men with alcoholic cirrhosis may have a spontaneous recovery of sexual function when they abstain from alcohol, despite the persistence of an abnormal hepatic histological appearance, but those with testicular atrophy are less likely to have an improvement in sexual function with abstinence from alcohol (61).

Boys with sickle cell anemia have impaired skeletal and sexual maturation in early adolescence (62). Indeed, in 32 adult men with sickle cell anemia, incomplete sexual maturation was present in all but two and testicular atrophy was noted in a third (62). The site of the defect is usually at the testicular level (62), but a hypothalamic abnormality has been noted in some patients.

Abnormalities in Leydig cell function, frequently accompanied by decreased sperm output, have been noted in a number of chronic systemic diseases including protein calorie malnutrition (63), advanced Hodgkin's disease and cancer before chemotherapy (64, 65) and amyloidosis (66). Except for amyloidosis, in which the abnormalities seem to be limited to the testis, all these disorders cause a lowered plasma testosterone coupled with normal-to-increased plasma LH, suggesting combined hypothalamic-pituitary and testicular defects. The low plasma testosterone is not the result of inhibitors that interfere with the binding to TeBG, and hence not analogous to the euthyroid sick syndrome (67). Since the mean plasma TeBG is elevated, the decrease in available testosterone may be even greater than indicated by the total level (67). The above pattern of changes in testosterone and LH may be nonspecific effects of illness since similar changes occur following surgery, severe burns, and myocardial infarction.

The changes in the hypothalamic-pituitary-testicular axis in thyrotoxicosis may be secondary to increased estrogen levels. These changes include decreased

total sperm counts and semen volumes, increased plasma total testosterone, and normal unbound testosterone (68). The testosterone response to chorionic gonadotropin is blunted in association with increased basal LH (68).

Certain neurological disorders are associated with an increased frequency of testicular dysfunction. Men with myotonic dystrophy usually have small testes, low plasma testosterone levels, and elevated plasma LH and FSH levels (69). Although the effects are variable, spinal cord lesions that result in quadriplegia or paraplegia initially cause diminished plasma testosterone levels that generally return toward normal, however, defective spermatogenesis tends to persist (70).

Men with trisomy 21 have impairment of both seminiferous tubule and Leydig cell function. Plasma FSH and LH are elevated (71).

Androgen Resistance. A limited form of androgen resistance with abnormalities of androgen receptor function results in underandrogenization and infertility in men who have normal development of the external genitalia (72). Gynecomastia and underandrogenization are not usually present, and as many as 40% of unselected men with apparently idiopathic azoospermia may have this disorder. The presence of elevated testosterone and/or LH levels is not a reliable predictor of which men have a receptor defect. Testicular biopsies have shown maturation arrests or germinal cell aplasia.

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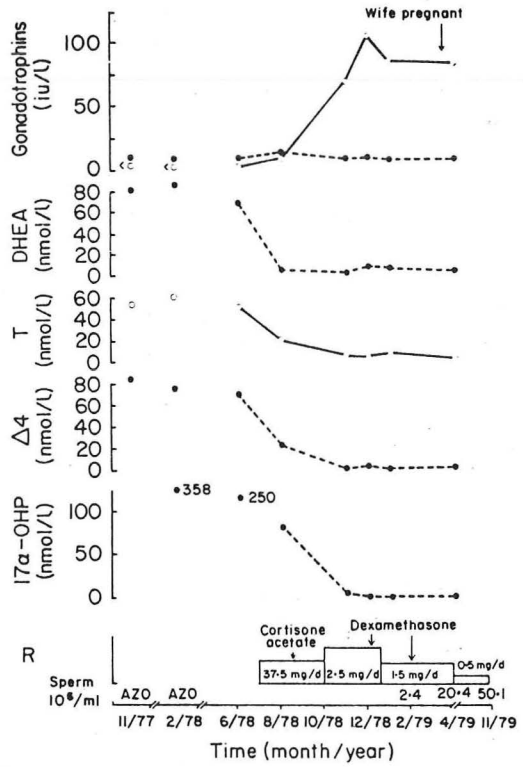
B. Infertility with Normal Virilization

Some conditions lead to infertility alone, and thus a separate group of diagnoses should be considered in infertile men with normal Leydig cell function and normal virilization (Table 1).

Hypothalamic-Pituitary Disorders. Isolated FSH deficiency has been reported in infertile men in whom virilization, plasma LH, and testosterone were normal but in whom plasma FSH was persistently low (73). Congenital adrenal hyperplasia due to 21-hydroxylase deficiency may lead to suppression of gonadotropin secretion and infertility in some men who are not treated or

undertreated (74). This diagnosis is suggested by small testes, normal or elevated testosterone, and low gonadotropins and confirmed by an elevated plasma 17-hydroxyprogesterone and androstenedione. An example of a 29 year old man with azoospermia is shown in Fig. 6 (74). His apparently premature pubertal development had not been evaluated, and his growth ceased at age 12. His serum testosterone was twice normal with low gonadotropins. His 30-fold elevation of plasma 17-hydroxyprogesterone confirmed the diagnosis of 21-hydroxylase deficiency and normal sperm density and eventual fertility followed glucocorticoid replacement (Fig. 6).

Figure 6



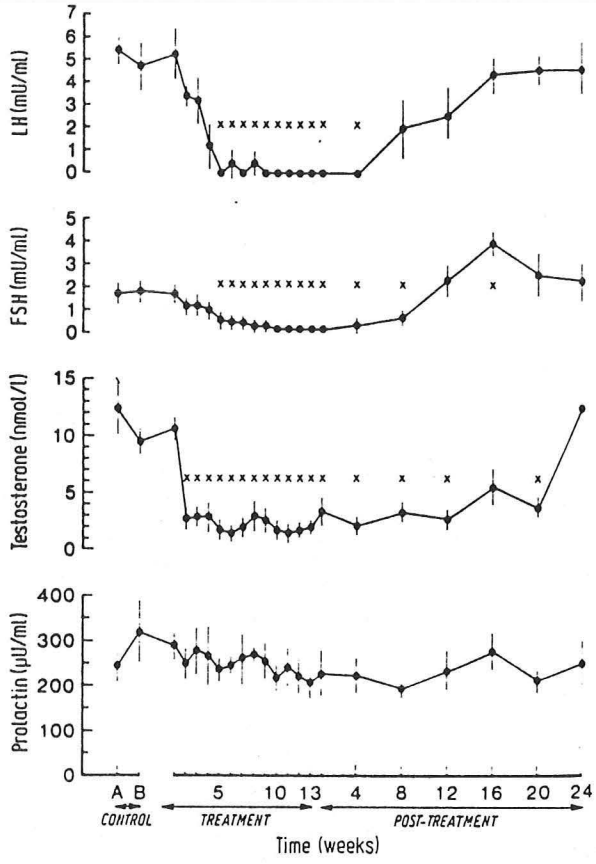
Changes in concentrations of gonadotrophins, FSH and LH, and of DHEA, T, A and 17α-OHP before and after treatment with glucocorticoids. Changes in sperm concentrations are also indicated. Azo = azoospermia; •– – –• LH; o——o FSH.

As mentioned above, hyperprolactinemia, which usually causes combined underandrogenization and infertility, can on occasion lead to an isolated decrease in sperm density.

When testosterone esters, the recommended form of androgen replacement, are administered intramuscularly in pharmacological doses to normal men, gonadotropins are suppressed and about half of men develop azoospermia (75). Although men who present with isolated infertility are unlikely to be taking testosterone replacement therapy, the use of androgens by weight lifters and body builders is common. Self-prescribed regimens may include parenteral testosterone esters as well as a variety of oral and parenteral substituted androgens often termed "anabolic steroids". Anabolic steroids have been shown to cause reversible azoospermia in normal men (76). In addition the typical combination regimen of testosterone and substituted androgens in controlled

trials has been shown to result in persistent suppression of gonadotropins (77). A study of the effects of 19-nortestosterone in 5 normal men is shown in Figs. 7 and 8 (76). Gonadotropins and testosterone decreased during treatment and remained below basal levels for 8 weeks (FSH) to 24 weeks (testosterone) after treatment was discontinued (Fig. 7). Azoospermia was first observed in one subject after 7 weeks, and by week 13 all subjects were azoospermic (Fig. 8). Azoospermia persisted for 4 to 14 weeks after treatment. The frequency of androgen administration as a cause of infertility among men has not been reported. However, I am told by Dr. Marvin Siperstein that it thought to be a common etiology in men residing in San Francisco!

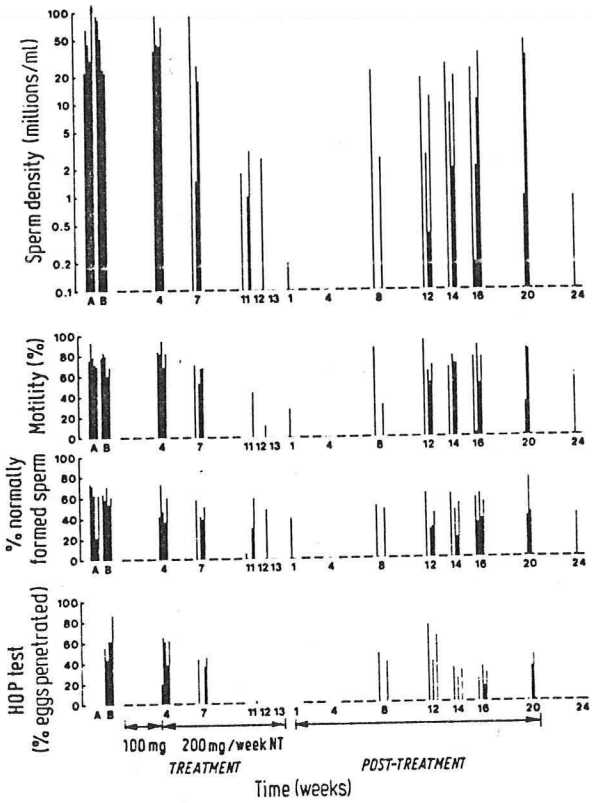
Figure 7



Serum levels of LH, FSH, testosterone, and prolactin.

Values at week 20 are derived from only three subjects. × = significant ($p<0.01$) differences from control values.

Figure 8



Seminal measurements.

Dots indicate azoospermic semen samples. Open circles in weeks 20 and 24 indicate that semen specimens from these subjects were not investigated, since measurements had returned to normal earlier. HOP test = heterologous ovum penetration test: could not be done if ejaculate contained <1 million sperm.

Testicular Disorders. Developmental and Structural Defects. Germinal cell aplasia (the Sertoli cell-only syndrome) can result from several etiologies, including a single gene defect of uncertain pathogenesis, viral orchitis, cryptorchidism (78), or androgen resistance (72). The distinguishing characteristic of the testicular biopsy is complete absence of germinal elements. The usual clinical findings of the Sertoli-cell-only syndrome include azoospermia in association with normal virilization, absence of gynecomastia,

normal-to-small testes, and normal chromosomal content. Plasma testosterone and LH are usually normal, and plasma FSH is usually elevated. In the absence of a familial presentation germinal cell aplasia cannot be considered an etiological diagnosis. It is found in biopsies from one-tenth to one-third of men with azoospermia (79).

More commonly, testicular biopsies obtained from infertile men demonstrate nonspecific decreased spermatogenesis or a maturation arrest in spermatogenesis at a particular stage such as the spermatid stage. There are multiple causes of this histological picture including subtle chromosomal abnormalities such as translocations or mosaicism that appear to affect the testis selectively. Most men with defective meiosis leading to infertility do not have a positive family history, and the cause is unknown (80).

Unilateral cryptorchidism, even when corrected before puberty, is associated with abnormal semen in many individuals (81). Indeed defective spermatogenesis is common in the descended testis in subjects with unilateral cryptorchidism, and mean sperm density is lower in adult men following surgical repair of unilateral cryptorchidism in childhood (81). This suggests that even in unilateral cryptorchidism the defect is bilateral. Basal FSH levels and FSH responsiveness to LHRH are higher on average in such subjects.

Varicocele is believed to be the most common treatable condition associated with male infertility, and it may be involved in the etiology in as many as a third of infertile men (82). Varicocele is caused by retrograde flow of blood into the internal spermatic vein that results in a progressive often palpable dilatation of the peritesticular pampiniform plexus of veins. It is thought to result from incompetence of the valve between the internal spermatic vein and the renal vein and is more common (90%) on the left (83), most likely due to the direct insertion of left spermatic into the left renal vein. The incidence is about 10-15% in the general population and 20-40% in men with infertility. The findings on semen analysis are inconsistent. Decreased sperm densities are often seen with medium or large varicoceles. The mechanism by which varicocele leads to infertility is unclear. Clearly not all men with varicocele are infertile. The leading theory as to the mechanism of the adverse effect of varicocele is that it leads to an increased scrotal temperature. Presumably an increased scrotal (and testicular) temperature would lead to poor quality semen and infertility. Studies of the effect of surgically induced left varicocele in rats and dogs demonstrated that a resultant increased blood flow to both testes was associated with an increased testicular temperature bilaterally and abnormalities in spermatogenesis in some animals (84). Assessment of retrograde flow in the internal spermatic vein by Doppler flow studies in fertile and infertile men with varicoceles was not able to distinguish competence of internal spermatic vein as measured independently by left renal venography (85). However, 10 infertile men whose varicoceles were associated with internal spermatic vein reflux had a significantly lower mean sperm density (4.8 million/ml) than that in 6 men without internal spermatic vein reflux (47.6 million/ml). Presumably the varicoceles in the latter group were the result of incompetence of other venous tributaries of the spermatic cord. The Doppler was able to identify accurately those varicoceles with significant elevation of scrotal temperature as assessed by scrotal thermography (85). However, the sperm densities of men with increased scrotal temperatures were not different than those with normal scrotal temperatures (85). Thus our understanding of

varicocele and its association with male infertility is still an enigma (83). The preferred surgical treatment of varicocele in high spermatic vein ligation at level of the inguinal canal. There is fairly good agreement that on average semen quality improves in patients who have had varicoceles repaired (86). There is not agreement on the efficacy of varicocele repair in regard to subsequent fertility. The pregnancy rate following varicocele repair is probably less than 50% overall. One large retrospective uncontrolled study of almost one thousand men claimed an association of subsequent fertility with the preoperative sperm density (87). Patients who had preoperative sperm densities greater than 10 million/ml (about 40% of the men in this study) had a 70% pregnancy rate after repair (87).

The immotile cilia syndrome is an hereditary disorder characterized by immotile or poorly motile cilia in the airways and spermatozoa (88). In most instances the disorder is inherited as an autosomal recessive trait. Kartagener's syndrome is a subgroup of the immotile cilia syndrome associated with situs inversus. The immotile cilia in the airways result in chronic sinusitis and bronchiectasis and the immotile sperm cannot fertilize. The structural abnormality leading to impaired motility of cilia can usually be defined by the electron microscopic appearance. Cilia from epithelia and sperm tails from the same individual usually exhibit the same defects. Other less well understood mutations can apparently lead to immotile sperm without involvement of cilia in the lung. In evaluating sperm for structural abnormalities care should be taken to evaluate a significant number of axonemes and confirm the motility defect since recent studies demonstrate that variations in axonenemal structure occur frequently in normal functional respiratory cilia and sperm (89).

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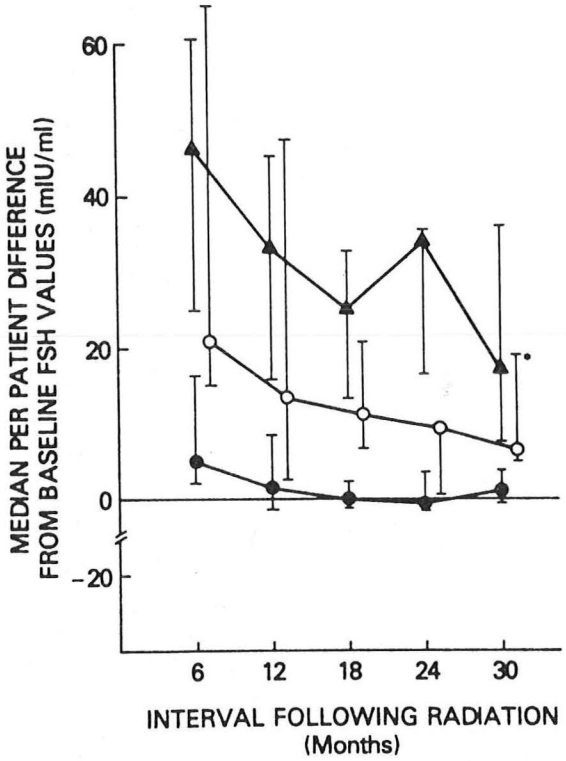
Acquired Defects. Mycoplasma infection occurs with increased frequency in women whose infertility is associated with a "male factor," suggesting that genital tract mycoplasma infection may cause male infertility (90). However, the presence of mycoplasma infection in the male cannot be correlated with any specific alteration in semen parameters.

Radiation can cause isolated infertility, a decrease in sperm density being demonstrable following a single dose of only 15 rads (91). With doses of over 100 rads extreme oligospermia or azoospermia develops. Recovery occurs in a dose-dependent fashion. Return to preirradiation sperm densities requires nine to 18 months after doses of 100 rads or less, 30 months for doses of 200 to 300 rads, and five or more years for doses of 400 to 600 rads. Fractionated radiation may have a more profound effect on the testes than does single-dose radiation (92). In a study of 27 men with variable radiation exposure to testes from scatter radiation associated with treatment of soft-tissue sarcoma, the testicular dose varied from 1 to 2,500 rads. There was dose-dependent increase in the median per patients difference from baseline in serum FSH values following irradiation with the maximal difference seen at 6 months (Fig. 9) (92). Only patients receiving less than 50 rads showed early complete recovery 12 months after radiation therapy. Only patients receiving greater than 200 rads showed statistically significant LH changes from baseline levels, and no significant changes were observed in total testosterone values. Permanent infertility may occur after radiation for treatment of malignant lymphoma of the abdomen, in spite of shielding (93). Men given radioactive iodine for treatment of thyroid cancer may also have impairment of spermatogenesis and elevation of plasma FSH levels. The threshold for this effect appears to be a cumulative ^{131}I dose of greater than 100 mCi. Recovery occurs in about two years (94).

Figure 9



Median per-patient difference from baseline serum FSH values at various time intervals following completion of radiation therapy. ● = group 1 (< 50 rad); ○ = group 2 (50 to 200 rad); ▲ = group 3 (> 200 rad). Bars at each time point represent the interquartile range, and the asterisked bar is used to represent the range when there are three observations or less.

The main drugs that cause isolated infertility are alkylating agents, especially cyclophosphamide. The primary histopathologic lesion produced by the drugs studied to date is progressive dose-related depletion of the germinal epithelium (95). Frequently, spermatocytes and spermatogonia disappear completely resulting in the appearance of germinal cell aplasia with only Sertoli cells remaining lining the tubular lumen. The serum FSH level rises about five-fold in men with absent germinal epithelium and serves as a marker for the presence of testicular germ cell loss. The serum LH and testosterone usually remain within normal limits in the presence of germinal cell depletion. However, in one study of men with normal total serum testosterone and LH associated with germinal cell aplasia due to cancer therapy, testosterone production rate and free testosterone were half that in normal men (Table 2) (95). These observations suggest that subtle Leydig cell dysfunction may contribute to the germinal abnormality and perhaps to the selective elevation of FSH.

Table 2 Hormonal Profile of Men with Germinal Aplasia Associated With Cancer Chemotherapy

Hormone	Patients mean (range)	Normal Men
FSH (mIU/ml)	45 (25 - 90)	10 (4 - 25)
LH (mIU/ml)	15 (8 - 25)	10 (4 - 10)
Testosterone		
Total (ng/dl)	351 (200 - 700)	500 (250 - 1200)
Free (ng/dl)	8.6	15.3
Production Rate (mg/day)	3.5	7.5

The anticancer agents most commonly associated with testicular germ cell depletion are listed in Table 3 (95). Studies of men receiving single alkylating agents for lymphoma have been a major source of information about drug-related infertility. Reversible oligospermia occurs in men receiving up to 400 mg of chlorambucil whereas azoospermia and germinal aplasia is more common in men treated with cumulative doses in excess of 400 mg. Similarly, germinal aplasia is less common in patients receiving less than 6 to 10 g of cyclophosphamide. Cessation of cyclophosphamide therapy is followed by return of spermatogenesis within three years in about half of patients who develop azoospermia during therapy (96). Vinblastine, doxorubicin, procarbazine and cisplatin have all been implicated as being toxic to the germinal epithelium of in both animals and man although specific dose toxicity relationships have not been established. Combination drug regimens have a profound impact on spermatogenesis. The effect of nitrogen mustard, vincristine, procarbazine, and prednisone (MOPP) have been investigated, and it is clear that more than 80% of men receiving this regimen develop azoospermia, germinal aplasia, testicular atrophy, and elevated FSH levels (45, 95). Some alternative combination chemotherapy regimens for treatment of advanced Hodgkin's disease may result in less toxicity to the germinal epithelium than MOPP. The combination of adriamycin, bleomycin, vinblastine, and DTIC (ABVD) has been claimed to result in azoospermia only one-third as often compared with MOPP, and apparently spermatogenesis nearly always recovers in the ABVD-treated patients (97). Similar issues confront patients being treated for testicular cancer. Chemotherapy-induced azoospermia that follows treatment with vinblastine, bleomycin, and cisplatin may be reversible in most men within two years of discontinuation of treatment (98).

Table 3 Antitumor Agents Associated with Testicular Germ Cell Depletion

Degree of Risk	Drug
Definite	Chlorambucil Cyclophosphamide Nitrogen mustard Procarbazine Busulfan Nitrosoureas
Probable	Doxorubicin Vinblastine Cisplatin
Unlikely	Methotroxate 5-Fluorouracil 6-Mercaptopurine Vincristine Bleomycin

Sulfasalazine therapy may also cause infertility associated with oligospermia (99). The occupational and recreational history should be evaluated in all men with infertility to search for such known environmental toxins as the nematocide dibromochloropropane and cadmium or other metals.

Although autoimmunity may cause combined underandrogenization and infertility, it usually results in isolated infertility. Antibodies to the basement membrane of the seminiferous tubules or, more commonly, to the sperm themselves are thought to be causative in a significant fraction of male infertility (100). There is no correlation between the presence of sperm-associated antibodies and specific abnormalities in the semen analysis (101). Not all men with antisperm antibodies are infertile, and decrease in antibody titers is not always associated with improved fertility. Thus, the exact role of antisperm antibodies in infertility is uncertain. Although the frequency of fertility after immunosuppression of men with antisperm antibodies by administration of prednisone is said to be greater than expected in control populations, such treatment remains investigational. The occurrence of antisperm antibodies is not always a primary phenomenon, since they have been identified in men with ductal obstruction that is either bilateral or unilateral, as well as following vasectomy.

90. Cassell GH, Younger JB, Brown MB, Blackwell RE, Davis JK, Marriott P, Stagno S: Microbiologic study of infertile women at the time of diagnostic laparoscopy. N Engl J Med 308:502-505, 1983.

91. Oakberg EF: Effects of radiation on the testis. In: Greep RO, Astwood EB, Eds. Handbook of Physiology. Section 7: Endocrinology, Vol. V, Male Reproductive System. Washington, DC: American Physiological Society 1975: 233-243.

92. Shapiro E, Kinsella TJ, Makuch RW, Fraass BA, Glatstein E, Rosenberg SA, Sherins RJ: Effects of fractionated irradiation on endocrine aspects of testicular function. J Clin Oncol 3:1232-1239, 1985.

93. Asbjornsen G, Molne K, Kleep O, Aakvaag A: Testicular function after radiotherapy to inverted 'Y' field for malignant lymphoma. Scand J Haematol 17:96-100, 1976.

94. Handelsman DJ, Turtle JR: Testicular damage after radioactive iodine (I-131) therapy for thyroid cancer. Clin Endocrinol 18:465-472, 1983.

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96. Buchanan JD, Fairley KF, Barrie JU: Return of spermatogenesis after stopping cyclophosphamide therapy. Lancet 2:156-157, 1975.

97. Santoro A, Viviani S, Zucali R, Ragni G, Bonfante V, Valagussa P, Banfi A, Bonadonna G: Comparative results and toxicity of MOPP vs ABVD combined with radiotherapy in PS IIV, III Hodgkin's disease. (Abstract) Proc Am Soc Clin Oncol 2:223, 1983.

98. Drasga RE, Einhorn LH, Williams SD, Patel DN, Stevens EE: Fertility after chemotherapy for testicular cancer. J Clin Oncol 1:179-183, 1983.

99. Birnie GG, McLeod TIF, Watkinson G: Incidence of sulphasalazine-induced male infertility. Gut 22:452-455, 1981.

100. Bronson R, Cooper G, Rosenfeld D: Sperm antibodies: Their role in infertility. Fertil Steril 42:171-183, 1984.

101. Haas GG Jr, Schreiber AD, Blasco L: The incidence of sperm-associated immunoglobulin and C3, the third component of complement, in infertile men. Fertil Steril 39:542-547, 1983.

Associated with Systemic Diseases. Isolated infertility may also occur in association with systemic diseases. Perhaps the most common association is the temporarily decreased sperm density that often follows an acute febrile illness. Men with celiac disease appear to have a distinct pattern of testicular dysfunction; namely, the hormonal pattern is typical of androgen resistance with elevated plasma testosterone and LH levels (103, 104). As discussed above, the neurological disorder that results in infertility alone is paraplegia (70).

102. Farthing MJG, Edwards CRW, Rees LH, Dawson AM: Male gonadal function in coeliac disease: 1. Sexual dysfunction, infertility, and semen quality. Gut 23:608-614, 1982.

103. Farthing MJG, Rees LH, Edwards CRW, Dawson AM: Male gonadal function in coeliac disease: 2. Sex hormones. Gut 24:127-135, 1983.

Impairment of Sperm Transport. Impairment of sperm transport may be the cause of the infertility in as many as 6% of infertile men (82). The abnormality may be unilateral or bilateral, congenital or acquired. In men with unilateral obstruction infertility may be due to antisperm antibodies. Obstructive azoospermia at the level of the epididymis may occur in association with chronic infections of the paranasal sinuses and lungs (104). Tuberculosis, leprosy, and gonorrhea are rare causes of acquired obstruction of the wolffian duct-derived structures. Congenital defects of the vas deferens that result in azoospermia or oligospermia may occur as an isolated abnormality associated with absence of the seminal vesicles (105), in patients with cystic fibrosis (106), or as a portion of a more extensive anatomical disorder in male offspring of women given diethylstilbestrol during pregnancy (107).

104. Handelsman DJ, Conway AJ, Boylan LM, Turtle JR: Young's syndrome. Obstructive azoospermia and chronic sinopulmonary infections. N Engl J Med 310:3-9, 1984.

105. Sivanesaratnam V: Male infertility due to absence of vas deferens. Eur J Obstet Gynaecol Reprod Biol 14:31-35, 1982.

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107. Whitehead ED, Leiter E: Genital abnormalities and abnormal semen analyses in male patients exposed to diethylstilbestrol in utero. J Urol 125:47-50,1981.

The preceding elaboration of the known causes and of conditions associated with male infertility unfortunately does not account for the problem in the majority of men. When large series of consecutive patients seen by referral groups are analyzed for the presence of known causal factors or associated conditions, approximately 40% of such men are classified as having idiopathic infertility (Table 4) (82, 108). Since at best only about half of the almost 40% of infertile men who are found to have a varicocele might achieve fertility following varicocele repair, it is probably more appropriate to consider 60% of infertile men to have idiopathic infertility.

Table 4 Relative Frequency of Causes and Associated Conditions in Infertile Men

Condition	Greenberg et al (82) (n=425)	Baker et al (108) (n=1041)
Hypogonadotropic hypogonadism	0.9%	0.6%
Klinefelter's syndrome	1.6	1.9
Cryptorchidism	6.1	6.4
Varicocele	37.4	40.3
Immotile sperm	0.5	0.6
Viral orchitis	1.9	1.6
Radiation/chemotherapy	-	0.5
Obstruction of epididymis or vas	6.1	4.1
Androgen resistance	-	0.1
Coital disorders	4.0	0.5
Idiopathic	41.5[a]	43.4[b]

[a]Includes miscellaneous semen abnormalities 10.2%, and undiagnosed primary testicular failure 5.9%.
[b]Includes possible obstruction 4.5%

108. Baker HWG, Burger HG, deKretser DM, Hudson B: Relative incidence of etiological disorders in male infertility. In: Male Reproductive Dysfunction: Diagnosis and Management of Hypogonadism, Infertility, and Impotence, Swerdloff RS, Santen RJ (eds). Marcel Dekker, New York, 341-372, 1986.

VI. MANAGEMENT OF MALE INFERTILITY

The management of male infertility is one of the most frustrating problems in clinical endocrinology. Conditions not amenable to therapy include azoospermia due to Klinefelter's syndrome, idiopathic germinal cell aplasia, viral orchitis, trauma, radiation, or androgen resistance as well as men with totally immotile or dead sperm. However, there are also a number of potentially correctable causes of male infertility, and the development of *in vitro* fertilization techniques offer promise for many men with idiopathic infertility that was previously untreatable.

A. Treatment of Associated Medical Disorders

Men with Cushing's syndrome may benefit from appropriate therapy for the specific cause of their cortisol excess (28). Men with congenital adrenal hyperplasia may be treated with hydrocortisone replacement (74). Hyperprolactinemia may be corrected by bromocriptine treatment of the prolactinoma (29). Men with hemochromatosis may be managed with phlebotomy. Drugs such as spironolactone, ketoconazole, cyclophosphamide, and sulfasalazine may be discontinued. Men with end stage renal disease may improve following renal transplantation (58), and men with alcoholic liver disease may improve with abstention from ethanol (61).

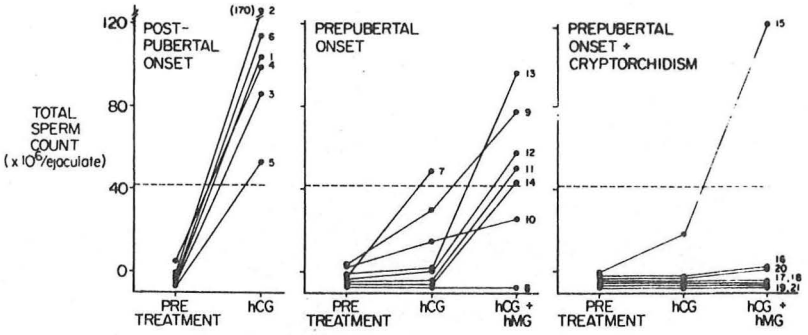
B. Endocrine Therapy

Gonadotropin Therapy. Gonadotropin treatment can establish or restore fertility in men who have gonadotropin deficiency either as an isolated disorder

or as part of a more extensive anterior pituitary failure. The customary therapy is to treat such patients initially with testosterone esters (109) to allow full virilization and to reserve gonadotropin therapy when fertility is desired. Previous androgen therapy does not impair subsequent gonadotropin induction of spermatogenesis in men with hypogonadotropic hypogonadism (110). Two gonadotropin preparations are available; menotropins (hMG) and chorionic gonadotropin (hCG). The usual preparation of hMG contains 75 IU FSH and 75 IU LH per vial. hCG is available in vials containing 5000 to 20,000 IU. hCG is devoid of FSH activity and resembles LH in its ability to stimulate Leydig cells. Because of the expense of hMG, treatment is usually begun with hCG alone, and hMG is added later, if necessary, to stimulate the FSH-dependent stages of sperm development. A high ratio of LH/FSH activity and a duration of treatment as long as six months are necessary to cause maturation of the prepubertal testis (111). Once spermatogenesis has been restored in hypophysectomized patients or initiated in hypogonadotropic hypogonadal men by combined therapy, it can usually be maintained by hCG alone.

In men with hypogonadotropic hypogonadism the dose of hCG required to maintain a normal plasma testosterone varies from 1000 to 5000 IU weekly (111). Most treatment regimens for the induction of spermatogenesis involve starting with hCG 2000 IU three or more times a week until plasma testosterone and clinical parameters of virilization are optimal. During initial treatment testis size may reach only 8 ml. hMG is then added with as little as a fifth of a vial required three times a week to complete development of spermatogenesis and further growth of the testes (110). The duration of therapy for optimal spermatogenesis may be as long as 12 months. The addition of hMG may not be necessary in many men with hypogonadotropic hypogonadism (110, 112, 113). The efficacy of gonadotropin therapy in regard to stimulating spermatogenesis was evaluated in one report of 21 men (113). The total sperm count increased to within the normal range of hCG therapy in the 6 in whom the hypogonadism had begun after puberty, but in only 1 of the 15 in whom it had begun before puberty (Fig. 10) (113). When the remaining 14 men with prepubertal hypogonadism were treated with hMG in addition to hCG, the sperm count increased to normal in 5 of the 7 who had not had cryptorchidism, but in only 1 of the 7 who had. The need for hMG as a replacement for FSH could not be predicted by pretreatment serum and urinary levels of FSH (113).

Figure 10



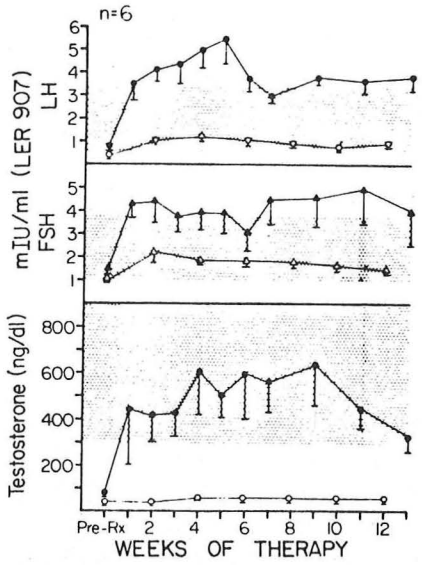
Effect of Treatment with Human Chorionic Gonadotropin Alone and in Combination with Human Menopausal Gonadotropin on Total Sperm Count.

Pretreatment values are means of two determinations made before treatment; treatment values are means of the three highest determinations made during treatment. The horizontal, dashed line represents the lower limit of normal. Numbers to the right of highest values denote patients listed in Table 1.

In response to hCG alone the sperm count increased to within the normal range in all 6 patients with postpubertal onset of hypogonadism, but in only 1 of 15 with prepubertal onset ($P<0.002$, contingency-table analysis). In response to combined treatment the count in the 14 other men with prepubertal onset increased to within the normal range in 5 of the 7 who had not had cryptorchidism, but in only 1 of the 7 who had ($P<0.05$).

LHRH Therapy. As discussed above, most men with hypogonadotropic hypogonadism due to isolated gonadotropin deficiency have a defect in synthesis and/or release of LHRH and eventually responded to repeated LHRH stimulation. Thus, LHRH therapy might be considered the most physiological approach to treating isolated gonadotropin deficiency. Induction of sexual maturation in men with isolated gonadotropin deficiency has been accomplished by long-term pulsatile administration of low-dose LHRH using a portable infusion pump; spermatogenesis was achieved in three of six men after 43 weeks of therapy with 25 ng of LHRH per kg of body weight administered subcutaneously every 2 hours, and one man achieved fertility (114). The frequency of the pulsatile administration, every 2 hours, was chosen based on the studies of the frequency of endogenous LHRH pulses in normal men (see above) (27). Over the initial 3 months of LHRH replacement, testosterone levels normalized in most men; however LH and FSH levels were initially above the normal range (Fig. 11) (27). Individuals treated with lower doses of LHRH (10 ng/kg) had LH and FSH levels within the normal range; however testosterone levels remained below normal (Fig. 11). This subthreshold dose of LHRH appeared to mimic the disorder of decreased amplitude of LHRH secretion (postulated in some Kallman patients, see above) in men who previously had an apulsatile pattern. The eventual doses of LHRH required to achieve normal adult male levels of testosterone and spermatogenesis in men with isolated gonadotropin deficiency vary considerably between individuals and range from 25 - 200 ng/kg.

Figure 11



Response of six IHH males to 10 ng/kg bolus of GnRH (*open circles*) *vs.* 25 ng/kg bolus of GnRH (*closed circles*) administered at 2-h intervals. Note the attainment of normal LH and FSH levels on the lower dose, with a complete failure of initiation of testosterone secretion. When the higher dose of GnRH was employed, a prompt rise in serum testosterone is shown with further increases in gonadotropin levels.

Stimulation of pituitary gonadotropin secretion requires pulsatile administration. When LHRH or its analogs are administered continuously,

inhibition of gonadotropin secretion results (115). Whether pulsatile LHRH therapy will prove to have advantages over gonadotropin therapy is uncertain.

LHRH can also be administered intranasally. In one study, following subcutaneous LHRH for induction of spermatogenesis, spermatogenesis with normal sperm density was maintained for as long as six months by the intranasal administration of 200 μg LHRH every two hours for 8 doses daily (116).

109. Wilson JD, Griffin JE: The use and misuse of androgens. Metabolism 9:1278-1295, 1980.

110. Ley SB, Leonard JM: Male hypogonadotropic hypogonadism: Factors influencing response to human chorionic gonadotropin and human menopausal gonadotropin, including prior exogenous androgens. J Clin Endocrinol Metab 61:746-752, 1985.

111. Rosemberg E: Gonadotropin therapy of male infertility, in Hafez ESE (ed.): Human Semen and Fertility Regulation in Men. St. Louis, C.V. Mosby Company, 464-475, 1976.

112. D'Agata R, Heindel JJ, Vicari E, Aliffi A, Gulizia S, Polosa P: hCG-Induced maturation of the seminiferous epithelium in hypogonadotropic men. Hormone Res 19:23-32, 1984.

113. Finkel DM, Phillips JL, Snyder PJ: Stimulation of spermatogenesis by gonadotropins in men with hypogonadotropic hypogonadism. N Engl J Med 313:651-655, 1985.

114. Hoffman AR, Crowley WF Jr: Induction of puberty in men by long-term pulsatile administration of low-dose gonadotropin-releasing hormone. N Engl J Med 307:1237-1241, 1982.

115. Cutler GB Jr (moderator): Therapeutic applications of luteinizing-hormone-releasing hormone and its analogs. Ann Intern Med 102:643-657, 1985.

116. Klingmuller D, Schweikert HU: Maintenance of spermatogenesis by intranasal administration of gonadotropin-releasing hormone in patients with hypothalamic hypogonadism. J Clin Endocrinol Metab 61:868-872, 1985.

C. Surgery

Two surgical therapies are of potential benefit in selected men with infertility: varicocele repair and vasoepididymostomy. The possibility of improving the semen analysis and increasing fertility in the 20 to 40% of infertile men with varicocele has been discussed above. Varicocele repair may have the best chance of improving fertility in men with less severe oligospermia or normal sperm densities (87). In one study of the success of surgical therapy of suspected obstructive azoospermia in 168 men, obstruction of the epididymis was more common than absence or obstruction of the vas deferens. Vasoepididymostomy resulted in sperm densities greater than 10 million/ml in almost half and pregnancy in a fifth (117). Pregnancy was more likely in the absence of antisperm antibodies (117).

117. Hendry WF, Parslow JM, and Stedronska J: Exploratory scrototomy in 168 azoospermic males. Br J Urol 55:785-791, 1983.

D. Empiric Therapy

As described above more than half of men with infertility do not have a specifically identifiable etiological factor and/or have a varicocele as an incidental associated condition. It is this large group then who may be considered candidates for some form of empiric therapy.

Although claims of success for a variety of empiric therapies of infertile men with oligospermia have been made, most of these reports fail to take into account the spontaneous fertility rate (25% in one year) (24). This problem of treatment-independent pregnancy among infertile couples occurs in all forms of human infertility (male and female factors) and stresses the need for evaluation of therapies by randomized clinical trials (118). When several different forms of empiric therapy including testosterone "rebound", nonaromatizable androgens (mesterolone), gonadotropins, antiestrogens (clomiphene), antibiotics, bromocriptine, varicocele repair (varicocelectomy), artificial insemination of husband's semen (AIH), and no therapy were evaluated by the Melborne group and compared in one large clinical retrospective analysis of oligospermic men, no improvement was demonstrated with any empiric therapy in the relative pregnancy rate compared with no therapy (Table 5) (119). Pregnancy rates were calculated by life table analysis which takes into account the time factor when the pregnancies occurred and duration of followup of unsuccessful couples. Although some individuals might have responded to treatment with improved semen quality and pregnancy, when all subjects are considered, none of the treatments was significantly better than no treatment.

Table 5 Treatments of Uncertain Value for Oligospermia and Decreased Motility

Melbourne Experience (Logrank test)

Treatment	Number of Courses	Number of Pregnancies	Expected Pregnancies	Relative Pregnancy Rate
Testosterone "rebound"	33	6	7.92	0.76
Mesterolone	49	7	12.93	0.54
hCG	10	2	2.15	0.93
Clomiphene	50	5	10.66	0.47
Antibacterial agents	95	25	18.83	1.33
Bromocriptine	13	3	3.15	0.95
Varicocelectomy	201	70	57.37	1.22
AIH	61	10	11.76	0.85
None	583	102	105.22	0.97

Note: Logrank $x2 = 11.37$, p NS.

In light of this such couples should be advised to consider the alternatives of artificial insemination with husband's semen using newer intrauterine techniques or in vitro fertilization (if available) or artificial insemination with donor semen. They may be counseled with respect to adoption or childlessness while waiting to see if fertility occurs spontaneously. Artificial insemination with donor semen has a 70% overall success rate in one year. Since fertility of the woman declines with increasing age, delay in decision to attempt artificial insemination with donor semen may reduce the likelihood of success.

Artificial Insemination with Husband's Semen. Artificial insemination with husband's semen is a logical method of treatment when natural insemination is not possible (e.g., ejaculatory disorders) or when the husband's semen has been collected and stored (120) before vasectomy, illness or therapy causing infertility. When used empirically in the past for male infertility artificial insemination had no more success than no therapy (119). The development of techniques for washing and concentrating motile sperm have made possible a reassessment of the utility of artificial insemination of poor quality semen. A controlled trial of intrauterine insemination of washed spermatozoa from infertile men carefully timed to coincide with ovulation resulted in a conception rate of approximately 20% per cycle compared with less than 3% for natural timed intercourse (121). This improved fertility following intrauterine insemination of washed spermatozoa appears promising and has been confirmed by a group at our institution with a 50% pregnancy rate in a small group of men with oligospermia or decreased motility (122). The average number of total motile sperm used was 2.8 million/insemination with the lowest number of motile sperm resulting in a pregnancy being 1.4 million. Most studies of the reported success of intrauterine insemination are not controlled and must be interpreted cautiously (123).

In Vitro Fertilization. Human ova can be fertilized in vitro with as few as 50,000 sperm. It is now clear that in vitro fertilization is a successful form of therapy for many forms of male infertility (124-126). Fertility has been achieved in men with less than 0.5 million/ml of motile sperm (126). Studies by the group at Monash University in Melbourne have attempted to determine prospectively which parameters in a routine semen analysis provide some indication of the success or failure of fertilization in vitro (127). A summary of the group's results in regard to fertilization rates is given in Table 6. The sperm samples in which a single parameter was abnormal such as low motility, high percentage abnormal forms, or a decreased density, demonstrate an overall fertilization rate of 60% over 77 treatment cycles. When dual defects in semen are present a fertilization rate of 55% was achieved in 25 treatment cycles. In those groups with isolated and dual defects the overall rate of fertilization cycles to treatment cycles ranged from 64 to 89%. This compares favorably with the same parameter for in vitro fertilization in whom the males have normal semen parameters where a rate of 94% was achieved by this same group. In the patients with triple defects (i.e., combinations of low density, low motility, and high percentage of abnormal forms), the fertilization rate was extremely poor (3.67 over 7 treatment cycles) (Table 6). Pregnancy rate per treatment cycle for those men with subnormal semen was 16% compared to the overall results in their in vitro fertilization program (16.7%). It appeared that the achievement of fertilization resulted in a zygote which had the same capacity of zygotes achieved with normal semen specimens.

Table 6 Results of In Vitro Fertilization Using Sperm from Infertile Men

Category	No. of Cycles	% Eggs Fertilized	% Cycles With Fertilization	Pregnancies
Isolated defects				
Motility <20%	4	41.6	75.0	1
20 - 40%	8	77.7	80.0	3
40 - 60%	24	62.6	87.0	1
Abn morphology	18	71.1	88.9	4
Density $<5x10^6$/ml	7	52.9	85.7	1
5 - $20x10^6$/ml	16	52.7	64.7	4
Dual defects				
Low density, motility	5	58.1	66.7	1
Low motil, abn morph	14	54.2	71.4	3
Low density, abn morph	6	54.1	71.4	2
Triple defects				
Low density and motility, abn morph	7	3.6	14.2	1

Dr. de Kretser concludes that in vitro fertilization is a reasonable treatment for men with isolated and dual defects. The observation that more severe motility defects are associated with decreased fertilization rate is in keeping with prior reports (125, 126). Some groups have used the hamster egg penetration assay as a prognostic indication for in vitro fertilization. Although there is a correlation, failure of penetration of zona-free hamster oocytes does not preclude successful fertilization of living human oocytes (128). The collection of split ejaculates and careful preparation of the spermatozoa are important in raising the chance of fertilization (126). In one study of male infertility comparing artificial intrauterine insemination of husband's semen and an in vitro fertilization by one group of investigators, the pregnancy per cycle was significantly higher with in vitro fertilization compared with intrauterine insemination (129). In vitro fertilization was particularly likely to result in success compared to artificial insemination in those men with sperm showing deceased motility, whereas no significant difference was found between the two methods when infertility was associated with oligospermia only (129). The main drawback to in vitro fertilization is the high cost, about $4000 per treatment cycle. As with intrauterine insemination of husband's semen, the enthusiasm for in vitro fertilization must be somewhat tempered by the lack of controlled studies.

118. Collins JA, Wrixon W, Janes LB, Wilson EH: Treatment-independent pregnancy among infertile couples. N Eng J Med 309:1201-1206, 1983.

119. Baker, HWG: Male infertility of undetermined etiology, in Krieger DT, Bardin CW (eds.): Current Therapy in Endocrinology and Metabolism 1985-1986. Toronto, B.C. Decker, Inc., 165-169, 1985.

120. Leto S, Paulson JD: Cryopreservation of human semen, in Negro-Vilar A (ed.): Male Reproduction and Fertility. New York, Raven Press, 327-338, 1983,

121. Kerin JFP, Peek J, Warnes GM, Kriby C, Jeffrey R, Matthews CD, Cox LW: Improved conception rate after intrauterine insemination of washed spermatozoa from men with poor quality semen. Lancet 1:533-535, 1984.

122. Byrd W, Ackerman G, Carr B, Edman C, Grun B, Guzick D, Johnson N, McConnell J: Results of intrauterine insemination in couples with male factor, idiopathic, and cervical factor infertility. (Abstract) Fertil Steril (In Press)

123. Allen NC, Herbert III CM, Maxson WS, Rogers BJ, Diamond MP, Wentz AC: Intrauterine insemination: A critical review. Fertil Steril 44:569-580, 1985.

124. Yovich JL, Stanger JD: The limitations of in vitro fertilization from males with severe oligospermia and abnormal sperm morphology. Journal of in Vitro Fertilization and Embryo Transfer 1:172-179, 1984.

125. Madadevan MM, Trounson AO: The influence of seminal characteristics on the success rate of human in vitro fertilization. Fertil Steril 42:400-405, 1984.

126. Cohen J, Edwards R, Fehilly C, Fishel S, Hewitt J, Purdy J, Rowland G, Steptoe P, Webster J: In vitro fertilization: A treatment for male infertility. Fertil Steril 43:422-432, 1985.

127. Yates CA, Trounson AO, deKretser DM: Fertilization rates of male infertility patients in IVF. (Abstract) Fourth World Conference on In Vitro Fertilization. Melbourne - November 1985.

128. Ausmanas M, Tureck RW, Blasco L, Kopf GS, Ribas J, Mastroianni L Jr: The zona-free hamster egg penetration assay as a prognostic indicator in a human in vitro fertilization program. Fertil Steril 43:433-437, 1985.

129. Hewitt J, Cohen J, Krishnaswamy V, Fehilly CB, Steptoe PC, Walters DE: Treatment of idiopathic infertility, cervical mucus hostility, and male infertility: Artificial insemination with husband's semen or in vitro fertilization? Fertil Steril 44:350-355, 1985.

VII. CONCLUSION

Male infertility is common, and no clear causal mechanism is recognized in more than half of the men affected. For some men treatment of associated medical disorders, gonadotropin replacement, alteration of drug therapy, or surgical therapy may be beneficial. Empiric therapy, which may have a role for half of infertile men, now offers new hope for success as a result of the development of the techniques for *in vitro* fertilization.