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THE PSYCHOSEXUAL EFFECTS OF KLINEFELTER SYNDROME

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BY

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DISSERTATION APPROVAL

This dissertation submitted by Thomas M. Duffy has been read and approved by three faculty members of the American Academy of Clinical Sexologists at Maimonides University.

The final copies have been examined by the Dissertation Committee and the signatures, which appear here, verify the fact that any necessary changes have been incorporated and that the dissertation is now given the final approval with reference to content, form and mechanical accuracy.

The dissertation is therefore accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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VITA

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ABSTRACT

The etiology and prevalence of Klinefelter Syndrome (KS) are examined in depth. A detailed explanation of the role of non-disjunction as the cause of cellular errors in both male and female gametes, leading to the chromosomal aneuploidy 47,XXY, is addressed as the putative cause of KS. This is followed by a comprehensive review of the literature regarding the variety, frequency and persistence of the symptoms typically associated with KS. The most common of these symptoms are infertility and hypogonadism. The effectiveness of treatments, particularly testosterone, for these symptoms is examined. Possible genetic links to the KS condition, including suggested explanations for its symptoms, are explored. Finally, the results of a qualitative study, which included responses from 33 participants, are analyzed in detail. Although a small convenience sample, much valuable information regarding their psychosexual experiences and challenges is presented. Common themes from the respondents are highlighted and areas for future research are available. The data presented offer the therapist a more complete knowledge and understanding with which to provide helpful and accurate counseling as well as appropriate referrals when working with KS men and their partners.

CONTENTS

CHAPTER 1

INTRODUCTION

Typically each human being is born with 23 pairs of chromosomes in each cell - other than the sperm and ovum- for a total of 46 chromosomes. Of these chromosomal pairs, 22 are common to both males and females and are called autosomes. The remaining pair is called sex chromosomes. Normally each female has two X sex chromosomes while each male has one X and one Y sex chromosome. So the normal male genotype would be 46,XY. This, however, is not always the case.

In 1942 Klinefelter et al. described a group of men who presented with gynecomastia, small testes, an inability to produce sperm and an increased excretion of follicle stimulating hormone (FSH). But it was not until 1959 (Jacobs & Strong) that these men were discovered to have an extra X sex chromosome resulting in a genotype of 47,XXY. The symptoms associated with this condition are referred to as Klinefelter Syndrome (KS). Some of these symptoms are hypogonadism, small testes, seminiferous tubule dysgenesis, learning difficulties, reduced or absent secondary sexual characteristics, a female type of fat distribution appearance, gynecomastia, increased height, and elevated gonadotropin levels (Ratcliffe 1999; Simpson et al. 2003, Visootsak et al. 2001).

Although the 47,XXY aneuploidy is the most common sex chromosome disorder, there are other variants in males that have been revealed by subsequent research. These include a 46XY/47XXY mosaicism; 47,XYY; 48, XXYY; 48,XXXY; and 49, XXXXY (Paulsen et al. 1968; Cammarata et al. 1999; Peet, Weaver, and Vance 1998). The focus of this study will be limited to the 47,XXY condition in males, even though cases have

been reported of individuals with a 47,XXY genotype and a female phenotype (Schmid et al. 1992; Saavedra-Castillo et al. 2005).

How many males does this actually affect? In 1991 Nielsen and Wohlert published the results of a study in Denmark of 34,910 newborns over a 13-year period. They found the 47, XXY condition in 1 per 576 boys. Another large study (Abramsky & Chapple1997) conducted in the UK, using a review of several population studies, concluded that about 1 in 800 had KS but nearly two-thirds of those estimated cases were never diagnosed. Those males who were diagnosed typically were karyotyped because of hypogonadism or infertility. A later large study done in Denmark (Bojesen et al. 2003) found that the prevalence of KS was 1 in 667 males, and reported that only approximately one fourth of males with KS are diagnosed - less than 10% are diagnosed before puberty.

In chapter 3 the author will discuss in more depth the history of the research on KS and the findings of recent studies, but first let's look at the cytogenic causes of the 47,XXY genotype. As noted above, sex cells (gametes - sperm and egg**)** are the only cells in the body containing only one set of chromosomes. These cells are made only in the gonads and are a result of a type of cell division called **meiosis**, which is unique in the body. To make gametes the body starts with a parent cell (germ cell) containing 2 sets of chromosomes. If it were to follow the usual cell division (mitosis) we would end up with 2 daughter cells that were identical to the parent cell. Although this is perfect for most cells in the body for the purposes of repair, replacement, growth, et cetera, it would not do for the production of sperm or egg, since each sex cell must contain only 1 set of chromosomes.

Instead the body uses the process of meiosis, which creates from the parent cell 4 different cells with only half the complement of the original parent cell. It does this by

going through 2 cell divisions. Let's look more closely at the details since this will be helpful in understanding how the process can go wrong. Before the germ cell goes through the 2 stages of meiosis, the DNA inside the cell is replicated. Following that replication, we have 4 sets of chromosomes (2 x 2 sets). The cell then goes through the first cell division (meiosis I) during which the genetic information splits into 2 cells - each containing 2 sets of chromosomes. This is followed by a second cell division (meiosis II) resulting in 4 cells - each containing only 1 set of chromosomes (Grimes and Warren 2004).

However, the process used to create these sex cells differs in males and females. In males the process is called spermatogenesis and takes place in the seminiferous tubules of the testes. In the developing embryo, germ cells enter the testes and differentiate into spermatogonia, immature cells that remain dormant until puberty. Spermatogonia are located around the periphery of the seminiferous tubules. At puberty, hormones stimulate these cells (46 chromosomes) to begin dividing by mitosis. Some of the daughter cells remain as spermatogonia but others become primary spermatocytes. Since they are produced by mitosis, primary spermatocytes have 46 chromosomes. Each primary spermatocyte goes through meiosis I (described above) to produce two secondary spermatocytes and then meiosis II to produce four spermatids, each having 23 chromosomes. For sperm there is a final step called spermiogenesis in which the spermatids become mature spermatozoa containing a head, midpiece, and tail. The head, or nuclear region, contains the 23 chromosomes and is surrounded by a nuclear membrane. The midpiece is the metabolic region, which contains mitochondria. The tail is the locomotor region used for movement. The sperm move into the epididymis where they mature and become capable of fertilizing a female gamete. Sperm production begins

at puberty and continues throughout the life of a male producing millions of sperm cells. The entire process, beginning with a primary spermatocyte, takes about 74 days (Young et al. 2004).

In females the process is called oogenesis and is more complicated. During the early stages of fetal development germ cells in the ovaries differentiate into oogonia, which divide rapidly to form thousands of cells - each having 46 (23 pairs) chromosomes. These oogonia do grow larger and become primary oocytes. The primary oocytes replicate their DNA and begin the first meiotic division, but the process stops in prophase (an early step of meiosis I) and the cells remain in this suspended state until puberty. Even though many of theses primary oocytes degenerate before birth, the two ovaries together still contain approximately 700,000 oocytes at birth. No more will be produced. This is the lifetime supply. And by puberty the number of primary oocytes has declined even further - to about 400,000.

Once puberty begins and the follicle-stimulating hormone exerts its influence, several primary oocytes start to grow again each month. One of the primary oocytes will outgrow the others and it resumes meiosis I. The other primary oocytes degenerate. This large primary oocyte undergoes an unequal division. Nearly all the cytoplasm and half the chromosomes go to one cell, which becomes a secondary oocyte. The remaining half of the chromosomes goes to a smaller cell called the first polar body. The secondary oocyte begins meiosis II but the process stops before completion (in what is called the metaphase stage). At this point ovulation occurs. Now if fertilization happens to take place, meiosis II continues. Again there is an unequal cell division with all of the cytoplasm going to the ovum with 23 chromosomes. The smaller cell from meiosis II is a second polar body. If fertilization does not occur, the second meiotic division is never

completed and the secondary oocyte degenerates. This then is another difference between the male and female. In spermatogenesis, four sperm cells capable of fertilization develop from each primary spermatocyte. In oogenesis, only one fertilizable cell develops from a primary oocyte and the others (the polar bodies) are not fertilizable and they degenerate. (Young et al. 2004). If fertilization does occur, a zygote with 46 chromosomes (typically) is created. Once the zygote is formed, mitosis takes over with 2 identical cells resulting from each cell division.

Errors, unfortunately, can occur at each stage of cell division. There are several possible patterns of meiotic cell division errors but it is believed that most errors are due to what is called non-disjunction; that is, the failure of members of a chromosome pair to separate properly. There are several types of non-disjunction that can occur. In true non-disjunction at meiosis I, the 4 chromatids (2 homologous pairs) fail to segregate. Instead, all 4 move to 1 cell and the other receives none. In another type of non-disjunction (independent), the 2 pairs do segregate from each other but, instead of each pair moving to a separate cell, both pairs move to the same cell. The result in each case is that one daughter cell has both pairs of parental chromatids and the other has none. Another possibility is that there could be premature segregation of sister chromatids within one of the homologous pairs during meiosis I. If this occurs, instead of 2 chromatids going to each daughter cell, 1 cell would receive 3 chromatids and the other cell only 1. Typically meiosis II cell errors occur when sister chromatids fail to separate. Of course, there are other possibilities. See figure 1 for a more graphic understanding of the various errors that may occur from non-disjunction.

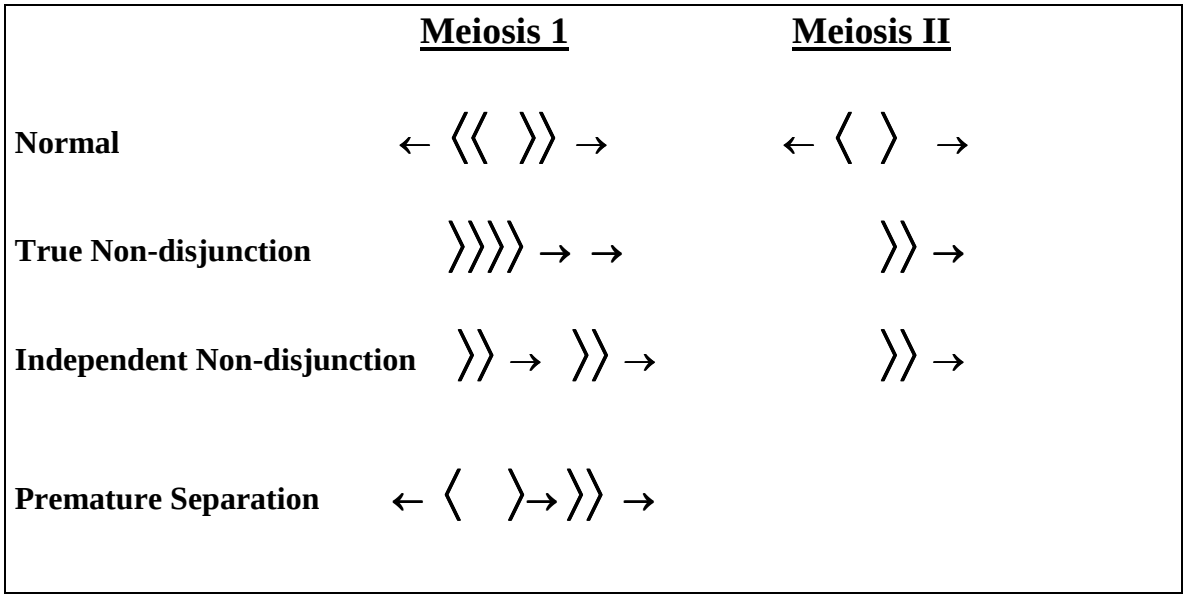

Figure 1. Meiosis. In normal meiosis I cell division, the homologous chromosomes segregate with 1 pair going to each cell. There are several abnormal meiosis I divisions including: true non-disjunction in which both pairs move together to 1 cell; independent non-disjunction in which each pair moves independently but to the same cell; and premature separation in which only 1 pair segregates resulting in 3 chromatids going to one cell and only 1 chromatid moving to the other. In normal meiosis II, one chromatid moves to each cell. In a non-disjunction division at meiosis II both sister chromatids move to one cell leaving the remaining cell with none of the pair (Adapted from Hassold and Hunt 2001).

So how exactly does this lead to 47,XXY? Figure 2 shows graphically how errors introduced at meiosis I, meiosis II or mitosis of the zygote can create the 47, XXY karyotype or a mosaic (a variation in the number of chromosomes in the body's cells). Remember that before meisosis I cell division takes place each individual chromatid has been replicated. So in figure 2 each cell example begins with 4 chromatids ready for cell division.

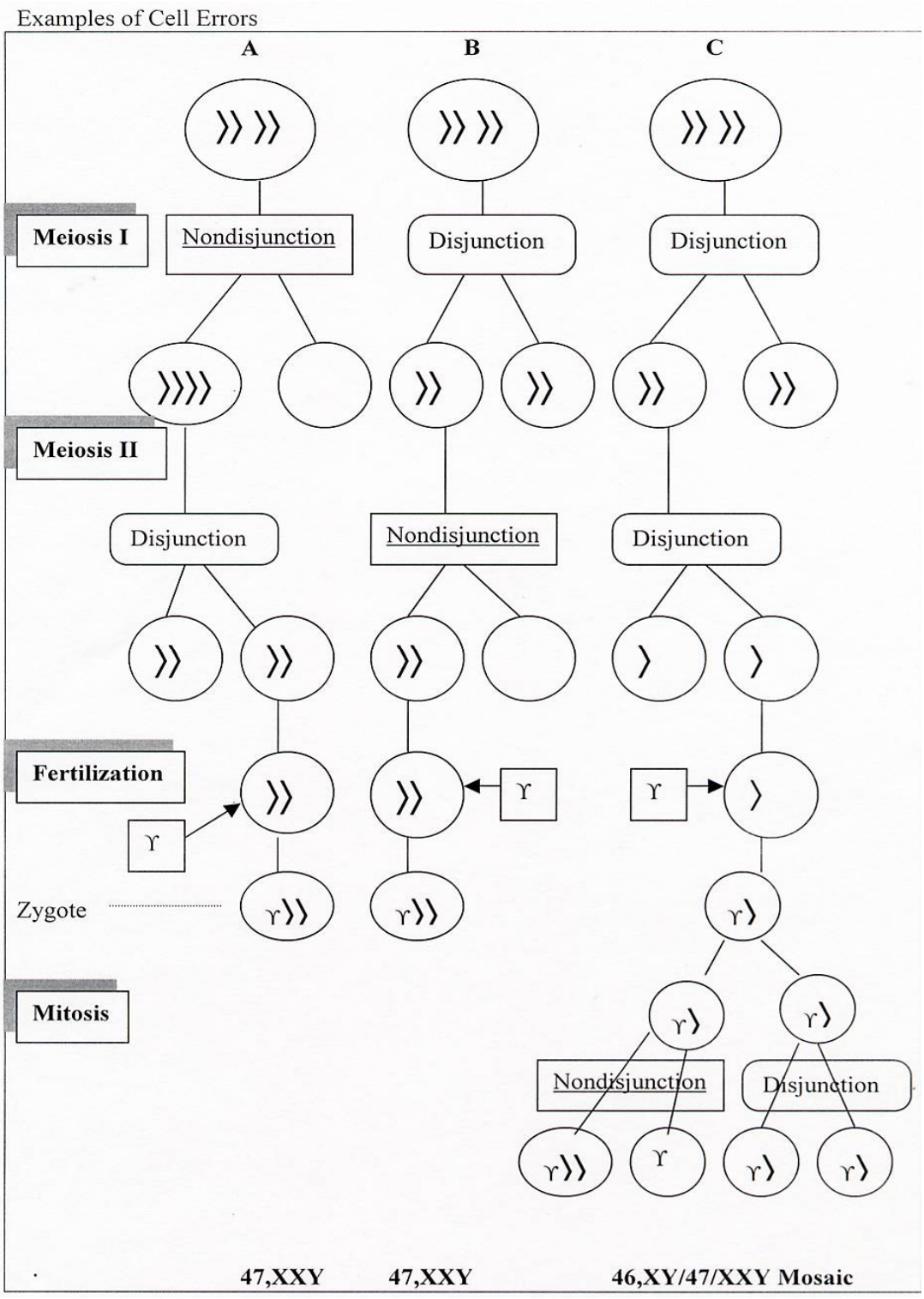

Figure 2. 47,XXY results when there is non-disjunction of paired chromosomes in either meiosis I (A) or meiosis II (B). It can occur in either spermatogenesis or oogenesis. But if the non-disjunction occurs in the fertilized egg (zygote) during mitosis (C) the result is a mosaic karyotype. Although 46,XY/47,XXY is the most common mosaic, there are many other forms (Adapted from Smyth 1999). [Prior to mitosis, replication of chromatids, not shown here, does take place.]

Although one might assume that 47,XXY occurs more frequently as a result of maternal errors, actually about one half of all cases are paternally derived and appear to occur at meiosis I. Maternal errors (the other half), however, occur mostly at meiosis I (48%) but also at meiosis II (29%) and even some at the post-zygotic (16%) stage. The other 7% were meiotic but unassigned. Maternal age may indeed be a factor (Thomas and Hassold 2003). But, whether a paternal or a maternal error in origin, KS is nevertheless the most common sex chromosome disorder. It is important for us to understand its effects.

CHAPTER 2

METHODOLOGY

The author used a qualitative analysis combining a review and summary of the research literature with a compilation of many personal accounts from the experiences of 47,XXY adult males diagnosed with KS. Their accounts were directed by a semi-structured questionnaire (see Appendix), which guided their input. For the development of the questionnaire, Haley and Mitchell (1995) was consulted. A semi-structured guideline stipulates specific points to be covered as well as open-ended questions. Respondents were gathered from the Internet.

The initial step of this study was a thorough review of the available research, current and historical, on KS. The research was analyzed to determine what the present knowledge is regarding the physical and psychosexual effects of KS. Research results, conclusions, and concerns are presented in chapters 3 and 4. The next step was to obtain input from those 47,XXY adult males diagnosed with KS who volunteered to participate in this study. Are there psychosexual effects that are common to this group of males? How have they been dealing with them? Has KS affected their relationships? Are there sexual issues of major concern? Are there gender identity issues? Have professionals been of any help? Responses to these questions and others, directed by the questionnaire described above, are presented in Chapter 5.

Qualitative research can help us better understand a target audience's range of behaviors as well as the feelings, perceptions and values that underlie and influence those behaviors. It uses in-depth studies of small groups of people to guide and support the construction of hypotheses and provisional answers to questions about conceptual relationships (Strauss 1987). Thus, the goal of this study was to provide a sound

knowledge base, which will be useful for sexological practice and future education and research. This includes an understanding of the KS condition, enriched with the personal accounts and insights of real people actually experiencing KS in their daily lives. Strauss refers to the inclusion of these two components in social research as the humanistic version. This approach to complex data is grounded theory. Compiling this study as described meets the design of qualitative analysis. The author compares the personal accounts submitted by the respondents with the gathered research and information. Additionally, the author interprets the personal data looking for recurrent themes (consistent threads) as suggested by Strauss.

This study incorporates confidentiality, informed consent and privacy. An independent and unique web site has been created on the Internet by the author to gather responses from adult male volunteers who have been diagnosed with KS. An invitation to inform potential volunteers was sent to seven Klinefelter organizations with a presence on the Internet. The invitation included the Internet address of the site and a brief description of the research. Upon entering the opening page of the site (www.klinefelter-xxy.org), the potential volunteer viewed a brief explanation of the research and an invitation to view an Informed Consent (IC) agreement (see Appendix) before deciding whether to participate or not. If he chose to participate, he was required to agree to the terms of the IC by clicking the appropriate item. At that point he was directed to the semi-structured questionnaire where he typed his answers to 26 items. This page on the web site is very secure as explained on the IC. Additionally, no personal information that would identify the volunteer was recorded. When completed, he submitted his responses by clicking on the button provided. The responses were electronically submitted to the

author. Only the author has access to the responses via a separate secured account that is password protected.

In the event a potential volunteer preferred a personal interview with the author/researcher, this option was offered on the web site from the IC page. By selecting the item that requests a personal interview (after agreeing to the terms of the IC), the volunteer was sent to a secure page where he was requested to enter his phone number and a best time to call. The entered information was sent directly to the author's secure, password protected account. When the researcher called the volunteer, the researcher confirmed that the volunteer had read and agreed to the IC, and that he understood that the interview was being recorded and that he agreed to that. Any volunteer was able to opt out at any time.

All computer-related communications were saved in password-protected files on a disk marked: *Confidential Research Data*. Non-computer communications (audio recordings) were filed in a locked drawer marked *Confidential Research Data.* Summarized data only will be published.

CHAPTER 3

RESEARCH FINDINGS

Although there have been numerous studies on KS over the past several decades, many were based on a small sample size or were subject to ascertainment bias or methodology flaws (Theilgaard 1984; Samango-Sprouse 2001; Simpson et al. 2003). Some of the earlier research, using populations from mental and penal institutions, arrived at questionable conclusions regarding the risks for severe symptoms, such as, mental retardation and psychiatric problems (Visootsak et al. 2001). Nevertheless, other studies have provided insights into the typical 47, XXY phenotype, clarified earlier findings and raised awareness as to the wide interindividual variability of the physical, cognitive and behavioral symptoms that often are part of KS. The author will review this research from the perspective of the major clinical conditions attributed to this complex and interesting condition.

Hypogonadism

Perhaps the most common symptom of KS is primary or hypergonadotropic hypogonadism as a result of a testicular disorder associated with small, undeveloped testes (Laron and Hochman 1971; Boisen 1979; Ratcliffe, Butler, and Jones 1990; Kamischke et al. 2003). In the adult male the testes (and the adrenals) secrete several steroid hormones, called androgens. Testosterone is the most potent and abundant androgen. Normal male serum levels of testosterone and its derivatives are thought to be important in the maintenance of male secondary sexual characteristics, bone and muscle mass, strength, cognition, sexual function, and overall well-being.

Of course, the testes also produce sperm. The production of both hormones and sperm is controlled by the so-called hypothalamic-pituitary-testes (HPT) axis. Here is how it normally works (Figure 3). The hypothalamus produces gonadotropin-releasing hormone (GnRH), which in turn stimulates the pituitary to produce luteinizing hormone (LH) and follicle stimulating hormone (FSH). LH stimulates the Leydig cells in the testes to synthesize and secrete testosterone (T). FSH promotes spermatogenesis and secretion of Inhibin B by binding to Sertoli cells within the seminiferous tubules in the testes. When T and its metabolites are produced, they inhibit in a negative feedback loop the pituitary's production of LH and FSH and the secretion of GnRH in the hypothalamus. Inhibin B also inhibits FSH (Grant and Anawalt 2003). Similarly, when T is below normal levels, additional LH is produced in a positive feedback loop, which in turn increases T. Agreement on the normal level of T, however, is a contentious issue, which we will discuss in a subsequent section.

It has been suggested that in KS males this feedback mechanism may be dysfunctional (Capell et al. 1973). The FSH and LH levels in KS males are often much higher than normal but their T level is typically in the low normal or below normal range (Smyth and Bremner 1998; Grant and Anawalt 2003; Jarow 2003). It is speculated that serum T levels may be normalized at the expense of elevated gonadotropins, or there could be partial androgen resistance (Simpson et al. 2003). There is some evidence that the loss of Sertoli cells may be involved in preventing the inhibition of FSH (Anawalt et al. 1996).

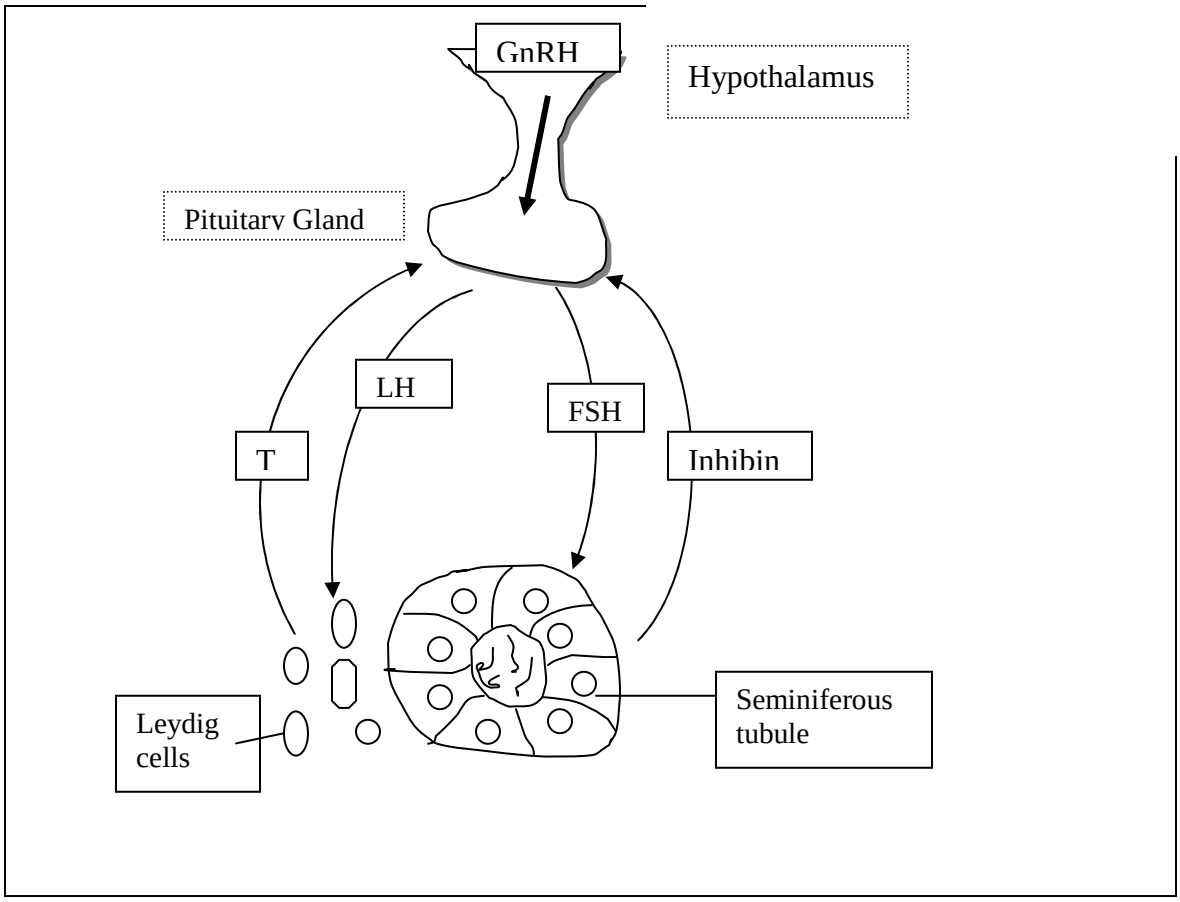

Figure 3. Schematic of the hypothalamic-pituitary-testes axis showing the interaction between the various components with positive and negative feedback loops (Adapted from Jarow 2003).

In a prospective study that included a testicular biopsy of each of 14 KS males ages 10 to 14, Wikstrom et al. (2004) found that early adolescent boys with KS have testicular germ cells that display a maturational arrest at the level of type A (immature) spermatogonia. No meiotic cells were detected in any of the biopsy specimens, and the onset of puberty was associated with depletion of spermatogonia. These KS boys had germ cells that vanished in early puberty when testicular volume increased. Their serum gonadotropin and inhibin B levels displayed pathological changes later during midpuberty. Christiansen et al. (2003) found similar results. That is, during late puberty

inhibin B levels decreased gradually to the low or immeasurable levels observed later in adult KS, while remaining unchanged in the controls. Inhibin B levels are considered to reflect Sertoli cell function (Andersson and Skakkebaek 2001).

Salbenblatt et al. (1985) looked at 40 KS males and found that early pubertal boys showed initial testicular growth and normal serum T levels; however, serum FSH and estradiol concentrations were significantly elevated. Leydig cells also produce and secrete estradiol, although the major source of estradiol in adult men is peripheral conversion of testosterone to estradiol in fat cells by an enzyme called aromatase. By midpuberty, the KS subjects were uniformly hypergonadotropic and their testicular growth had ceased. Serum T concentrations after age 15 remained in the low-normal adult range.

In a longitudinal study of children born in Scotland with sex chromosome abnormalities, Ratcliffe, Butler, and Jones (1990) reported on the follow-up of 19 KS males from ages 10 to 22 years. The researchers noted no delay in the onset of puberty but gonadotropin became raised six months after the onset of puberty. As puberty progressed, a pattern of low androgen levels was noted (n=8). By age 16 they were significantly lower than in controls. The size of the penis was normal (no definition of normal was offered) in 77 % of their sample, but testicular size was seldom greater than 5 ml, as compared with social class-matched controls.

Fertility

The post-pubertal, non-mosaic KS man usually has an absence or subnormal concentration of live spermatozoa in his semen. As a result, he is infertile (Brugh and

Lipshultz 2004). Testis biopsies often show sclerosis and hyalinization (Turek and Pera 2002). However, testicular spermatozoa can be retrieved in most KS men using microscopic testicular sperm extraction. When followed by intracytoplasmic sperm injection, the results (healthy births) have been encouraging (Hopps, Goldstein, and Schlegel 2002). Unfortunately, recent research indicates that there are no clinical parameters that predict successful sperm retrieval in non-mosaic KS males (Vernarve et al. 2004). Furthermore, the inheritance of genetic conditions remains a valid concern (Okada et al. 1999; Ulug et al. 2003; Staessen et al. 2003; Lanfranco et al. 2004; Foresta 2005).

Gynecomastia and Breast Cancer

Gynecomastia is the growth of glandular tissue in male breasts. Physiologic gynecomastia occurs in newborns and in adolescents at puberty. In the newborn the increased breast tissue usually disappears in a few weeks. Adolescent gynecomastia is common during puberty and usually regresses by age 20 years. Pathologic gynecomastia is due to T deficiency, increased estrogen production, or increased conversion of androgens to estrogens. KS is one of the conditions associated with gynecomastia.

Estradiol is the growth hormone of the breast. Too much estradiol leads to the excess growth of breast tissue. When there is a decrease in androgen production, an absolute increase in estrogen production, and an increased availability of estrogen precursors for peripheral conversion to estradiol, you often get gynecomastia. T is an antagonist of estradiol; that is, it acts to oppose estradiol's actions. So a given estradiol level will lead to breast growth in a man with low T, and not in a man with higher T levels. This is referred to as the T to estradiol ratio (T/E_2). Estradiol is one of three

naturally occurring estrogens. In the body these are all produced from androgens through enzyme action. KS men commonly have abnormal T to estradiol (T/E_2) ratios. Fertile men have T (ng/dL)/E_2 (pg/mL) ratios of 14.5 +/- 1.2, whereas men with Klinefelter's syndrome have a T/E_2 of 4.4 +/- 0.5 (Hopps, Goldstein, and Schlegel 2002; Raman and Schlegel 2002). Although one might think that the logical solution is to provide KS men with supplemental T, T administration has inconsistent effects on this population (Fawzi and Bain 2005).

Although Ratcliffe, Butler, and Jones (1990) noted pubertal gynecomastia in many of their subjects, progressive gynecomastia had occurred in only 1 of the 19 KS boys in their study. The results are limited since puberty was incomplete for the whole cohort. In a subsequent article Ratcliffe (1999) notes that she observed gynecomastia in 56%, compared to 36% in the controls, but most of these were transient, lasting from 1 to 3 years. No additional data were provided so it is difficult to generalize based on this sample.

Zitzmann et al. (2004) report that gynecomastia was present in half their KS patients (N=77); however, the sample was selected from a larger cohort of 244 KS patients based on certain inclusion criteria. Thus it may not reliably represent the total population.

Sasco, Lowenfels, and Pasker-de Jong (1993) reported the results of a meta-analysis on male breast cancer. They concluded that those with KS were at major risk for breast cancer. In a retrospective study of 93 male breast cancer patients in Sweden, Hultborn et al. (1997) found a 50-fold increased risk of developing breast cancer in males with KS, relative to normal males. It is important to highlight not only the possible

ascertainment bias in this study but also that the median age at diagnosis for this group was 72 years of age.

In Britain the mortality and cancer risks of 646 KS males were assessed. The researchers found a significantly increased risk for diabetes, breast cancer and lung cancer among 47,XXY males (Swerdlow et al. 2001). Note that only 2 of the 47,XXY male deaths were due to breast cancer. The cancer incidence in 696 KS men was examined in Denmark (Hasle et al. 1995). That study indicated that the overall cancer incidence was **not** increased when compared to the specific cancer rates for Danish men. No cases of breast or testis cancer were observed.

A more recent study done in Denmark on a cohort of 781 KS males and a control group of 3803 men looked at the causes of death in each group. In this study KS was associated with an increased mortality risk of 40% and a reduction in median survival of 2.1 years compared with an age-matched control group. The mortality was significantly increased for infectious, neurological, circulatory, pulmonary, and urinary tract diseases but not due to breast cancer and cerebrovascular diseases (Bojesen et al. 2004). This study did not address socioeconomic conditions and lifestyles that may have contributed to the increased mortality risk.

However, Weiss, Moysich, and Swede (2005) reviewed the existing body of evidence for genetic and epidemiologic risk factors for breast cancer in men. These researchers found KS to be a major genetic factor associated with an increased risk of breast cancer.

Osteoporosis

Osteoporosis is a condition that features loss of the normal density of bone leading to abnormally porous bone. This disorder of the skeleton weakens the bones resulting in an increase in the risk of bone fractures. Bone mineral density was measured in 42 patients with Klinefelter's syndrome (Kubler et al. 1992). In this study half the subjects were given T substitution; 10 patients before the age of 20 and 11 patients beginning after the age of 20. The other 21 patients were without therapy. They found significantly lower bone mineral density in patients without therapy and in patients when the therapy began later compared to normal individuals. There was a positive correlation between bone mineral density and plasma T and a negative correlation between plasma T and age for patients without therapy. They concluded that low T levels before or during puberty cause inadequate bone development and low bone mineral density in Klinefelter syndrome. Only early T substitution may prevent bone mineral deficiency. Although these findings do suggest that early testosterone substitution may prevent bone mineral deficiency in this small sample, there is no causality demonstrated in the data provided.

Horowitz et al. (1992) studied the bone-related biochemical variables in a group of 22 KS males and found decreased bone density in about 25% of them compared to controls. Androgens may in fact protect men against osteoporosis (Vanderschueren et al. 2004) so KS males with an androgen deficiency could be at increased risk.

Cardiovascular and Other Risks

Three researchers in Romania (Lichiardopol, Mota, and Panus 2004) assessed 31 Klinefelter patients for metabolic changes that might increase their cardiovascular risk. When compared to controls, 56% of the KS males evidenced hypercholesterolemia. None had diabetes but 16% had elevated glycemic levels and 16% were obese.

In a series of 412 KS patients observed over periods ranging from 1 to 20 years, the frequency of hypostatic ulceration, deep vein thrombosis and pulmonary embolism was found to be raised. The prevalence of past or present hypostatic ulceration was 6%, which is 20-50 times higher than in the general population. The incidence of deep vein thrombosis in KS subjects was 22.8 cases per 10,000 patient-years at risk compared to around 4 new cases in the community. The frequency of pulmonary embolism was 16 cases per 10,000 patient-years at risk compared with an expected figure of 0.9 to 3 cases (Campbell and Price 1981). In a much smaller study (n=13) restrictive lung defects were found in 61 percent of the KS patients (Morales et al. 1992).

Several autoimmune diseases, such as systemic lupus, have been associated with KS but most of the research is based on very small sample sizes. Many are studies of only 1 to 5 KS subjects - the majority with a sample size of 1 or 2 subjects (case studies). These sample sizes are too small from which to draw any reliable or meaningful conclusions. Admittedly, some of the other studies cited above also suffer from limited sample sizes.

And, finally, Lachman, Kim, and Koo (1986) claim that the incidence rate of KS among patients with mediastinal germ cell tumor is 30 to 40 times that of the general control population.

Intelligence, Learning Disabilities

The Denver Study, a 36-year study which followed 11 non-mosaic 47,XXY subjects and controls since birth, concluded that the XXY males had lower verbal and performance IQ scores than their sibling controls but their scores were in the normal range (Bender, Linden, and Harmon 2001).

In another study completed in Canada (Rovet et al. 1996), the researchers presented findings from a 20-year study of an unselected group of 36 KS boys and 33 sibling controls. The KS boys evidenced a verbal cognitive deficit and significant underachievement in reading, spelling and arithmetic. They were most likely to have a generalized type of learning disability along with deficits in written language skills. Nevertheless, many of these KS males had completed high school

Similarly, Ratcliffe, Butler, and Jones (1990) found in their cohort of 19 KS boys the mean verbal IQ scores and performance IQ scores to be significantly lower than controls and siblings. 42% of KS boys required speech therapy and 77% experienced difficulty in learning to read compared to 18% of controls.

Thirty-five KS males, aged 16 to 61, and 22 controls were evaluated with a comprehensive neuropsychological battery by Boone et al. (2001). The Klinefelter patients scored significantly below controls in language skills, verbal processing speed, verbal and nonverbal executive abilities, and motor dexterity. Fales et al. (2003) suggest that men with KS have intact nonverbal reasoning abilities, but that a difficulty in encoding verbal information into working memory may underlie their executive and linguistic impairments. Geschwind and Dykens (2004) suggest that further research needs

to be done to determine how the learning disabilities respond to hormonal or cognitive-based therapies.

Khalifa and Struthers (2002) screened DNA samples from 1205 patients referred for fragile X syndrome because of mental retardation (MR) of unknown cause. Of these 8 were found to have KS. The researchers state, “KS might be the most common cause of MR of unknown etiology among prepubertal males.” This seems to be an unwarranted and misleading conclusion since by definition the causes of the other cases of MR are of unknown etiology and thus one cannot make the appropriate comparisons. Nor has causality been demonstrated even in these 8 cases. The 8 KS cases represent less than .7 % of the total selected cohort.

In summary, although there is much evidence of learning disabilities being associated with KS, there is no evidence that mental retardation is a feature of this syndrome.

Brain Structure

Patwardhan et al. (2000) did some interesting research on brain morphology using a small, unselected cohort of 10 KS subjects and high-resolution magnetic resonance imaging (MRI). They compared the regional brain volume measurements of the KS subjects to 10 age-matched controls. The KS subjects showed a significant reduction in left temporal gray matter. They concluded that this is consistent with the language deficits associated with KS. Half of their subjects had received T supplementation since puberty to which they ascribed a relative preservation of gray matter and increased verbal fluency. This is a stretch based on the low sample size (5) of those taking T.

Seeking to find evidence of an alleged link between sex chromosome aneuploidies and an increased risk of psychiatric illnesses, Patwardhan et al. (2002) again focused the MRI on 10 subjects (47,XXY) and controls. The researchers looked at the morphology of the hippocampus and the amygdala. Amygdala volumes were significantly reduced in the XXY men compared to controls. The researchers concluded that the alteration in the amygdala volume might provide a neuroanatomic basis for mild psychopathology and behavioral dysfunction in XXY men. The amygdala is part of the limbic system of the brain and functions to control autonomic, emotional and sexual behavior. It is important to note, however, that no causality was demonstrated in this small study (n=10) but it is an interesting hypothesis.

Rose et al. (2004) also used the MRI on 20 XXY children and 40 age matched controls. They not only found the XXY patients to have smaller amygdala volumes but also smaller hippocampus volumes when compared to controls. What does this mean? Since the interactions between hormones, sex chromosomes and the brain are so complex, it is difficult to arrive at any definitive conclusions. But the researchers are looking at the vulnerability to stress of the brain based on these factors.

Itti et al. (2003) studied cerebral perfusion (the injection of fluid into a blood vessel in order to reach an organ or tissues) in 9 right-handed KS men with language difficulties compared to 22 controls. They found asymmetry toward the left hemisphere in controls but perfusion for KS patients was mostly symmetrical in the upper temporal and lower parietal regions of the brain. Interestingly, verbal test scores were inversely correlated with perfusion changes. The typically asymmetric regions of the brain could be altered in KS men.

Shen et al. (2004) obtained similar results in their study. They examined the brains of 34 XXY males and 62 normal male controls and found a pronounced volume reduction in the brains of XXY males compared to controls, localized at the insula, temporal gyri, amygdala, hippocampus, cingulate, and occipital gyri. They also found an overall enlargement of ventricles and overall volume reduction of both white matter and gray matter in XXY males. These correlations are intriguing and warrant further study but to date no evidence of direct causality exists.

In a study done using the Danish Cytogenic Central Register and the Psychiatric Central Register, Mors, Mortensen, and Ewald (2001) found no increased risk for schizophrenia or bipolar disorder in the KS population.

Psychosocial/Psychosexual

The Denver Study, a 36-year study that followed 11 non-mosaic 47,XXY subjects and controls since birth, concluded that the XXY males had lower psychosocial scores than their sibling controls and had lower levels of educational achievement and career success. But 10 of the 11 had completed high school and held full-time employment, most were married and were financially independent. Their overall adaptation was positive (Bender et al. 2001) particularly given that earlier in this study these same young men were found to have decreased psychological resources and about half were diagnosed with mild to moderate psychiatric disorders (Bender et al. 1995). They appear to have navigated the challenges of early adulthood with moderate success, although less so than their siblings (Bender et al. 1999).

An assessment of personality and psychosexual development of 12 KS boys at a mean age of 16.7 years, identified at birth in a population screening study and compared with a control group matched for age and social class, showed the XXY boys to be more timid and less self-confident and to have more problems in relating to their peer group than the controls. They also showed some evidence of delayed or impaired development of sexual interest. In general, the differences were not marked (Bancroft, Axworthy, and Ratcliffe 1982).

Ratcliffe, Butler, and Jones (1990) in their longitudinal Edinburgh study reported that the XXY boys (n=10) were more fearful, solitary and not liked by peers, and had more psychiatric referrals. Personality questionnaire results indicated the XXY boys were more affected by feelings, were tender minded and dependent. Parents and clinical observations confirmed these results. This study is limited by its small sample size.

Comparison of 16 Danish KS boys, 15 to 16 years old, with normal controls indicated that on average these subjects had increased height, reduced weight, impaired hearing, slightly lowered intelligence, poor school performance, increased incidence of psychological consultation and lowered sexual activity compared with their peers (Sorensen 1992).

Raboch, Mellon, and Starka (1979) looked at 110 adult KS men and found that the sexual activity of those KS men was weaker than the controls. Unfortunately their study suffered from ascertainment bias and perhaps some methodology problems.

There are several interesting case reports of psychosexual variants in KS males (Money 1991; Davidson 1994; Herzog and Money 1993; Seifert and Windgassen 1995) but they have little, if any, significance to the general KS population since interesting and unique psychosexual variants occur in all sub-populations.

A self-referred group of 38 non-mosaic KS men with a chief complaint of infertility was evaluated for sexual function disturbances (Yoshida et al. 1997). No significant difference between the KS men and the controls was found in sexual function disturbances but the frequency of sexual intercourse per month in KS patients was significantly higher than controls.

Gotz, Johnstone, and Ratcliffe (1999) compared rates of criminal convictions in 17 XXY men to controls and found no increase in the rate of criminal convictions. Nielsen and Pelsen (1987) did a 20-year follow-up study on 34 KS males with evaluations at 27, 37 and 47 years of age. They found that the KS males made considerable improvement as they aged in the areas of mental health, working capacity, social adjustment, relations with other people and activity level.

Raboch, Pietrucha, and Raboch (2003) assessed the coital activity of 77 KS patients as well as their serum T levels and compared them to a group of men with normal semen parameters. As you would expect, the serum T levels of the KS males were significantly lower than the controls, but the coital activity did not differ significantly.

Testosterone

The major medical treatment suggested for many of the clinical conditions discussed above is testosterone (T) supplementation. Some of these studies have already been referenced in the preceding sections. Let's look at some of the other relevant studies.

Nielsen, Pelsen, and Sorensen (1988) reported that 77% of the 30 KS adults – average age of 25 years - who received T for the first time as adults were judged to have

benefited. They showed better mood, less irritability, more energy and drive, more endurance and strength, better concentration and better relations with others. This was based on a follow-up exam conducted an average of 3.6 years after treatment.

Several immunological parameters were evaluated in 26 patients with KS prior to androgen replacement treatment (ART) and the results were compared with those in 19 healthy control subjects. Patients were then treated with T for 6 months. The pre- and post-treatment findings were compared. The study concluded that the **lack** of testosterone in patients with KS enhances cellular and humoral immunity and that ART may suppress this (Kocar et al. 2000).

Recently, Lahlou et al. (2004) looked at 18 prenatally diagnosed 47,XXY infants and 6 XXY adolescents. They compared their various hormone levels, over a period of 1 to 3 years, to reference values of 215 infants. In XXY infants, only T differed from controls during the first trimester, which suggest that testosterone secretion is impaired in infants with XXY. Since there is experimental evidence in primates that testosterone secretion in the neonatal period can be important for adult sexual competence, they offered that the benefit of compensatory testosterone administration in XXY infants during the first trimester of postnatal life deserves consideration.

There are several issues regarding T supplementation that influence decisions regarding the appropriateness of T supplementation for a specific KS male. First, the best method for measuring serum T is controversial. Ideally, one would want to determine a patient's serum bioactive T level, that is, the amount of T in the serum that is available to produce an androgen effect in the end organ. But serum bioactive T levels are difficult to determine since most circulating T is protein bound. About 40% is vigorously bound to the sex hormone-binding globulin (SHBG). Thus, it is not bioactive. An additional 58%

is weakly bound to albumin but may be bioavailable because T quickly dissociates from albumin into body tissues (Wheeler 1995). About 2% of free (unbound) T is bioactive. Therefore, the level of bioavailable T is the sum of T bound to albumin plus free T (Grant and Anawalt 2003). Some labs use complicated formulae to calculate free T levels. Vermeulen, Verdonck, and Kaufman (1999) studied simple methods for the estimation of free testosterone and concluded that a value obtained by a calculation from total testosterone (TT) and SHBG, as determined by immunoassay, appeared to be a rapid, simple, and reliable index of bioavailable T. In a more recent study, based on a large dataset of nearly 4000 blood samples from a routine diagnostic endocrinology laboratory, employing the centrifugal ultra filtration free testosterone (FT) assay, Ly and Handelsman (2005) concluded that a simple, empirical calculation can provide a robust, reliable and valid estimate of blood FT from TT and SHBG in the same sample. They developed empirical equations to determine FT after dividing blood samples into 2 groups: above and below 5nM of TT. They compared the results of their FT equations and 3 widely used calculated FT methods with the laboratory FT measurements. Not only did their new empirical FT equations have improved fidelity with laboratory measurements but also the other 3 calculated methods deviated systematically from the laboratory FT values. The researchers do note, however, an important caveat on the present empirical approach, that is, its reliance on the specific TT and SHBG assays used in this study. It cannot be assumed that the specific equations would be portable to other assay combinations, or even the same assays if they were significantly modified. Ly and Handelsman (2005) remind us that the concept of FT being the most biologically active part of a circulating hormone with the protein-bound part a biologically inactive buffer lacks theoretical validity or empirical proof. Neither do they find that the bioavailable

assay demonstrates any convincing evidence of providing either superior or additional biological information to TT measurements. Will FT measurements provide any additional clinical value over the well-established clinical gold standard of blood TT measurements to confirm the clinical diagnosis of treatable androgen deficiency? Grant and Anawalt (2003) suggest we use serum TT as the initial assay until the measurement of bioavailable T or calculated free T levels become widely available and validated in a wide spectrum of patients.

The second issue regarding the appropriateness of T supplementation is the timing of drawing the blood for testing, since TT levels vary with a circadian rhythm. TT peaks at about 8 AM and declines to a low point by 8 PM (Bremner, Vitiello, and Prinz 1983). If the normal range for TT levels is based on the peak morning levels of young normal men, then the blood sample should be taken close to the 8 AM time. This may be a minimal issue for older men since the circadian rhythm in elderly men is considerably blunted and shifted in time compared to young men (Tenover et al. 1988).

Third, how many T measurements are needed to confidently confirm a diagnosis of hypogonadism? About 35% of men who were classified as hypogonadal on the basis of a single low T level were found later, within 24 hours, to have average T levels within the normal adult male range (Swerdloff et al. 2000). The variation within a given subject in T levels is particularly problematic in older men who exhibit T levels that fluctuate between the lower part of the normal range and slightly below normal. Because the diagnosis of hypogonadism usually implies a need for, and commitment to, long-term T treatment, experts in the field recommend that at least two low T values be obtained to confirm the diagnosis of hypogonadism. And finally, the significance of low normal T

levels and the ability of low T levels to predict improvements in clinical outcomes with T therapy are not known. Matsumoto and Bremner (2004) sum it up this way:

> What is needed now is refocusing of attention to more rigorous validation and standardization of the accuracy and normal reference ranges for these assays to alleviate the confusion that has arisen in the clinical and research community as a result of the variability and discrepancies in T assays.

Wang et al. (2004) examined serum T levels in pedigreed samples taken from 62 normal and 60 hypogonadal males by four commonly used automated immunoassay instruments and two manual immunoassay methods and compared results with measurements performed by a gold standard method. They concluded that these immunoassays are capable of distinguishing non-hypogonadal from hypogonadal males *if adult male reference ranges have been established in each individual laboratory.* They did note, however, that at low serum T levels there was a lack of precision and accuracy.

Aromatase Inhibitors

Aromatase is an enzyme that is present in the testes, adipose tissue and brain. This enzyme is responsible for the conversion of testosterone to estradiol. In the testes aromatase activity is primarily localized in Leydig and Sertoli cells. It is thought that increased estradiol levels are detrimental to sperm production and may impair fertility. And it may also be implicated in gynecomastia.

Aromatase inhibitors are pharmaceutical agents that inhibit the aromatization of testosterone to estradiol. They can be either steroidal or nonsteroidal. Pavlovich et al. (2001) studied a cohort of men with severe infertility who had a T to estradiol ratio (T/E_2) of less than the 20^{th} percentile of normal distribution. They were treated with 50 to

100mg of testolactone, a steroidal aromatase inhibitor, orally twice daily. Serum testosterone increased, serum estradiol decreased and testosterone-to-estradiol ratios increased dramatically overall and were well within the normal range. Of the 45 treated patients 44 had an increased ratio while on testolactone - an average increase of 254%. LH levels did not change during treatment. However, only 6 of the treated patients were KS males, 2 of whom were obese, so this study may have limited applicability to the KS population.

Raman and Schlegel (2002) evaluated the effect of anastrozole, a nonsteroidal aromatase inhibitor, compared to the effect of testolactone on the hormonal and semen profiles of a group of infertile men with abnormal baseline testosterone-to-estradiol ratios. The testolactone group had an increase in the testosterone-to-estradiol ratio, including 17 with Klinefelter syndrome. The anastrozole group also showed an increase in the testosterone-to-estradiol ratio **with the exception of the KS men who did not**.

Additional research needs to be done to determine the relative benefit of aromatase inhibitors as compared to, or in addition to, T supplementation,

CHAPTER 4

GENETICS

We reviewed the putative causes of the 47,XXY genotype in chapter 1, but what is it about this XXY genotype that causes the widely varying group of symptoms called Klinefelter Syndrome (KS)? Although evidence points to various endocrine disorders as being implicated, what causes those disorders; that is, what actually is the root cause of KS? One possibility is X-inactivation.

To appreciate the theory of X-activation we must first understand its genetic context. Each chromosome contains a molecule of DNA with hundreds to thousands of genes arrayed along it. Each gene contains a segment of DNA. Genes provide the templates for the production of proteins - molecules that perform a wide variety of specialized tasks. The instructions for making proteins are written with a four-letter alphabet. Each letter represents one of the four chemical units, called nucleotide bases, strung together in a precise order in DNA. A single misspelling in the DNA sequence can make a protein malfunction and perhaps cause disease or disorder.

But genes do not simply provide templates; they also include instructions for when a gene should initiate protein production. Although most cells contain a complete copy of the genome, they specialize for a particular task. So what is critical in a cell is which of its genes are switched on. By switching on only at specific times and in specific environments, genes can control the growth of proteins in different ways in different cells (Marcus, 2004). And the expression of 1 gene can act as a precondition for the expression of another. The result can be a single gene indirectly launching the expression of many others – perhaps hundreds or even thousands of other genes.

X-inactivation

As noted earlier, the X chromosome is only one of the sex chromosomes normally present in humans. Typical females, since they have 2 X chromosomes, have 2 alleles (alternate forms of a gene) for every gene on the X chromosome. Males (XY), having (usually) only 1 X chromosome, have only 1 allele. Early in the embryonic development of females, most of the genes on 1 of the X chromosomes in each cell (except future oocytes) are inactivated. This phenomenon is called X-inactivation or Lyonization. This physiological mechanism of X-inactivation equalizes the gene dosage effects on the sex chromosomes (Lyon 2002). The inactive X-chromosome can be maternal or paternal in origin. The choice of the X-chromosome to be inactivated is random with respect to origin and independent of choice of other embryonic cells. So a female may express X chromosome genes inherited from her father in some cells and those from her mother in others. There is a specific region, called the X-inactivation center, under the control of the XIST gene that shuts off much of the chromosome. A few genes do, however, remain active. Because this inactivation occurs early in development, the adult has patches of tissue that are different in their physical expression of the X-linked genes. (Lewis 2001).

Since males (XY) typically have only 1 X-chromosome, X-inactivation is unnecessary. However, KS males do have 2 X chromosomes in addition to the Y, so X-inactivation is relevant. Also, there are some genes in the tip of the long and short arm of the Y-chromosome that do have homologues on the X chromosome. These areas on the Y are called the pseudoautosomal regions (PARs). As a result, in the typical XY male there are 2 active copies of these genes (1 on the X and 1 on the Y) that normally escape

inactivation. In the XXY male we could see faulty X-inactivation of some genes with altered results, perhaps even 3 copies of the gene instead of the 2 normally present (Geschwind et al. 2000).

Iitsuka et al. (2001) studied 17 XXY males and found results suggestive of skewed X-inactivation, which might be involved in the phenotypic variability between KS subjects. Zitzmann et al. (2004) studied 77 newly diagnosed and untreated KS adult patients (ages 18 –65), who had no history of previous androgen use, for the influence of X chromosome inactivation. They also investigated the relationship to the androgen receptor (AR) gene's CAG length in order to explain the marked variation in the KS phenotype. Of the 77 subjects, 48 were hypogonadal. The study also investigated the pharmacogenetic effects occurring under T substitution.

To understand the results of this study it is important to remember that androgen receptors allow the body to respond appropriately to androgen hormones. The receptors are present in many of the body's tissues, where binding to androgens activates them. The active androgen-receptor binds to DNA and regulates the activity of androgen-responsive genes. By turning the genes on or off as necessary, the androgen receptor helps direct the development of male sexual characteristics. In one region of the AR gene, a DNA segment, known as CAG, is repeated a number of times. Normally, the number of CAG repeats ranges from fewer than 10 to about 37. Mutations, inserts or deletions of multiple DNA base pairs (repeats) in the gene can affect how the gene is processed into a protein, which can lead to an abnormal protein or prevent the receptor from binding to androgens. If this happens, cells would be less responsive to androgens or unable to use these hormones at all. The length of the CAG repeats is inversely associated with androgen action and might account for the marked variation in phenotypes.

The results of the study indicated that the shorter (less repeats) CAG allele was the one preferred for X-inactivation; the presence of long CAG repeats was predictive for gynecomastia and smaller testes. There was a positive association between CAG length and body height but an inverse relationship to bone density. In addition, the relation of arm span to body height were correlated to CAG length. With T substitution, men with shorter CAG length exhibited a more profound suppression of LH levels, augmented prostate growth, and higher hemoglobin concentrations. Zitzmann et al. (2004) concluded that the CAG repeat polymorphism of the AR gene in conjunction with X-chromosome inactivation patterns could explain variations in the phenotype of KS patients. The androgen effects of T substitution are pharmacogenetically modified. This finding is increased by the preferred inactivation of the more functional short CAG allele.

More recently, Zinn et al. (2005) looked at genetic factors, including skewed X inactivation and AR CAG repeat lengths, that might influence the phenotypic variability of KS. They studied 35 XXY boys and men ranging from 0.1 to 35 years of age, 24 of whom were ascertained by antenatal diagnosis for advanced maternal age. Only 2 of the subjects were older than 18. The investigators found a highly significant negative correlation between AR CAG repeat length and penile length SD score but no significant correlation with testicular volume, height or the presence of gynecomastia. Skewed X inactivation alone did not account for the variability of the KS phenotype. The young ages of their subjects may have been a factor in their results.

Delisi et al. (2005) looked at 11 XXY men, 10 of who had some form of psychiatric disturbance. Compared to age-matched controls the XXY males had significantly smaller frontal lobes, temporal lobes and superior temporal gyrus cortical volumes on both sides of their brains. They noted cognitive deficits in executive

functioning and verbal communication. The researchers concluded that the excess expression of one or more X-chromosome genes influences certain related structural brain developments and might contribute to the deficits noted. They suggest that genes that escape inactivation would be prime candidates. Although this study has severe limitations, it does add another voice to the hypothesis of X-inactivation. Van Rijn et al. (2005) recently reviewed the evidence regarding a link between KS and an increased risk for schizophrenia. While stating that the genetic basis remains unclear, they suggest that a genetic abnormality on the X-chromosome might play a role in an increased risk for schizophrenia via resulting structural abnormalities in the amygdala that may account for subtle emotional processing deficits. It should be noted, however, that there are no creditable studies indicating what that increased risk, if any, might be. Nevertheless, the correlational associations are intriguing.

While research continues on suspected genetic causality, we are left to consider the consequences to the individual of medical confirmation of the diagnosis of 47,XXY. In addition to the symptoms already discussed, there is the issue of gender identity. Is the XXY carrier a male or an intersex person? What are the possible ramifications?

Intersexuality

Is the XXY condition an Intersex condition? To answer this, of course, we need a definition of intersexuality, often also referred to as pseudohermaphroditism. Perhaps not surprisingly, there is a great deal of controversy surrounding the definition itself. How it is defined seems to be dependent on current technologies and social concepts. Is sex determined by unambiguous genitalia or an examination of the gonads themselves? How about chromosome conformance to the standard XX for females and XY for males?

Some have described KS as having sexual ambiguity in some cases but not all (Dreger 1998). Blackless et al. (2000) suggest that all KS conditions are intersex conditions because they deviate from the Platonic ideal at the chromosomal level. Other researchers (Diamond and Watson 2004; Hyun and Kolon 2004) seem to agree that KS is an intersex condition. According to Money (1980), "..nature herself is less absolute in creating sexual dimorphism than we humans are in thinking about it." Perhaps so, but Sax (2002) offers a more clinically useful definition of intersex. It includes those conditions in which the phenotype is not classifiable as either male or female **or** one in which chromosomal sex is inconsistent with phenotypic sex. Under this definition KS would not be an intersex condition.

The resolution of the intersex issue has legal and diagnostic implications for KS clients. For instance, it has been suggested that an apparently heterosexual marriage could be successfully legally challenged if one person is unknowingly intersex (Frankle 2003). Being unsure of your actual sex, coupled with the uncertainties regarding the status of intersex (Is it a 3rd sex? Is sex on a continuum?) might precipitate gender confusion in a KS client. The DSM-IV (American Psychiatric Association 1994) specifies a diagnosis of *Gender Identity Disorder Not Otherwise Specified* (GIDNOS) that, when appropriate, can be given for Intersex conditions with accompanying gender dysphoria (an emotional state marked by anxiety, depression, and restlessness). The responses to our questionnaire, which we will discuss in the next chapter, provide additional data on this issue.

And finally it is important to remember that, because genes are not blueprints but complex recipes, there is no reason to conclude that biology leaves no room for change.

There is significant progress being made in the field of pharmacogenetics. Perhaps in the future drugs will be available based on a patient's unique biology. Researchers are using genetic techniques to track down the altered receptors or enzymes that cause a particular disorder. This knowledge may eventually lead to customized treatments, including personalized drug treatments and nutritional advice, based on a patient's unique genetic profile. However, genes are not only very complex but also useless without the environment:

> Most interesting behavior is the product of a complex interplay between a wide variety of neural systems for perception, attention, decision-making, motivation, and more, and so the mapping between genes and behavior is never simple (Marcus 2004).

Sex Therapists in collaboration with other professionals, and armed with the most current knowledge, will continue to help their clients to cope with and adjust to the psychosexual challenges this syndrome presents.

CHAPTER 5

QUESTIONNAIRE RESULTS

There were 33 respondents to the questionnaire. Their ages range from 19 to 66 years old with a median age of 40 years. Of the 33 respondents, 23 were from the US representing most geographical areas of the country; 4 were from the UK, 3 from Canada, 2 from Australia and 1 from Europe.

Of the 33, only 2 respondents have a family member who also has been diagnosed with KS; 1 is an identical twin brother and the other is a stepson. 4 are college graduates and 6 have completed some level of college courses but have not graduated yet. An additional 7 respondents have completed high school or its equivalent and 3 indicated they did not graduate from High School or its equivalent. The balance did not state whether they graduated high school or not.

A common theme among most of the respondents was the difficulty of their early (primary and secondary) school years, even among those who went on to complete college successfully. School and academic experiences were often described as “hard”, “hated”, “rough and difficult” or with comments such as:

> “I was slow...”
>
> “I did poorly”
>
> “I was lucky to pass”
>
> “[I] could never comprehend all the school work”,
>
> “I was withdrawn and clinically depressed most of the time”
>
> “[I] got in trouble at school all the time, could not focus in classes … people thought i was just lazy eventially [sic] was told to leave so my parents took me to a special school.”

"Bad- did not graduate but ended up in jail for breaking and entering at 20."

"I hated PE - large breasts- kids made fun of me so I stopped going and flunked."

A few described much-improved college or technical school experiences as they matured, became more interested or were diagnosed with KS and began taking testosterone. And several others described successful school and academic experience with above-average success. But the most common theme was one of distress and difficulty.

Each respondent stated the primary symptom that caused him to be diagnosed with KS. The results are consistent with the research literature. The responses are summarized in Table 1. The author also asked each respondent to provide information relative to any medical conditions he might have. 21 of the 33 respondents listed medical conditions. 16 of those 21 reported more than 1 medical condition. There was a wide variety of disorders reported but the most common were asthma, heart conditions, acid reflux, osteoporosis, and diabetes. However, 4 respondents did report psychologically related conditions: bipolar, depression, anxiety and Gender Identity Disorder (Intersex).

TABLE 1

SYMPTOMS THAT CAUSED RESPONDENTS TO BE DIAGNOSED WITH KS

Symptom	**Number of Respondents**
Small testes	10
Infertility	5
Gynecomastia	2
Circumcision	1
Heart disease	1
Hernia	1
High voice, lack of body hair, small penis and testes.	1
Injury to crotch	1
Learning Disabilities	1
Loss of strength and temper	1
Low sex drive and premature ejaculation.	1
Severe heartburn	1
Tired and depressive mood	1
Twin brother had KS	1
Very lethargic	1
Unknown *	4
Total	33

* Diagnosed as infant or child – no memory of symptom(s), if any.

A number of items on the questionnaire addressed hormone replacement therapy and the use of other medications. 26 of the 33 respondents indicated that they had taken hormone replacement therapy, specifically, testosterone (T) supplementation in various applications. 2 of the 26 are no longer taking T because of the cost. The median age at the start of T was 28.5 years with an age range of 12 to 56 years. Based on the respondents' comments (only 25 provided comments) regarding the results they received

from T, the author subjectively categorized them as Good (n = 13), Bad (n = 2) and Mixed (n = 10). A common theme was that T required a trial and error period as the respondent's physician adjusted his dosage and the delivery method to obtain optimal results. In the interim, however, there were unpleasant side effects. A few reported a change in mood and energy within T supplementation cycles.

The following are several of the respondents' comments categorized as **Good results** from T supplementation:

> "...facial hair is more … feeling less lethargic …. my sleep pattern is better… my sex life has increased"
>
> "Many improvements…more energy…"
>
> "…able to do better in high school…my libido was better."
>
> "…feeling less tired, plus increase in sexual desire."
>
> "…more hair on chest, better libido, …better esteem of myself. My voice changed for the better. ...acne occasionally"
>
> "Tremendous improvements across the board… fatigue has tremendously decreased … upper body muscle strength that was never there before… my sex drive is up … my moods are better, my self-esteem and self-confidence improved tremendously…."
>
> "… got my strength back and my temper was under control, also started to look more mature"
>
> "Better sex"
>
> "Whole different person; horny; 66 going on 25; 10 to 12 shoe size; penis grew 2 + inches flaccid and fatter when erect; more energy; lost 120lbs; regained 98% of muscle loss."
>
> "Made me feel solid, more centered. I was less anxious. I felt stronger. I felt vindicated as I had always known something was wrong, even when told there was nothing to it. I felt unique in a positive way, for the first time. Increased my stamina. Increased energy."
>
> "…more energy started to grow facial hair. [N]o side affects."
>
> "…less tired, a little bit more active."

"Not as tired, more social [sic] easier to concentrate."

The following are the comments categorized as **Bad results** from T supplementation:

"Depressed and an emotional wreck. …. Testosterone is killing me…. wish I knew how to deal with the side effects long ago."

"I saw testosterone as a violation of my gender (intersex) having attributes of both sexes, the secondary male sex characteristics almost drove me to ending my life."

The following are several of the comments categorized as **Mixed results** from T supplementation:

"The treatment is like a roller coaster: get a shot and feel better then gradually decrease in stamina, word and motor validity ... My LD seems to get worse in ...the week that ends with getting another injection. Side effect: acne, maybe increased sex drive...erections last a long time, even after ejaculation.)"

"...acne bad, the higher dose the better I felt, mood swings stopped after switching to taking the shot every week"

"… made me a man!! improved confidence, less aggression, … more muscle, hair growth on body, beard, baldness. Gyno[comastia] became worse tho, along with serious acne."

"... good for psyche', good for sex, good for secondary male characteristics, good for attitude, same could be said for all on the bad side as I now have a cyclic mood which may be best associated with a woman's menstrual cycle, I get moody."

"...I started feeling more human, more manly... my mood swings were gone... I had more confidence. I stopped being a push over at work, so I got fired ... been off the medicine since then.**"**

"More energy… felt more like other guys ... wet dreams … horny all the time (problem - very distracting). Before T, brain is horny but body is not able; mood swings before and very emotional, now more confident."

"Sexually aroused all day long - horny a couple hours after sex; gynecomastia surgery in 1999 but it returned in 2004"

> "...started being agitated, aggressive, flirting with many women and wanting sex everyday … it brought on problems at my work… endocrinologist .. changed [my dosage] …and that change has helped my behavior…the results were a greater sex drive, … increased hair growth on my face and chest and back… When I was young, I could … never lift more than about 100 pounds. Now I bench 225 with no problem and squat over 400 pounds."
>
> "…energy for couple of days but more aggressive with larger muscles."
>
> "Body filled out…more energy initially but not anymore. I get horny after injection but no erections."

The author also asked the respondents to state who had explained their KS diagnosis to them as well as the accuracy of the information they received. The median age at which the respondents received an explanation of their diagnosis was 24.5 with a range of 12 to 54 years of age. Most of the respondents (20) received their explanation from a "doctor" or "physician" and all but 2 indicated that the information they received was accurate if not comprehensive or complete. Several of those respondents indicated that the information they received was supplemented by explanations from a parent, a specialist or the Internet. Interestingly an additional 5 of the respondents specifically mentioned "endocrinologist" as the source of their explanation and 3 of those 5 indicated that the information provided was not accurate. The other 2 described the explanation of the endocrinologist as adequate. These results may be explained by the age of the respondent and/or the research information available at the time of the delivered explanation. An additional factor might be the influence of the parent on the amount and type of information that was made available to the child if he has not yet reached legal majority. Of the remaining respondents, the sources of their information varied widely (urologist, specialist, university, internet, mother, study, consultant) but most reported

that the information they received was accurate. The only exceptions were the information received from the consultant and the mother.

When completing the questionnaire, the respondents were asked whether they communicated their KS condition to others and how KS affected their relationship with others. Of the 31 usable responses, only 6 respondents stated that they did confide in others while the other respondents stated that they kept their diagnosis private or limited the information to only family, spouse and/or close friends. In responding to the question of how others managed dealing with their KS, the overwhelming majority of respondents indicated that those family and friends who were aware of their KS responded supportively - but with some exceptions. The following are representative of the responses to this item:

> "They tell me not to make a 'crutch.' It's there but you can overcome it."
>
> "My family were supportive but like me they didn't [k]no[w] enough about it. My current girlfriend is very supportive she understands me totally."
>
> "Those friends that know don't care. My parents have finally accepted who I am. My ex-wife couldn't accept that I was sterile…My current wife is completely alright with my KS.."
>
> "I began to get new information on KS…. Now I am more open about it and those around me try to help me deal with my problems."
>
> "[I]t's just another part of life if they cant handle [sic] they don't say anything"
>
> "[M]y wife struggles with my temperament and lack of emotion. Friends except me as I am."
>
> "Parents were and still are confused as to what happened to me and if it was their fault in some way. Partner could care less, Loves me for who I am."
>
> "No worries for friends, parents may see it more as an issue, I don't know for sure."
>
> "My dad thin[k]s the doctors are wrong, and the problems that I have are not related to KS. My mom, feels sorry that she didn't figure it out when [I] was younger, but

still is very unhelpful to me as an adult. My two sisters are the ones that understand me the most, whereas my friends don't really understand it either."

"[N]o problems"

"[T]he ones [I] told we[re] ok about it, none knew anything about it so [I] gave them a web site to read more about it."

"My wife of now is always looking for a way for us to have children."

"We haven't spoken about it since I was told."

"Partner is divorcing me. [S]he is tired of carrying the family finances. I'm not working and everybody thinks I'm a bum."

"Apart from my wife, the others reckon its all in the mind and I should put it to one side and get on with life. What they fail to understand is 'it is my life' and has been from day one"

"Careful telling others; feel them out; if they might not understand."

"Very well. Some have revealed similar experiences with abnormalities of their own."

"[T]hey didn't think anything about it just treated me the same, except for my father."

"No problems, mot[h]er is a bit concerned. Wishes it was discovered earlier."

"[T]hey don't care - no support- mother does not believe."

"[I] was living with my wife … when I discovered I had KS. She encouraged me to go to the Doctor because I am a premature ejaculator. She would like sex more but we manage pretty well. …."

The author also asked the respondents what effect KS had on <u>their</u> relationships with others. Of the 33 responses to this item only 10 could be categorized as positive or neutral (a response of "none" or "no difference"). The other responses were categorized as a **negative** perception of the respondents' relationships with others. The following are some representative responses from this category:

“It comes out in my mistakes... or when LD makes me look stupid because I couldn't verbally communicate in the right fashion.”

“I'm too emotional, my feelings get hurt too easy. depressed when things don't go my way.”

“I feel uncomfortable around people.”

“Well when at work I don’t think before [I] say thing so sometimes they don’t understand me. And it takes me along time to explain things.”

“I[t] is hard for me to make friends. I tend to withdraw within myself ... It has been very difficult to have friends of the opposite sex and keep them as just friends.”

“My best friend gets upset with me a lot because I forget things easily and I have a tendency to be late a lot because I get side-tracked easily.”

“Because of enlarged breasts and higher pitched voice I tend to feel embarrassed about letting anyone see my torso. And also conversations, especially on the telephone, … people think they are speaking to a female. That often angers me even though I know it's not their fault.”

“[I] feel inferior around men, that [I] am a fraud! [W]ith women [I] feel they would not be attracted to me and that if they knew [I] had ks would not want to date me.”

“I get along better with everyone if [I] stay on my testosterone and not go off of it, when I didn’t have insurance or any means to pay for it, I went without and it effected my libido and moods.”

“I am totally unable to relate to the male population and indeed feel threatened in their company.”

“I'm moody and that seems to be my biggest problem, otherwise I have a lot of friends who are very loyal and have had them for a very long time.”

“With my first wife it was the beginning of the end. She wanted more children and I couldn't give her any. …”

“I have been single for 5 years, I have the tendency to not get involved in anything since my divorce… prior to that I have had only 1 other major relationship. …”

“Slight impotence sometimes.”

“It has an effect I think in my communications. I've never been able to say what I think. I get nervous and all tongue-tied many times. In my mind, I have a good thing to say, but when I go to say it, it doesn't come out as planned….”

"It makes me a little afraid of getting attached."

"I feel I am above male and female. I also can perceive others rea[c]tions before they do."

"I have a small set of good friends. I am still shy…. I've opted out of the dating game. I am getting better at talking about it."

"[W]hen [I] was you[n]ger it seemed like [I] had a normal life. [I'}m 32yrs old now and my social life is down the tubes. [S]eems like [I'}m invisible sometimes."

"I wish [I] was more active with my friends and done more with them."

"I have trouble focusing and remembering and putting thoughts into words. Been very sad, ignoring everybody - no energy."

"[I] find it very hard and having a real tough time with my girlfriend at the moment."

"I'm depressed which affects my partner."

In a related item the author asked the respondents how they managed to cope with or adapt to their KS condition. The author subjectively categorized the responses into Successful Coping and Poor/Questionable Coping. Slightly more than half of respondents (17 of 33) indicated at least moderate success coping with KS. The following are responses that are representative of those categorized as **Successful** Coping:

"Just work with it, around it, stay silent when I can't talk in sentences, double, triple check things. Do the best I can"

"Just tried to get on with my life."

"I rule my own life, my being xxy doesn't rule me. ... I don't feel that I have KS anymore. The multiple symptoms ... have been taken away with testosterone treatment, so I consider myself an xxy male, not a male with KS."

"I have always done best when living by myself, without a [significant] other. I write notes and post them on a bulletin board. I keep a pocket planner and try to remember to check it once a day. I am taking college slowly, only going part-time in order to have time to allow my mind to wander until it's ready to study (it works)."

"[J]ust like ... anything else that happens in life you move on and deal with it. [I] learned about it early on not like a lot of guys that are finding out late in life."

"It has been a gradual acceptance of the situation. In the past four or five years with more self-help groups and internet information becoming available I have got to understand the condition. I no longer feel embarrassed about talking about it with trusted friends, though not with work colleagues."

"I turned to the bottle (alcohol) ... and found that didn't help matters as I was still XXY. I am now a confirmed alcoholic, with 22 years sobriety. I now realize that once I understand myself and not feel sorry for myself, I have become a better person to me and eve[r]yone around me, People actually like me for me, no matter what genetic disorder I was born with."

"I have been using oestrogen for one year, I see it as an antidote to the previously administered testosterone. I would like to think I am more at peace with who I am, I guess only time will tell"

"Just by doing that, adapting, knowing myself and staying aware of myself and my needs, adjusting and adapting to circumstances that arise as best I can …"

"I've done just fine. I just needed a couple of months after my diagnosis to sort out my feelings and be comfortable with having a disease no one knew about and wasn't publicized."

"I have seized the day with Humor. I guess I'm more glad I found out now before things got really out of hand."

"Therapy in past; changes as you get older; not that big a deal now."

"Fine - I am what I am. T made me better"

"I tried to live with it."

"[Y]es, I have managed to cope with it."

"Realizing I cannot cha[n]ge it, [I] must accept."

"I spent lots of time on introspection. I have examined issues of gender identity. I have made contact with others. I've come to realize who I am, and that I really like me. I do admit to some disappointment, that the condition isn't as severe a disability as previous studies would suggest. I like being unique, I don't want to give that up!"

The following responses are representative of those categorized by the author as **Poor/Questionable** Coping:

"Not very well. I wish that I never started taking testosterone. Wrecked my life and my family. Had no support and no outlets for my anxiety. Lashed out at whoever wronged me and have lost most of my friends … my wife left me ..."

"I've managed to live with it, but I refuse to take the recommended treatment as it goes against my feelings of being intersexed. I don't think I cope very well with it and my days / weeks can go up and down but I haven't had a major depression in over 9 months so far."

"Man[a]ging is stressful, because I have to hide my gender, but at t[h]e same time I have to express the other to live within society's bound[a]ries."

"[B]y joining the self help group, ... and meeting other men, [I]have tried to except what [I] am but some days [I] cant get over the fact [I] am a biological error!"

"I've kept it a secret"

"SOMETHINGS DO NOT COME EASY; REGIMENTED; anti-social behavior-uncomfortable with men my age (gay)"

"[S]ometimes it is hard to cope with, wish [I] would of found out when [I] was a teenager."

"Still trying to accept it."

"I am very self-conscious about it. Lack of size."

"[I] have coped with it but [I] wish [I] didn't ha[ve] ks. [I] just want to have a normal life and be like other males….[I] know people start to wonder about people who never have girlfriends they thin[k] they are gay. if [I] was gay [I] would have killed myself along time ago. [I] just [hope I] would get married someday like all the normal people do."

"I try my best [to] manage with KS but it gets hard sometimes."

"I'm trying to take care of myself but avoiding others; after diagnosis I took 2-3 months off but when I returned to work I kept injuring myself (4x) - could not concentrate- have not worked since. Have been feeling depressed and anxious since diagnosis."

"Anti depression tablets"

"Yes but still sometimes feel insufficient because … of the size of my genitals."

"Day by day - some days I just don't understand ks."

Each of the respondents was asked whether or not he had ever received psychological or psychiatric therapy and, if so, were the results helpful. 17 of the 33 indicated they had received therapy. Of those 17 only 9 indicated that the therapy was helpful. These are some of their comments regarding therapy the respondents judged to be helpful:

> "… yes got pill to keep my mood swings under control for the most part."
>
> "Psychiatric help when 14 - long before I knew about KS. Also at 21 when fears tended to overwhelm me… Some counselling occasionally since. The medical counselling was of limited help. Christian counselling far more beneficial."
>
> "[I] am currently receiving psychological treatment. [S]o far so good."
>
> "Yes, …I found the psychiatric therapy to be more beneficial…"
>
> "…The results during my teenage years were helpful because there was someone there to talk to who listened and didn't judge me by the way I was feeling. I have received limited counseling since then, although it, for the most part, has been helpful."
>
> "Yes, 10 yrs with a psychiatrist for pills only. Also saw social worker for 7 months which was pretty helpful."
>
> "Yes, plenty! I was diagnosed at 16 with depression. I learned about the Klinefelter's at 17 or 18. I have been on lots of meds. I have had several forms of therapy. I see a psychiatrist, and a counsellor, now. I've also seen psychologists, in the past."

These are some of the respondents' comments regarding therapy they judged **not** to be helpful:

> "The results were not helpful. They say this is the cause and this is the remedy, and I say this is the cause. I haven't seen anyone that I feel is qualif[i]ed in this field."
>
> "Only when I was very young, before I was diagnosed. I believe it was no help."
>
> "…I did not find it helpful, … I think it takes one to know one in this case and the therapeutic relationship was difficult to accomplish."

> "Tons of help, yet nothing really helped at all…"
>
> "Helped but would have been better if I knew about KS…. Spent a huge amount of time trying to understand why I was so unhappy emotionally. I'm angry that no one referred me for [this] possible medical condition."

The majority of the respondents (24) indicated that they recalled sexual maturity occurring during their early to mid-teen years. An additional 3 respondents stated they entered puberty at ages 10 to12. The other respondents described delayed or protracted sexual maturity as follows:

> "Ejaculation-wet dream ten yrs old, the rest slowly progressed until I was 36 and started HRT"
>
> "I had pubic hair (female pattern) at age 11. Ejaculation didn't happen until I started on testosterone, maybe age 12 or 13, facial hair (which I always wanted) didn't grow in full until I hit age 30."
>
> "18yrs old pubic hair, 14 yrs old ejaculation, body changes 20yrs old"
>
> "mid twenties"
>
> "now at 30 - none as teenager"

When asked if they felt different from other males, 31 respondents stated that they did feel different. However, when asked whether their KS diagnosis affected their sense of virility or maleness, 11 of those 31 respondents stated that it did <u>not</u>. An additional 2 said it only affected them a little and 1 said he was not sure. Of the other 17, who stated that it did affect their sense of maleness, several provided some comments. The following are representative of those comments:

> "[Y]es - different- never could fit in not even now."
>
> "Yes, I was shocked. I used condoms because I thought I had bad fluids…"
>
> "[A]t first it didn't but later in life it was upset[t]ing to know I couldn't produce a child to carry on the legacy of my family."

"I have never felt truly male, so the diagnoses came as a relief."

"It explained to me why I had smaller penis than others, why I had breasts bigger than most women I knew."

"Small penis…"

Regarding sexual orientation, see Table 2 for a summary of the responses. Note that 1 of the gay respondents stated, "gay - but I am not a male thus not homosexual." And 1 of the straight respondents stated, "straight but with fantasies about adult hermaphrodites", while another stated "straight AB/DL [Adult Baby/Diaper Lover]".

TABLE 2

SEXUAL ORIENTATION AS REPORTED BY RESPONDENTS

Orientation	Number	% of Total
Straight:	25	76%
Gay	4	12%
Bisexual	3	9%
Intersex	1	3%
Total	33	100%

Each of the respondents was also asked to describe his sexual history. 5 of the respondents chose not to answer this item. Of the remaining 28 responses, some are very succinct, such as:

"Nothing unusual"

"[H]ave always been promiscuous"

"[M]arried for almost 24 years. Wife moved out in Feb."

"I'm a virgin."

"I am very submissive."

"[C]an fuck for ever with out cumming, enjoy dominating others."

"[F]requent sexual intercourse with whores"

"[N]ever had one."

"SUCCESS"

Most of the other respondents did offer more insight into their successes, struggles and failures. The following responses are representative of that group:

"My success is being with my current pa[r]tner, my struggles and failures are when I lose my erection it feels like [I] have failed to satisfy my partner [sic] this is not always the case."

"The only success is with my current wife. Failures are all the rest of my sex life. Not many, 5 overall, not much to tell."

"Only one real girlfriend - and I have been married to her for 22 years. It was not easy building relationships in my teens, partly due to ill-health and mostly due to shyness."

"[A]ll my sexual "CONQUESTS" have been after getting to know the women first over a period of weeks/months. [O]nly one or two were the result of chatting a stranger up and bedding on the first night."

"[N]ever found the right person, searched for many years in all the wrong places and only until 4 years ago did I find my soulmate. Especially with the AIDS and HIV, I am now monogam[o]us."

"I've never had a problem with sex, I have had many partners, I'd guess somewhere in the range of 60 or so, sexual activity is not an issue... the relationship itself is the issue."

"Virgin until 34 - Not normal pattern - sex is a problem now - low desire - success first 3 or 4 years after diagnosed – was very active."

"Virgin at marriage; 2x week first 10 to 15 yrs of marriage- then slowed due to normal aging - now have ED but use injectable med in cavernosa that works well. When started taking T my GAY urges returned; now have a gay partner; I am neither male nor female. I am intersexual."

“Didn’t lose virginity until 18, after High School. Didn't date in HS, didn't have good self-esteem or image. Didn't date regularly after that. Would go find a girl ever[y] 6 to 9 months just to show my friends I wasn't gay. Stay[ed] celibate for 7 yrs, pretty much. Always thought I was small. Been in a relationship for 2 1/2 yrs now; sex 2-5 times a week, sometimes 2-5 times a day. Prostrate problems before, but burning sensation less when fornicating on regular basis.”

“Married at 26 (1st sexual experience), Divorced at 31, At age 41 I discovered the internet and fell in love again. However, after I met her in person and had spent several wild weekends with her, it failed. There were three more such relationships, … all failed. Then I … got married again. … Separated after 3 years, …. Then I moved here for love and sex but both have failed, however, she is now my best (and only) friend.”

“I have always had a high sex drive, having sex and ejaculating was never a problem even before my diagnosis and lack of testosterone. Since diagnosis and starting testosterone, things have obviously gotten much better and I could hold out a lot longer before ejaculation occurred. I was never blessed with a large penis or testicles, but they still work and work well.”

‘… I have always been very guarded, not really into the whole thing. Reserve it for people I am for sure with if that makes any sen[s]e. So I have only had sex with 4 people. 2 of them were long term relationships. 1 of them was a screwed up short term, my bad judgment. … the last one was a one nighter shortly after my marriage. Never do that again, I still feel uneasy about it. Since being single I do understand that self ejaculation is important for my prostate, so I normally try when I feel I'm at my peek energy level for the day (provided I am at home). This normally occurs one either new moons or full moons. But then again I have gone months without it.”

“I was very shy when I was young and not on testosterone. I liked girls but didn't have the courage to ask them out, even when some of them asked me out, I turned them down. …. not feeling manly to ask a woman out, I went to college and still never had sex with a woman. …[until] …I was about 21 years of age. And it was a prostitute … my friends .. always talked about their conquests and I felt compelled to be able to talk about a conquest even if I had to pay for it. Of course that experience made me very scared, and even though I used protection I still went to the health department for verification, which turned up negative for any STD's. I then .. met a fat girl .. and had a sexual relationship with her for 4 years, then I got rid of her, because she was crazy and [I] moved … and found my first wife and it was on her that I found the KS. But many problems with our marriage and when I got diagnosed … and started getting testosterone, it was like the high school life I never had and I started looking for other women, I had confidence I never had ... I kept asking till I ended up cheating on my first wife, but our marriage was bad before I got diagnosed… I was like an animal, going after many women and having a lot of sex. I loved it, loved the attention and loved what I could now do and never could before. Before I always had a small penis and now, when I get aroused, my penis grows to a

very nice size and thickness. So I love what testosterone has done for me and I am still working on my urges for other women and for that I am seeking counseling. .."

"I lost my virginity at 24, with a 50 year old woman. She encouraged me to pursue my inclinations, fetish-wise. We were together 3 months, illicitly. I next had a girlfriend openly - 46 years old. for 4 years. My current girlfriend is 50, and online. We have been in contact for 10 months. She is going to visit me, soon. Otherwise, I was too shy and fetish-obsessed to get involved with a woman. I have learned to accept myself, in regards my fetishes. Nothing fazes me about other people's kinks."

"…[I] was a virgin for 31yrs of my life until [I] met this girl 1 night. [M]y sexual history has been a struggle my whole life. [I] wish [I] was just like every other guy out there who has 100 or so girlfriend[s] in his life."

"Sex has been good since taking testost[e]rone, was not as strong when not taking."

"I'm shy, except when I drink. It takes me a long time to come-not much feeling in the head of my penis."

"…I was shy as an adoles[ce]nt and did not have a girlfriend until I was seventeen ... I lost my virginity at seventeen. That lasted about a year. Never had much of a sex life until I was in my mid twenties and then I was not that active. I married at 32 after a four-year relationship and divorced two years later. I dated a lot after that until I got together with the woman who is now my wife of eighteen years. Sex has always been a struggle for me and still is even after all these years. I do not have much of a sex drive. If I have sex once a week I am satisfied."

"[S]ex started at 30 and was okay until 1999 when I had back surgery; since then, desire but no erections."

In a related question the author asked the respondents if KS affected any of their sexual activities, that is, vaginal anal, oral or any other. Of the 30 respondents who provided information, 17 reported that KS had **no** affect on their sexual activities. The remaining 13 did report a variety of problems. The following responses are representative of their problems:

"…not being able to keep an erection and not being able to ejaculate."

"I was kind of nervous about having oral sex with me not really having the 'correct' size testicles. But not one of my partners ever said anything and I think it was all in

my head. Other than that, I just wish I had taken more advantage of being sterile when I was younger. I could have had more sex and not had to worry about getting anyone pregnant!"

"… [I] like sex and have lots of guys that enjoy that [I] can out last most the only problem [I] have is [I] dont cum much from getting head."

"…erections have always been difficult and downright problematical now [that] I have had diabetes for ten years."

"I have always had a very low libido, so these sexual activities are not important to me."

"…never got into anal, unless you count the time I was molested as a young boy by the babysitter who was an older guy… Oral, I dont know I have been single for too long to give an answer."

"Vaginal is a problem; usually mutual masturbation with wife. When on testosterone you want to masturbate all the time - do it more often - but prefer to target the energy to other activities."

"I prefer to be given oral and to penetrate anal. I am experiencing this with hookers only."

"I suffer from retarded ejaculation. I used to be able to ejaculate through masturbation, with my fetishes. I can't seem to even ejaculate that way, much anymore. I've never ejaculated in the company of a woman. I want to, but my equipment doesn't comply. My partners have all complained about this to me, they want me to ejaculate within them."

"Even oral take me a long time to come. I have to be able to see her face…not much feeling in my penis."

The author also asked the respondents what impact KS had on their sexual desire, arousal or orgasm. 4 stated simply "none" while 3 others indicated that they were "not sure". The author subjectively categorized the remaining responses as Negative, Positive or Testosterone Dependent. The following comments are representative of the **Negative** category:

"I currently have very little sexual desire. It's difficult to get aroused, however about once a month I get the urge and, with pictures and movies, I get myself to an orgasm."

"[O]rgasm takes along time to achi[e]ve unless [I']m jacking off that's the only time [I] can cum with in 20 mins."

"Nowadays I find it very hard to get an orgasm, even in masturbation. Sexual desire is often quite depressed, though about a week after my testosterone injections I am at my peak of sexual desire."

"Orgasming is like pulling teeth, arousal, hmmm I feel like a bad snake charmer, sexual desires only occur in the fantasy world, but never in real life…. it might take over an hour to get in the mood with a porno in the player…"

"Sometimes no lust. But no influence to perform kinky sex."

"I don't have much desire and when I do it takes a long time to get an erection."

"[I] find sex very hard and it puts me down."

"I sometimes wonder that myself. I know that my sex drive is low. I am fifty and do not have a problem with erections if I have some coaxing from my wife. I do get aroused looking at porn. Orgasms are not a problem ex[c]ept that they come to[o] fast. If I wait about two weeks I can have strong orgasms but otherwise they are often weak."

"After surgery I have desire but no arousal; before surgery I had arousal but no orgasm in 7 of 10 times... orgasm takes a long time."

The following comments are representative of the **Positive** category. It should be noted, however, that all but 1 of the respondents in this category were receiving testosterone, so the distinction between this category and the following category is subtle and based only on the fact that the respondent did not directly attribute his activities to T in his response:

"I am turned on by the thought of having sex with pre op transsexuals (I have never acted on it, they are just thoughts)."

"Perhaps I am more aware than most people about my needs and even my partner's needs."

"…increase[d] arousal and allowed me to explore and understand some of the reasons I get aroused by different body parts and that allows my desire to increase."

"I am arous[e]d easily, and I am kind of a nymp[h]o" [not using T]

"Enjoyed sex with my wife as long as I was making believe I was having sex with a guy. But at 57 [received] anal sex for the first time; it was beautiful; doctor said

there's a good chance you have vaginal nerve endings in your sphincter muscle; I would have physical and emotional feelings that last for 48 hrs. …"

The following comments are representative of the **Testosterone Dependent** category:

"[B]efore KS ejaculations were short erections and small amounts of sperm. After Testosterone injections, long erections lots of sperm and recovery time for repeat sex is 2 hours."

"Being XXY and being on hormone therapy has boosted my sexual desire 100 times! I am constantly aroused and could have an orgasm every day if I could. It was worse when I was younger. At age 15, I think I masturbated at least 3 times a day, just because I was so aroused all of the time. Drove me nuts! …. Now, if I drop off the testo to a lower dose, it effects my libido and my energy level, so I cannot really screw with my energy, I would rather have full energy and high libido, than no energy and low libido."

"[B]efore treatment my ejaculate was very small and orgasm was not intense. [S]ince treatment started ejaculate has increased along with intensity of orgasm. [I] get aroused very easily."

"Being XXY and not on any Testosterone, there is no sexual desire, arousal or orgasm. These things are only possible with the Testosterone daily patch that I take, NOW I enjoy life like a normal male."

"Pre T it was hard work to get to arousal and orgasm but desire was in the brain. Post T it was amazing to wake up in the morning with an erection; still is. I'm horny all the time; hard to satisfy; would prefer to focus energy on other things."

"If no T, no side effects; always short to ejaculation; with no T it's difficult to concentrate, there is memory loss, difficulty with words; It's all much better with T"

"[O]ther than taking a shot every week has made me feel like a teenager all again."

"I think it gives me more range in regards what I find sensual. I have several fetishes. There are weeks where I am horny, and weeks when I am not. I haven't been able to ejaculate, though. And, on other meds, I was able to remain erect for long periods. Eventually, my girlfriends started blaming it on the shots, and grew to resent the fetishes. I can't reach orgasm unless my fetish is involved somewhat. Plus, I want to be the one who gets wooed! I've always wanted to be picked up by the "older woman" and carried off. I don't know how to make the first move, and be convincing. I find dating to be very awkward."

> "ks has had a big impact on sexual desire. [I] do note that when [I']m on [testosterone] it helps me at a lot. almost makes me feel normal. [I] don't take it much because for a 1 month supply it cost $200.00."

And finally, the respondents were asked how infertility had affected their relationships. Of the 33 responses, 13 indicated that it did **not** negatively affect them. Of those 13 who did provide additional comments, the following are representative of those:

> "I'm a virgin."
>
> "[B]eing gay it dont matter i still cum just cant have kids …"
>
> "My wife and I have been together for 17yrs, before diagnoses we tried for many years to concieve, the diagnoses brought relief for my wife and has made our relationship stronger. My wife already had two children from a previous relationship."
>
> "If anything it was a license to screw freely without the fear of pregnancy. Never thought about procreation because it wasn't possible when I was a younger XYX."
>
> "[N]o – adoption."
>
> "[Knew] all along i was gay, so that really didn't bother me."
> "No effect beyond the fact that I won't be parent, anytime soon. I prefer women 35-50, for whom fertility is no longer an option. I like being younger than my partner."
>
> "Have[n']t come to that crossroad yet, but hopefully if [I] ever meet the right girl it doesn't effect relat[ion]ship."

The remaining 20 respondents were affected negatively - some only temporarily or mildly but many quite significantly. Here are the representative responses from those so affected:

> "Horrible. All the women want kids and I can't give them any. Also have problems with friendships because I have no kids, and they do, so they more likely to hang with couples that have kids and I am less important."
>
> " [I] feel very lonely and have no acceptance to the male gender."

“Infe[r]tility has effected me over the years it is a bit of a shit but life goes on. It hasn't effected this relationship but one other lady I was with rejected me cause of the infertility bit.”

“Infertility killed my first marriage and did nothing to change my second marriage. Infertility sucks when you want children very badly, but it is nothing that I could do about it, so I go on. My current wife is completely alright with my KS….”

“At times it makes me sad that I will never father a child, but I don't think about it much. I have accepted it as something I can do nothing about. As to relationships, it's made it easier to have sex because she won't get pregnant accidentally.”

“… it almost destroyed our marriage.”

“[I]nfertility broke my first marriage - my wife left me. [A]nd it is about to break my second marriage cause [I] am about to leave her. [I] am desperate to be a dad and it has driven me mad to the extent that last year [I] was put on to a psychiatric ward.”

“I was mad as hell at first when I found out I was sterile, I always thought I would have kids and especially for when I get old, But now I just will have to depend on my Niece and Nephews.”

“None now, as my wife has two kids from her previous marriage and that works for me. It affected me initially because I'm the last one in my family and knew I could never keep the family name going. I was initially sad because I was told [I] was infertile and I wanted to have at least a child of my own.”

“With my first wife it was the beginning of the end. She wanted more children and I couldn't give her any….”

“Not much at all but did have the thought, ‘what's the use of doing this -sex? What's the meaning of it?’”

“I am a little dreary about it.”

“My present wife wants to have my baby very badly, and I think its not possible, but she reads on the KS site that it could be and she wants, but I tend to feel not possible and it causes us to have a fight.”

“It makes me a little afraid of the future and getting into new relationships.”

“It was very hard when my wife was trying to get pregnant. It was also hard to find out that I was never going to pass on my seed, as it were.”

“Relationship not affected, but I do often regret not being able to have children.”

“I did not find out until I was with the my wife. When I found out I could not have kids I was very disap[p]ointed. I had always loved kids and wanted my own badly. My savior was that my wife had been previously married and … had a … daughter…. My wife and I discussed adopting at the time… but decided that raising her daughter would be enough.”

“[V]ery sad and angry - wife disappointed.”

CHAPTER 6

CONCLUSION

The preceding chapters described how non-disjunction of paired chromosomes causes the 47,XXY genotype. The author reviewed the research regarding the prevalence and variety of symptoms associated with the resulting condition, Klinefelter Syndrome. The following statements can be supported by the research data. Only about 1/3 of those born with 47,XXY are diagnosed with KS, usually after puberty. Of those that are diagnosed, the most common symptoms are hypogonadism (with small testes) and infertility, although other conditions, such as gynecomastia, osteoporosis, diabetes, and autoimmune diseases may lead to the diagnosis (Bojesen 2004). The root cause of these symptoms (KS) is unknown but current research investigations suggest possible genetic links.

The most common form of medical therapy is the administration of T supplementation, which is effective for many, but not all, and it requires careful monitoring by a medical professional, such as an endocrinologist. From the data provided by the respondents to the questionnaire, one can argue that the effect of T on the lives, particularly the sexual lives, of most was profound. Since the endocrine effects of KS may become more severe with age, early referral is a priority. Although many KS males have struggled through puberty and adolescence, often with learning disabilities, most of these men have managed to adjust and cope successfully with their lives. Infertility remains a very distressing symptom of KS and appears to affect almost every non-mosaic KS male.

The 33 respondents to this author's Internet questionnaire provided additional data. The responses to many items were consistent with the published research,

specifically, the symptoms leading to diagnosis of KS and the school experiences of the respondents. In addition, 79% of the respondents (26) had taken T supplementation and all but 2 were still using it. Among the T users the effectiveness varied but most found it to be at least somewhat effective especially in improving their sexual functioning. However, there were a few who experienced significant and unacceptable or distressing side effects, such as acne, gynecomastia, gender issues, mood swings or constant sexual arousal. For those individuals in particular the help of a knowledgeable therapist would be very valuable.

Most of the respondents indicated that they preferred to keep their condition private but that they received positive support from those close family and friends they chose to disclose to. However, most of them stated that they had rather unsatisfactory relationships with others even though they were at least moderately successful in coping with their condition. 52% of the respondents received psychological or psychiatric therapy but only slightly more than half (9 of 17) found it to be helpful.

Regarding sexual maturity, only 18% related delayed or protracted puberty but 31 respondents (94%) stated that they felt different from other males. And, when asked if their KS diagnosis affected their sense of virility or maleness, 52% said that it did.. In providing data regarding their sexual orientation, 1 of the gay respondents stated, “gay - but I am not a male thus not homosexual.” And 1 of the straight respondents stated, “straight but with fantasies about adult hermaphrodites” and another stated his sexual orientation as “intersex”. The data suggest that there might be a gender identity issue that is significant to this cohort, but from this small sample no conclusion is possible. This could be a theme for future research.

Most of the respondents did provide some information regarding their sexual history but it is in general unremarkable when compared to the successes and struggles of the non-KS community - with the exception of the use of T supplementation. Actually 52% of the respondents (17) claimed that KS had no effect on their sexual activities. But when responding to what impact KS had on their sexual desire, arousal or orgasm, 82% (27) described some impact – whether positive or negative- and 21 of those 27 were currently receiving T supplementation. The impact on their sexual desire, arousal or orgasm was predominantly positive and the majority of the responses indicated that it was a result of T supplementation. In addition, most of those respondents who stated that KS had no effect on their sexual activities did report increased arousal, longer erections and increased sperm volume and more intense orgasms with T supplementation. There was little difference in the median age between those respondents who described negative sexual effects compared to those who described positive sexual effects from T. Another area of future research might be the relationship between the type of T (injection, patch, gel, implant) supplementation and its effects on sexual functioning in KS men.

And finally, the respondents provided a dismal picture of the effects of infertility on their relationships with 61% of them indicating that it had a negative effect. T supplementation, which is readily available for most KS men and often does offer improvement in other symptoms, unfortunately does not provide any relief from infertility. Based on the comments of the respondents, this may indeed be the most difficult and intractable issue for adult KS males to deal with.

For sexologists and other clinicians it is important to be aware of the KS condition when working with your male clients. Knowledge of the syndrome might lead to an appropriate referral for diagnosis and treatment. Understanding the information provided

here, will improve the therapist's ability to provide more helpful and accurate counseling to the KS client and his partner. Although there are many resources available on the Internet to clients, some from prestigious organizations, such as the National Institute of Health (Brock 1992), it is prudent to caution your clients concerning these sources since often the information is dated and incomplete. There are, however, many reputable support organizations on the Internet (see Appendix) that do offer current information and peer support.

APPENDIX

Informed Consent Agreement

Purpose of Research: To learn more about the psychological and sexual effects experienced by males, aged 18 years and older, with Klinefelter Syndrome (XXY).

Principal Researcher: Thomas M. Duffy, LMHC, Doctoral Candidate
American Academy of Clinical Sexologists at Maimonides University.

Research procedures: I understand that I will be asked to provide an account of my personal experiences as related to Klinefelter Syndrome. A semi-structured questionnaire will be provided to me, which will guide me in typing or verbalizing my personal history with this condition. All Internet transmission will be handled via a server with Secure Sockets Layer, a transaction security standard that provides data encryption, server authentication and message integrity. I will choose whether to transmit my personal account to the principal researcher via the Internet or to request a personal telephone interview with the researcher. If I choose a personal telephone interview, I will be asked to supply a telephone number where the researcher can contact me. The interview will be recorded for data analysis. In either case it is estimated that this will require about 30 minutes or more to complete.

Risks and Benefits: I understand that this research is being done for research purposes and that taking part in it provides no immediate benefit for me. However the findings of

this research should improve our knowledge of the psychological and sexual effects of Klinefelter Syndrome. There are no risks involved in this research. The information I provide will be kept confidential. Only the information provided will be recorded. This site will not attempt to learn any information about me that I do not specifically input. I will not be put on any mailing lists and no attempt to contact me, other than participating in this study, will be made. If I do participate, I may withdraw at any time. All communications (internet, recordings) will be saved at the researcher's site in password-protected files on a disk marked *Confidential Research Data* in a locked cabinet with restricted access.

Costs and Compensation: There will be no compensation for participation in this study. If I choose to review the summarized results of this research when it is complete, the summarized results will be posted on this web site on or about September 2005.

My Rights: I have a right to have all my questions answered to my complete satisfaction before I participate in this research. I understand that my participation is strictly voluntary and that I have the right to refuse to participate and the right to withdraw from the research at any time and for any reason. I understand that my right to privacy and confidentiality will be safeguarded. I understand that only summarized results will be published. **No information that will identify me will appear in any form whatsoever.** All responses will be coded in such a way that no one will be able to determine the identity of the respondent. I understand that if I have questions about my participation in this study I may email Tom Duffy at researcher@klinefelter-xxy.org.

I have read all the above and am willing to participate in this study.

I Wish to Participate via the Internet I Request a Personal Interview

I Decline to Participate

Questionnaire

Klinefelter Syndrome Research

Please respond to the following 26 items to describe your personal experiences with Klinefelter Syndrome (KS).

1) Enter your birth date:

2) Enter your general location (state or territory only) where you live now:

3) Any other family member(s) with KS? If so, what relationship?

4) What were your school and academic experiences?

5) What symptoms caused you to be diagnosed with KS?

6) Currently do you have any medical conditions?

7) Did you ever take testosterone or any other medication for KS??

8) If so, how old were you when you began taking medication?

9) What type and amount and for how long? If no medications taken, simply type none.

10) What were the results? Any improvements or complications? Any side effects?

11) Who explained your KS to you? How old were you?

12) Was the information you received accurate?

13) Did you keep your KS condition private or did you confide in others?

14) How do others (friends, parents, partner) manage dealing with your KS?

15) What effect does KS have on your relationship with others?

16) Did you ever feel different from other males?

17) How have you managed to cope with or adapt to your KS?

18) Have you ever received psychological or psychiatric therapy? If so, were the results helpful?

19) At what age do you recall sexual maturity (body changes, pubic hair, ejaculation)?

20) What is your sexual orientation (straight, gay, bisexual)?

21) Do you have a partner or spouse?

22) When diagnosed with KS, did it affect your sense of maleness or virility?

23) Describe your sexual history (successes, struggles, failures).

24) How has infertility affected you and your relationships?

25) Has having KS affected any of these sexual activities for you: vaginal, anal, oral, other?

26) What impact, if any, has KS had on your sexual desire, arousal or orgasm?

Support Organizations

American Association for Klinefelter Syndrome (http://www.aaksis.org/)
2945 W. Farwell Ave.
Chicago, IL 60645-2925

Klinefelter Organisation (http://www.klinefelter.org.uk/)
234 Turton Road
Bolton
BL2 3EE
United Kingdom

Klinefelter Syndrome and Associates (http://www.genetic.org/ks/)
11 Keats Court
Coto de Caza, CA 92679

Klinefelter's Syndrome Association UK (http://www.ksa-uk.co.uk/)
56 Little Yeldham Road
Little Yeldham, Halstead
Essex CO9 4QT. UK

Internet sites with additional information and links: (http://www.47xxy.org/)
(http://klinefeltersyndrome.org/)

Glossary

Adrenals: Glands located adjacent to the kidneys that are responsible for synthesis and secretion of various hormones. The outer portion of the adrenal gland, the adrenal cortex, secretes important steroid hormones including cortisol, which mediates various stress reactions. The inner portion of the adrenal gland, the medulla, secretes epinephrine and norepinephrine, important in the "fight or flight" reaction to a threat or sudden stress.

Allele: One of the variant forms of a gene at a particular locus, or location, on a chromosome. Different alleles produce variation in inherited characteristics such as hair color or blood type. In an individual, one form of the allele (the dominant one) may be expressed more than another form (the recessive one).

Androgen: A male sex hormone that promotes the development and maintenance of the male sex characteristics. The major androgen is testosterone.

Amygdala: A structure in the anterior part of the temporal lobe of the cerebrum. It is intimately connected with the hypothalamus and the hippocampus and the cingulate gyrus. As part of the limbic system it plays an important role in motivation and emotional behavior.

Aneuploidy: One or more chromosomes above or below the normal chromosome number.

Aromatase: An enzyme involved in the production of estrogen that acts by catalyzing the conversion of testosterone (an androgen) to estradiol (an estrogen). Aromatase is located in estrogen-producing cells in the adrenal glands, ovaries, placenta, testicles, adipose (fat) tissue, and brain.

Ascertainment bias: Refers to a systematic distortion in measuring the true frequency of a phenomenon due to the way in which the data are obtained.

Assay: Qualitative or quantitative analysis of a substance, especially of a drug, to determine its components.

Autosome: Any chromosome other than the sex chromosomes (X and Y).

Azoospermia: The production of an ejaculate devoid of spermatozoa.

Biallelic: Pertaining to both alternative forms of a gene.

Cell: The basic unit of any living organism. It is a small, watery, compartment filled with chemicals and a complete copy of the organism's genome.

Chromosome: One of the threadlike "packages" of genes and other DNA in the nucleus of a cell. Humans have 23 pairs of chromosomes, 46 in all: 44 autosomes and two sex chromosomes. Each parent contributes one chromosome to each pair, so children get half of their chromosomes from their mother and half from their father.

Chromatid: A chromatid is one-half of a replicated chromosome.

Cytoplasm: The term cytoplasm refers to everything between the cell membrane and the nuclear envelope. It consists primarily of water. It also contains various organelles as well as salts, dissolved gasses and nutrients.

Developmental Dyspraxia: This is a neurologically based disorder of the processes involved in praxis or the planning of movement to achieve a predetermined idea or purpose, which may affect the acquisition of new skills and the execution of those already learned. More specifically, it is a disorder of praxis, or the process of ideation (forming an idea of using a known movement to achieve a planned purpose), motor planning (planning the action needed to achieve the idea), and execution (carrying out the planned movement).

Dihydrotestosterone: A hormone formed in the prostate gland, testes, hair follicles and adrenal glands when the enzyme 5-alpha reductase acts on testosterone.

Dimorphism: Having two different distinct forms of individuals within the same species: for example, male and female.

DNA: Deoxyribonucleic acid (DNA) is a double-stranded helix of nucleotides (subunits), which carries the genetic information of a cell. It encodes the information for the proteins and is able to self-replicate.

Endocrine: Secreting internally, most commonly into the systemic circulation.

Epididymis: The tightly coiled, thin-walled tube that serves to store, mature and transport spermatozoa between the testis and the vas (the vas deferens).

Estradiol: One of the two active metabolites of testosterone in males (the other being dihydrotestosterone).

Fertilization: The union of male and female gametes to form a zygote.

Follicle-stimulating hormone (FSH): A hormone of the anterior pituitary gland that stimulates the growth and maturation of eggs in females and sperm in males, and sex hormone production in both males and females.

Fragile X Syndrome: A defect of the X chromosome, which causes mild mental retardation. The disorder occurs more frequently and severely among males than females. This condition is the leading known familial cause of mental retardation in the United States. Language delays, behavioral problems, autism or autistic-

like behavior (including poor eye contact and hand-flapping), enlarged external genitalia, large or prominent ears, hyperactivity, delayed motor development and/or poor sensory skills are among the wide range of symptoms associated with this disorder.

Gamete: An egg or sperm cell. Such cells are haploid, meaning they have half the number of chromosomes an organism needs.

Genome: All the genetic material in the chromosomes of a particular organism.

Genotype: All or part of the genetic constitution of an individual or group. This is the internally coded, inheritable information carried by all living organisms.

Gonadotropin: A hormone that stimulates the growth and activity of the gonads, especially any of several pituitary hormones that stimulate the function of the ovaries and testes.

Gonads: A reproductive gland (ovary or testis) that produces germ cells (gametes).

Gynecomastia: A benign enlargement of the male breast resulting from an altered estrogen-androgen balance, in favor of estrogen, or increased breast sensitivity to a normal circulating estrogen level.

Hippocampus: A complex neural structure (shaped like a sea horse) consisting of gray matter and located on the floor of each lateral ventricle; intimately involved in motivation and emotion as part of the limbic system; has a central role in the formation of memories.

Homologous: Having the same morphology and linear sequence of gene loci as another chromosome.

Hyalinization: The formation of hyaline, a uniform matrix of a glassy, translucent cartilage material.

Hypogonadism: Functional incompetence of the gonads especially in the male with subnormal or impaired production of hormones and germ cells.

Hypergonadotropic: Of or involving increased production or excretion of gonadotropic hormones.

Immunoassay: A laboratory technique that makes use of the binding between an antigen and its homologous antibody in order to identify and quantify the specific antigen or antibody in a sample

Inhibin: A peptide hormone secreted by the follicular cells of the ovary and the Sertoli cells of the testis that inhibits secretion of follicle stimulating hormone from the anterior pituitary.

Interstitial: Relating to or situated in the small, narrow spaces between tissues or parts of an organ.

Karyotype: A display of the chromosomes of a single cell. To obtain it, the cell is stained and then a picture is taken of it through a microscope just before cell division, when the chromosomes are easiest to see.

Leydig cells: Also known as interstitial cells of Leydig, they are found adjacent to the seminiferous tubules in the testes. They produce the hormone testosterone when stimulated by Luteinizing Hormone (LH). Leydig cells are named after Franz Leydig, who discovered them in 1850.

Mediastinum: The region in mammals between the pleural sacs, containing the heart and all of the thoracic viscera except the lungs.

Meiosis: The type of cell division by which germ cells (eggs and sperm) are produced. Meiosis comprises two successive nuclear divisions with only one round of DNA replication. Each resulting daughter cell receives half of the original number of chromosomes.

Metaphase: The second stage of meiosis cell division.

Mitosis: A process of cell division which results in the production of two daughter cells from a single parent cell. The daughter cells are identical to one another and to the original parent cell.

Mosaicism: A variation in the number of chromosomes in the body's cells. Normally, all body cells would have the same number of chromosomes (46). But in mosaicism, some cells may have 47 chromosomes (such as, an extra chromosome X) while other cells do not.

Non-disjunction: The failure of paired chromosomes or sister chromatids to separate and go to different cells during meiosis.

Oocytes: A cell from which an egg or ovum develops by meiosis.

Oogonia: A cell that arises from a primordial germ cell and differentiates into an oocyte in the ovary.

Oogenesis: The formation, development, and maturation of an ovum.

Ovaries: Small oval-shaped glands which are located on either side of the uterus.

Ovulation: The release of a mature fertilizable egg from the ovary. Ovulation should continue throughout a woman's reproductive lifespan typically at regular monthly intervals.

Ovum: The female reproductive cell; egg.

Oligospermia: The production of an ejaculate containing less than 20 x 100 spermatozoa per milliliter of semen.

Pharmacogenetics: The study of genetic factors that influence an organism's reaction to a drug.

Phenotype: The visible properties of an organism that are produced by the interaction of the genotype and the environment. This is the outward, physical manifestation of the organism.

Polymorphism: A common variation or mutation in DNA.

Polar Body: A small cell (which eventually disintegrates) that is the by-product of meiosis in female animals. One functional ovum and potentially three polar bodies result from meiosis of each primary oocyte.

Prophase: One of the most important stages of meiosis. During this stage, many crucial events occur. The chromatid threads begin to twist and condense, creating chromosomal structures, which are visible to the microscope. Each chromosome then actively seeks out its homologous chromosome. After the homologous chromosomes pair, the structure is referred to as a tetrad (four chromatids). The point at which two non-sister chromatids intertwine is known as a chiasma. Sometimes a process known as crossing over occurs at this point. This is where two non-sister chromatids exchange genetic material. This exchange does not become evident, however, until the two homologous pairs separate.

Puberty: The period during which a child's body becomes sexually mature and develops into adult form. Onset is usually in the early teens and is accompanied by a large increase in hormone production.

Psychosexual: Of or relating to the mental, emotional, and behavioral aspects of sexual development and the mental or emotional attitudes concerning sexual activity.

Sclerosis: A thickening or hardening of a body part or system especially from excessive formation of fibrous interstitial tissue.

Seminiferous Tubules: The glandular part of testicles that contains the sperm producing cells. Long thread-like tubes packed in the lobes of each testis where sperm is produced.

Sertoli cells: The elongated, striated cells of the seminiferous tubules of the testis to which spermatids attach for nourishment during spermatogenesis**.**

Spermatid: A young spermatozoa.

Spermatocytes: The primary germ cells undergo division and produce a number of cells termed spermatogonia, and from these the primary spermatocytes are derived. Each primary spermatocyte divides into two secondary spermatocytes, and each secondary spermatocyte into two spermatids or young spermatozoa; thus a primary spermatocyte gives rise to *four* spermatozoa.

Spermatogenesis: It starts with the spermatogonia or germinal cells dividing mitotically to produce a small clone of (46XY) cells termed spermatocytes. The spermatocytes migrate through the tight junctions at the base of the Sertoli cells and undergo two meiotic divisions. The resulting cells, thus, contain 23 single half chromosomes and are called spermatids.

Spermatogonia: Cells, each with 46 chromosomes (23 pairs) located around the periphery of the seminiferous tubules.

Spermatozoa: Male reproductive cells, developed in the testes. Each consists of a small but greatly modified cell possessing a head, a neck, a connecting piece or body, and a tail

Spermiogenesis: The process by which spermatids mature into sperm cells.

Steroid: Any of numerous naturally occurring or synthetic fat-soluble organic compounds including the sterols and bile acids, adrenocortical and sex hormones, certain natural drugs such as digitalis compounds, and the precursors of certain vitamins.

Testes: Male reproductive organs that makes sperm.

Trisomy: Having three copies of a particular chromosome instead of the usual two.

Vas deferens: A duct that carries spermatozoa from the epididymis to the ejaculatory duct.

Zygote: The cell formed by the union of a sperm and an egg.

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