Intrinsa: An Inquiry into Female Sexual Dysfunction and Testosterone

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Intrinsa:
An Inquiry into Female Sexual Dysfunction and Testosterone

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Abstract

In December 2004, the Food & Drug Administration rejected Intrinsa, a testosterone transdermal system for the treatment of hypoactive sexual desire disorder in surgically menopausal women. Intrinsa, as well as the FDA's decision, sparked considerable controversy. Principally, it raised questions about the use of testosterone to treat sexual dysfunction in women. This paper examines the relationship between testosterone and female sexual dysfunction and explores, specifically, whether there is a causal relationship between depressed testosterone levels and sexual problems in women. It discusses normal female sexual response and female sexual dysfunction as well as the association between testosterone and sexual difficulties in normal and surgically menopausal women. Ultimately, this paper concludes that there is little evidence for a causal relationship between low levels of testosterone and sexual dysfunction in normal women, but that depressed testosterone levels may be associated with sexual problems in surgically menopausal women. Though Intrinsa was purportedly created for use in surgically menopausal women, its off-label use by normal women was probable. Facing this widespread use by women unlikely to be helped by testosterone and subject to its unknown adverse side effects, the FDA appropriately requested more safety data before approving Intrinsa.

In December 2004, the Food & Drug Administration rejected Intrinsa, a testosterone transdermal system for the treatment of hypoactive sexual desire disorder in surgically menopausal women. Intrinsa, as well as the FDA's decision, sparked considerable controversy. Many sexual health researchers argued that Intrinsa was not an appropriate treatment for female sexual dysfunction, but was, instead, the result of the pharmaceutical industry's efforts to create a disease for financial gain. Others believed that Intrinsa should have been approved and that the FDA's grounds for rejection were improper. The debate surrounding Intrinsa heightened awareness of women's sexuality and sexual difficulties. It also raised questions about female

sexual dysfunction and testosterone. Specifically, given testosterone's association with maleness, why was it being used to treat sexual problems in women?

This paper seeks to understand the relationship between testosterone and female sexual dysfunction. It explores whether there is a causal relationship between depressed testosterone levels and sexual problems in women and whether testosterone is an appropriate treatment for women's sexual difficulties. The discussion is divided into three parts. The first part explores normal sexual function and sexual dysfunction in women. It details several models of normal human sexual response as well as the physiological mechanisms underlying this response. It then discusses female sexual dysfunction: how it is defined, its prevalence and presentation in women, and its causes. The second part of the paper focuses on testosterone. It examines the association between testosterone levels and sexual functioning in women, and it inquires into whether women actually suffer from low levels of testosterone. It concludes with a study of testosterone and sexual dysfunction in surgically menopausal women. The third, and final, section evaluates Intrinsa and the FDA's decision in light of the prior sections of this paper. It specifically addresses whether testosterone should be used to treat women's sexual problems.

As will become clear, there is little evidence for a causal relationship between testosterone and sexual dysfunction in the majority of women. In normal women, the data on the association between depressed testosterone levels and sexual problems are sparse, and there appear to be few instances in which women exhibit low testosterone concentrations. The data suggest, however, that surgically menopausal women—women who have had their ovaries removed—experience decreases in testosterone levels. For this small group of women, testosterone may be implicated in sexual dysfunction and may be an appropriate treatment. Though Intrinsa was purportedly created for use in these women, its off-label use by normal women was probable. The FDA thus faced widespread use of Intrinsa by women unlikely to be helped by the drug and subject to its unknown adverse side effects. In light of these circumstances, the FDA's request for more safety data before

approving Intrinsa was an appropriate, cautious response.

Normal Sexual Functioning

Our understanding of sexual health—of what is normal sexual behavior and response—is shaped by political, social, and historical factors and has evolved over time.[1] The prevailing definition of sexual health, put forth by the World Health Organization, is as follows:

> [A] state of physical, emotional, mental and social well-being related to sexuality; it is not merely the absence of disease, dysfunction or infirmity. Sexual health requires a positive and respectful approach to sexuality and sexual relationships, as well as the possibility of having pleasurable and safe sexual experiences, free of coercion, discrimination and violence. For sexual health to be attained and maintained, the sexual rights of all persons must be respected, protected and fulfilled.[2]

Central to this definition is the notion that sexual health is not just a physical condition but a state of total corporeal, psychological, and social wellbeing.[3] The right to sexual health includes negative and positive entitlements: with respect to the former, it includes the right to be free from fear, shame, guilt, false beliefs, and other psychological factors inhibiting sexual response and impairing sexual relationships; it includes the right to be free from organic disorders, diseases, and deficiencies that interfere with sexual and reproductive functions.[4] Sexual health also implies affirmative rights: it refers to the capacity to enjoy and control sexual and reproductive behavior in accordance with social and personal ethics as well as to benefit from access to information and services.[5]

[1] Weston M. Edwards et al., *Defining Sexual Health: A Descriptive Overview*, 33(3) Archives of Sexual Behavior 189, 189 (2004).
[3] *Id.*
[4] *Id.* at 191.
[5] *Id.*

Many scholars argue that sexual health is not a scientific concept and thus cannot be defined. Rather, what we view as normal and healthy sexuality reflects cultural mores and values and changes "with the ebb and flow of time, culture, residence... sexual preference, social class, religious background, relationship status, and ethnic background."[6] Any normative definition of sexual health fails to account for this fluidity and relativity and results in ethnocentric labels of "healthy" and "unhealthy."[7]

With these concerns in mind, researchers have still attempted to decipher and to describe normal sexual response in men and women. The driving force behind these efforts has been the recognition that, to determine what's abnormal, we must have an understanding of what is normal. Accordingly, we begin with a review of several models of human sexual response, paying particular attention to Masters & Johnson's framework,[8] that purport to describe normal sexual functioning. We then consider the physiological processes associated with female sexual response before moving onto a discussion of sexual dysfunction in women.

Models of Sexual Response

Masters & Johnson were the first researchers to observe, describe, and ultimately define the gross physical changes in men and women as they engaged in sexual activity.[9] They sought to address the question: what physical reactions develop as the human male and female respond to effective sexual stimulation?[10] Though conducted in the early 1950's, their research remains the seminal exploration of human sexual response.

[6] *Id.* at 192.
[7] *Id.*
[8] William H. Masters & Virginia E. Johnson, Human Sexual Response 4 (1966).
[9] *Id.*
[10] *Id.*

To devise a universal model of human sexual response, Masters & Johnson studied and recorded the anatomic and physiologic responses of 382 women (aged 18 to 78) and 312 men (aged 21 to 89) to sexual stimulation in their reproductive biology laboratory.[11] As a result of their work, they developed a four-phase model of sexual response, with the four stages being excitement, plateau, orgasm, and resolution.[12] The physiologic changes women experience during each of these phases is as follows. During the excitement phase, physical and/or psychological stimulation produces physical changes: the uterus elevates, vaginal lubrication begins to appear, the clitoris engorges with blood, and both the labia majora and labia minora swell.[13] The breasts enlarge slightly, the nipples may become erect, and muscular contracts may occur with increasing frequency.[14] During the late excitement, or plateau, phase, sexual tension appears to level off. The uterus elevates further (a process called "tenting"), the outer third of the vagina swells to form what is known as an orgasmic platform, the clitoris withdraws under the clitoral hood, and the color of the labia deepens.[15] The areola begin to swell, and a reddish, spotty skin color change ("sex flush") may develop in the skin around the upper abdomen.[16] During the third phase, the orgasm phase, sexual tension peaks and discharges, with the uterus, vagina, and rectal sphincter contracting.[17] During the last phase, or resolution, the body returns to its unaroused state.[18] The uterus lowers, the orgasmic platform disappears, the vagina returns to normal, and the clitoris returns to its unaroused position.[19]

Masters & Johnson's model remains the dominant and most widely used depiction of human sexual response. However, their model is not without flaws, and it has been widely critiqued. A central criticism is that the model concentrates on the biological aspects of sexual response at the expense of affective aspects.[20] The

[11] *Id.* at 13.
[12] *Id.* at 3-8.
[13] *Id.* at 69-75.
[14] William H. Masters, Virginia E. Johnson, & Robert C. Kolodny, Human Sexuality 76 (5th ed. 1995).
[15] Masters & Johnson, *supra* note 8, at 75-77.
[16] Masters et al., *supra* note 14, at 79.
[17] Masters & Johnson, *supra* note 8, at 77-78.
[18] *Id.* at 78-80.
[19] *Id.*
[20] Bryan Strong et al., Human Sexuality: Diversity in Contemporary America 98 (5th ed. 2005).

model does not consider, for example, forces that drive women to engage in sexual activity, such as desire and intimacy.[21] Even more, in focusing on physiological changes, the model fails to examine the body as a whole, but looks only at various body parts that move in and out of focus as the response sequence progresses.[22] A second central criticism is that the model is unduly focused on orgasm as an end point, when many women neither orgasm nor expect to orgasm during intercourse.[23]

Tiefer, a particularly vociferous critic of the model, also criticizes Masters & Johnson's presumptions, methodology, and default treatment of men's experiences.[24] First, she argues that Masters & Johnson's work was a self-fulfilling prophecy and that their research aims biased their results.[25] Wanting to describe the "overall sexual cycle," Masters & Johnson assumed that sexual response is an orderly, cyclic sequence of events that does not vary from person to person.[26] In keeping with their presumptions of order and uniformity, Masters & Johnson failed to include components of sexual response that have been shown to vary, namely initiating variables like libido, desire, and passion.[27] By omitting factors that are variable and hard to measure, Masters & Johnson increased the likelihood that they would, in fact, find a sequential and uniform model of sexual response.[28]

Secondly, Masters & Johnson's subjects were hardly representative of the general population.[29] Their pilot subjects were prostitutes,[30] and, for their central study, they weighted their subjects toward "higher than average intelligence levels and socioeconomic backgrounds."[31] Though Masters & Johnson did not appear troubled by their subject selection, it can hardly be asserted that prostitutes' sexual experiences are

[21] Rosemary Basson, *The Female Sexual Response Revisited*, 22(5) J. Soc'y Obstetrics & Gynecology Can. 378, 379 (2000).
[22] Leonore Tiefer, *Historical, Scientific, Clinical and Feminist Criticisms of "The Human Sexual Response Cycle" Model*, 2 Annual Review of Sex Research 1, 18 (1992).
[23] Strong et al., *supra* note 20, at 105.
[24] Tiefer, *supra* note 22, at 2.
[25] *Id.* at 5.
[26] *Id.* at 2-3.
[27] *Id.* at 4.
[28] *Id.*
[29] *Id.* at 5.
[30] Masters & Johnson, *supra* note 8, at 10.
[31] *Id.* at 12.

typical. Furthermore, it has been shown that sexual behavior does vary among women with different educational attainment.[32] Additionally, Masters & Johnson required that each subject have "a positive history of masturbatory and coital orgasmic experience before... [being] accepted into the program."[33] Tiefer writes,

> This requirement would seem to invalidate any notion that the [human sexual response cycle] is universal. Rather, it indicates that the Masters & Johnson research was designed to identify physiological functions of subjects experienced with *particular* preselected sexual responses. That is, rather than the [human sexual response cycle] being the best-fit model chosen to accommodate the results of the their research, the [model] actually guided the selection of subjects for the research... [T]here are many sexually active and sexually responsive men and women who do not regularly experience orgasm during masturbation and/or coitus whose patterns of physiological arousal and subjective pleasure were deliberately excluded from the sample. No research was undertaken to investigate "human" sexual physiology and subjectivity, only to measure the responses of an easily orgasmic sample.[34]

Essentially, Masters & Johnson chose subjects well versed in communicating about sexual activity and in achieving orgasm. As Tiefer writes, the selection of subjects precluded an examination of *general* human sexual response; what Masters & Johnson examined was the trajectory of sexual response that ultimately led to orgasm. However, not all humans are inclined towards sexual communication or orgasm and, as a result, the human sexual response cycle cannot be said to be universal.

Finally, Tiefer criticizes Masters & Johnson's model for depicting and thereby favoring men's sexual interests over those of women.[35] Specifically, with its focus on genitals—vaginal intercourse and masturbation—the model ignores women's sexual socialization and preferences.[36] For most of history, women have been subordinated socioeconomically and have lived under threat of pregnancy, male violence, and society's double standards.[37] As a result, they have been socialized against sexual assertiveness and candor and have been

[32] Edward O. Laumann, Anthony Paik, & Raymond C. Rosen, *Sexual Dysfunction in the United States: Prevalence and Predictors*, 281(6) JAMA 537, 540 (1999).
[33] Masters & Johnson, *supra* note 8, at 311.
[35] *Id.* at 18.
[36] *Id.*
[37] *Id.* at 19. By double standards, Tiefer refers to the traditional belief that it is socially acceptable for men to behave promiscuously but socially unacceptable for women to do the same.

raised to prefer intimacy and emotional communication to varied sexual experience and physical satisfaction.[38] In focusing on genital stimulation and response, however, Masters & Johnson's model ignores women's social reality and sexual training, and it ultimately becomes a model that details men's experiences and preferences.

Researchers have responded to these critiques by formulating models of sexual response that expand upon or diverge entirely from Masters & Johnson's model. Three well-known alternatives to Masters & Johnson's model—Kaplan's, Loulan's, and Basson's models of sexual response—are as follows. Kaplan's model altered Masters & Johnson's work to bring in an element of psychological willingness.[39] Kaplan created a tri-phasic model of sexual response, with desire, excitement, and orgasm phases.[40] She added the desire phase to the beginning of the sexual response process; she collapsed Masters & Johnson's excitement and plateau phases into one excitement phase; she retained the orgasm phase; and she eliminated the resolution phase.[41] During the desire phase, individuals experience some form of thought, fantasy, or erotic feeling that causes them to seek sexual gratification.[42] During Kaplan's excitement phase, individuals experience the physiological changes detailed in Masters & Johnson's excitement and plateau phases.[43] Finally, during Kaplan's orgasm phase, individuals experience the changes in Masters & Johnson's orgasm phase.[44]

Loulan's model, like Kaplan's, attempts to incorporate biological and affective components of sexual response.[45] The stages of her model are as follows: willingness, desire, excitement, engorgement, orgasm, and pleasure.[46] During the first stage, willingness, two individuals consciously decide to engage in sex, even if

[38] *Id.* at 18-19.
[39] Strong et al., *supra* note 20, at 98.
[40] *Id.*
[41] *Id.*
[42] *Id.* at 100.
[43] *Id.*
[44] *Id.*
[45] *Id.*
[46] *Id.*

there is a lack of physical or emotional desire.[47] The second stage, desire, is identical to Kaplan's desire phase, and the third, fourth, and fifth phases—the excitement, engorgement, and orgasm phases—are identical to Masters & Johnson's excitement, plateau, and orgasm phases, respectively.[48] During the final phase, the pleasure phase, the body returns to its unaroused state.[49] Pleasure, which Loulan states is the purpose of sexuality, can be defined only by each individual and can be experienced during any and all of the prior phases.[50]

Finally, Basson's model of female sexual response considers female sexual response in the context of a long-term relationship.[51] She describes a continuous cycle, rather than a model with discrete phases. From a state of sexual neutrality, women begin to sense the opportunity to be sexual.[52] Though women may initiate or agree to engage in sexual activity for a variety of reasons (such as anticipation of physical and emotional pleasure), Basson theorizes that they do so primarily as a means of enhancing intimacy with their partners.[53] As women begin to seek out and to be receptive to sexual stimuli, they may begin to experience sexual desire and arousal.[54] These sexual sensations then drive women to continue engaging in sexual activity, though they may have initially instigated or agreed to sexual activity for intimacy reasons.[55] As the sexual encounter draws to an end, women may experience positive physical and/or emotional feelings, which in turn enhance their feelings of intimacy, affection, and commitment towards their partners.[56] These feelings feed back into the cycle and once again drive women to seek out or agree to sexual activity.[57]

Though Masters & Johnson's model of human sexual response remains the dominant depiction of normal

[47] *Id.*
[48] *Id.*
[49] *Id.*
[50] *Id.*
[51] Basson, *supra* note 21, at 379.
[52] *Id.*
[53] *Id.*
[54] *Id.* at 380.
[55] *Id.*
[56] *Id.*
[57] *Id.*

sexual behavior and response, much can be learned from the other models. Whereas Masters & Johnson describe physical responses on the path to orgasm, the other models consider the psychological, emotional, and relational factors that drive individuals to seek out sexual activity in the first place. In addition, Loulan and Basson's models consider endpoints of sexual activity that are neither physical pleasure nor orgasm. Rather, their cycles remind us that there are emotional and relational benefits to engaging in sexual activity and that many individuals do not achieve orgasm or expect to when engaging in intercourse.

Physiology of Sexual Response

Having examined models of human sexual response, we now review briefly the complex interactions in the body that result in these sexual responses as individuals engage in sexual activity. Generally, sexual arousal and response involve the brain, specifically the cerebral cortex and limbic systems, as well as the nervous system, the circulatory system, the endocrine glands, and the genitals.[58] Sensory stimulation, thoughts and feelings (such as expectations, fantasies, hopes, and fears), and relational and cultural influences combine to bring individuals to a point at which they are able and willing to engage in sexual activity.[59] In the brain, these inputs activate the central nervous system, particularly the medial preoptic, anterior hypothalamic region, and related limbic hippocampal structures.[60] These structures, in turn, transmit electrical signals through the parasympathetic and sympathetic nervous systems that result in the relaxation of vaginal and clitoral smooth muscles and increased genital blood flow.[61] Specifically, these vasocongestive

[58] Strong et al., *supra* note 20, at 100-103.
[59] *Id.* at 100-101.
[60] J.R. Berman, *Physiology of Female Sexual Function and Dysfunction*, 17 Int'l. J. Impotence Res. S44, S46 (2005).
[61] J.R. Berman et al., *Clinical Evaluation of Female Sexual Function: Effects of Age and Estrogen Status on Subjective and Physiologic Sexual Responses*, 11 Int'l J. Impotence Res. (Supp. 1) S31, S31 (1999).

and neuromuscular events culminate in increased clitoral and vaginal length and diameter as well as increased vaginal lubrication and wall engorgement.[62] Hormones, such as estrogen, testosterone, and oxytocin, are thought to contribute to these changes. Estrogen, for example, affects cells throughout the peripheral and central nervous systems and influences nerve transmission.[63] It also has

vaso-protective and vasodilatory effects, which result in increased vaginal, clitoral, and urethral arterial blood flow.[64]

We have thus far reviewed the physiological and affective changes associated with sexual response as well as the underlying biological mechanisms that result in these changes. With a sense of what constitutes normal sexual functioning, we now consider sexual dysfunction.

Female Sexual Dysfunction

The distinction between normal and abnormal sexual functioning is not always clear.[65] Cultural norms differ, as do individual perceptions of what is healthy and what is problematic sexual behavior and response. Furthermore, levels of sexual desire and forms of sexual activity vary enormously in any given population, and these differences do not inevitably imply sexual dysfunction.[66] Unsurprisingly, there has been great debate among researchers about how to describe and classify sexual difficulties.

[62] *Id.*
[63] Berman, *supra* note 60, at S46.
[64] *Id.* at S47.
[65] Strong et al., *supra* note 20, at 488.
[66] *Id.*

In this section, we begin with a review of three classification systems used to define female sexual dysfunction. First, we discuss the American Psychiatric Association's classification system, found in the Diagnostic and Statistical Manual of Mental Disorders (the "DSM-IV"), which is currently the standard medical diagnostic classification system.[67] We then consider the system proposed by a recent Consensus Development Panel (the "consensus panel") on female sexual dysfunction.[68] Thirdly, we review the framework proposed by the Working Group for a New View of Women's Sexual Problems (the "working group").[69] After discussing these models, we examine research that inquires into the prevalence and patterns of female sexual dysfunction. Finally, this section closes with a delineation of the numerous causes of sexual dysfunction in women.

Defining Female Sexual Dysfunction

We begin with the DSM-IV classification system, the most widely used categorization of sexual dysfunctions. The DSM-IV defines sexual dysfunction as "characterized by a disturbance in the processes that characterize the sexual response cycle or by pain associated with sexual intercourse."[70] The DSM-IV classification is based on a combination of Masters & Johnson and Kaplan's models of human sexual response.[71] The manual recognizes a four-phase sexual response cycle with an appetite/desire phase, an excitement/arousal phase, an orgasmic phase, and a resolution phase, and it classifies disorders in accordance with these phases.[72]

[67] American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders IV (2000), http://online.statref.com/document.aspx?fxid=37&docid=7.

[68] Rosemary Basson et al., *Report of the International Consensus Development Conference on Female Sexual Dysfunction: Definitions and Classifications*, 163(3) J. Urology 888, 888 (2000).

[69] The Working Group on A New View of Women's Sexual Problems, *A New View of Women's Sexual Problems*, 3(15) Electronic J. Hum. Sexuality (2000), http://www.ejhs.org/volume3/newview.htm.

[70] American Psychiatric Association, *supra* note 67.

[71] *Id.*

[72] *Id.*

Specifically, the central sexual dysfunctions are sexual desire disorders, sexual arousal disorders, orgasmic disorders, and sexual pain disorders.[73]

The sexual dysfunctions experienced by women are as follows:

Sexual desire disorders:

♣

Hypoactive sexual desire disorder: persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity, causing marked distress or interpersonal difficulty.[74]

♣

Sexual aversion disorder: persistent or recurrent extreme aversion to, and avoidance of, all (or almost all) genital sexual contact with a sexual partner, causing marked distress or interpersonal difficulty.[75]

Sexual arousal disorder:

♣

Female sexual arousal disorder: persistent or recurrent inability to attain, or to maintain until completion of the sexual activity, an adequate lubrication-swelling response of sexual excitement, causing marked distress or interpersonal difficulty.[76]

Orgasmic disorder:

♣

Female orgasmic disorder: persistent or recurrent delay in, or absence of, orgasm following a normal sexual excitement phase, causing marked distress or interpersonal difficulty.[77]

Sexual pain disorders:

♣

[73] *Id.*

> Dyspareunia: recurrent or persistent genital pain associated with intercourse, causing marked distress or interpersonal difficulty.[78]

♣

> Vaginismus: recurrent or persistent involuntary spasms of the musculature of the outer third of the vagina that interferes with sexual intercourse, causing marked distress or interpersonal difficulty.[79]

In addition to these disorders, the DSM-IV includes the three categories "Sexual Dysfunction Due to a General Medical Condition," "Substance-Induced Sexual Dysfunction," and "Sexual Dysfunction Not Otherwise Specified."[80] The first refers to conditions that are the direct physiological effect of a general medical condition; the second refers to conditions that develop as a result of substance-induced intoxication; and the third refers to conditions that do not meet criteria for any specific dysfunction.[81] For all categories of sexual dysfunction, the DSM-IV specifies onset (lifelong versus acquired) and contextual (generalized, occurring in all sexual situations, versus situational) subtypes.[82]

Disorders of sexual desire describe problems with the first phase of the sexual response cycle, the appetite or desire phase. Individuals with hypoactive sexual desire disorder have inhibited or low sexual desire and participate reluctantly in sexual activity that is initiated by a partner.[83] However, because there is no "normal" level of sexual desire—"normal" people differ in their sexual fantasies and needs—defining and identifying low sexual desire is a difficult and subjective task.[84] Whereas hypoactive sexual desire disorder is characterized by an absence of desire, sexual aversion disorder is characterized by an active dislike or fear of sexual contact. Individuals respond to the possibility of sexual conduct with anxiety, disgust, or fear and,

[80] *Id.*
[81] *Id.*
[82] *Id.*
[83] *Id.* at § 302.71.
[84] Strong et al., *supra* note 20, at 496.

in some cases, may experience physiological responses such as sweating, dizziness, or nausea.[85]

Women with sexual arousal disorders want sexual activity but are unable to maintain their physiological levels of arousal. This often results in vaginal dryness or tightness that can make intercourse uncomfortable.[86] However, it is important to note that some women experience a disconnect between physiological and subjective arousal: they may report an absence of lubrication but may still experience sexual excitement or they may report lubrication but may not feel aroused.[87] The DSM-IV fails to consider psychological arousal and its connection, or lack thereof, to physiological arousal.

Orgasmic disorders, like arousal disorders, implicate arousal rather than desire. Women with orgasmic disorder often want and enjoy sexual activity, but they are unable to climax. Orgasmic disorder is usually a lifelong condition, because once women learn to achieve orgasm, they rarely lose that capacity.[88] This category of sexual dysfunction has been criticized because, first, many women do not have orgasms and, second, women vary with respect to the type and intensity of stimulation that results in orgasm.[89] Specifically, 10-15% of women report never having orgasms, and another 10-15% report rarely having them.[90] Additionally, some women achieve orgasm through manual or oral stimulation only, whereas others require intercourse.[91] This considerable variation suggests that we, as a society, may unduly pathologize the inability to orgasm.

Finally, women with sexual pain disorders experience pain or vaginal muscle contractions that limit their ability to engage in intercourse. Though most women report occasional pain during intercourse, women with dyspareunia report persistent pain.[92] In women with vaginismus, the muscles around the vagina go into involuntary contractions, which can prevent the insertion of any object.[93] Both dyspareunia and vaginismus

[85] American Psychiatric Association, *supra* note 67, at § 302.79.
[86] Strong et al., *supra* note 20, at 497-498.
[87] *Id.* at 498.
[88] American Psychiatric Association, *supra* note 67, at § 302.73.
[89] Strong et al., *supra* note 20, at 499.
[90] *Id.*
[91] *Id.*
[92] *Id.* at 502.
[93] American Psychiatric Association, *supra* note 67, at § 306.51.

are not the result of medical or physiological conditions, but are thought to have strong psychological components.[94]

The DSM-IV classification system has been criticized for a number of reasons, many of which are similar to the critiques of Masters & Johnson's model of human sexual response. Researchers challenge the fact that the classification examines body parts in isolation and fails to consider both the body as a whole as well as the psychological and relational contexts in which the body engages in sexual activity.[95] They also find the DSM-IV's focus on heterosexual intercourse and orgasm shortsighted and limiting.[96] Tiefer's critique of Masters & Johnson's human sexual response model highlights the fact that the DSM-IV criteria are based on a sexual response cycle that is not necessarily universal.[97]

In the late 1990's, a panel of 19 experts in female sexual dysfunction gathered to "evaluate and revise existing definitions and classifications of female sexual dysfunction."[98] They developed a "new" consensus based classification system that purported to include organic, as well as psychological, causes of sexual dysfunction. In reality, however, the framework is very similar to that found in the DSM-IV. Generally, the panel retained the four major DSM-IV categories (desire, arousal, orgasm, and pain disorders) and made some changes to the definitions of particular disorders.[99] The altered definitions are as follows, with additions to the DSM-IV criteria in bold and deletions from the criteria crossed out.

Sexual desire disorders:

[94] *Id.* at § 302.76, 306.51.
[95] Strong et al., *supra* note 20, at 489.
[96] *Id.*
[97] Tiefer, *supra* note 22, at 5-6.
[98] Basson et al., *supra* note 68, at 888.
[99] *Id.* at 890.

Hypoactive sexual desire disorder: persistently or recurrently deficient (or absent) sexual fantasies and desire for **or receptivity to** sexual activity, causing personal distress or interpersonal difficulty.[100]

♣

Sexual aversion disorder: persistent or recurrent extreme aversion to, and avoidance of, all (or almost all) genital sexual contact with a sexual partner, causing marked distress or interpersonal difficulty.[101]

Sexual arousal disorder:

♣

Female sexual arousal disorder: persistent or recurrent inability to attain or maintain sufficient sexual excitement, causing personal distress or interpersonal difficulty, which may be expressed as a **lack of subjective excitement** or genital (lubrication/swelling) **or other somatic responses**.[102]

Orgasmic disorder:

♣

Female orgasmic disorder: the persistent or recurrent difficulty, delay in or absence of attaining orgasm following sufficient sexual stimulation and arousal, which causes personal distress or interpersonal difficulty.[103]

Sexual pain disorders:

♣

Dyspareunia: recurrent or persistent genital pain associated with sexual intercourse, causing marked distress or interpersonal difficulty.[104]

♣

Vaginismus: recurrent or persistent involuntary spasm of the musculature of the outer third of the vagina that interferes with vaginal penetration, which causes personal distress or interpersonal difficulty.[105]

♣

Noncoital sexual pain disorder: recurrent or persistent genital pain induced by noncoital sexual stimulation.[106]

Each diagnosis is subtyped as lifelong versus acquired and generalized versus situational and is classified as organic, psychogenic, mixed, or unknown in origin.[107]

Several changes are worth highlighting. The panel broadened sexual aversion disorder to refer to aversion to all sexual contact, rather than just genital sexual contact. Similarly, sexual arousal disorder was expanded to recognize a wide range of non-genital physical arousal (called "other somatic response") and subjective arousal (called "subjective excitement") characteristic of sexual response in women. The panel also included a new disorder, noncoital sexual pain disorder, to recognize that women may experience pain during noncoital sexual activity. Finally, whereas the DSM-IV considers personal and interpersonal difficulty as hallmarks of sexual dysfunction, the consensus panel asserted that only women's distress, and not their partners', would result in a diagnosis.

Above all, the consensus panel maintains that its new classification system differs from others, namely the DSM-IV, because it is "based on physiological as well as psychological pathophysiologies" (it suggests that the DSM-IV is purely a psychological model).[108] However, it is not apparent from the diagnostic criteria that this physiological angle has been "added." Even more, it's not apparent why the panel felt the need to add this element, because the DSM-IV does, in fact, consider physiologically-based female sexual dysfunction. In its introduction of sexual disorders, the DSM-IV states that a sexual dysfunction may be due to a combination of psychological and physiological factors when "psychological factors are judged to

[107] *Id.*
[108] *Id.* at 888.

have a role in the onset, severity, exacerbation, or maintenance of the Sexual Dysfunction... and a general medical condition or substance use is also judged to be contributory."[109] Furthermore, the DSM-IV includes a category entitled "Sexual Dysfunction Due to a General Medical Condition."[110] The consensus panel fails to acknowledge these points, and it appears to assert the physical causes of female sexual dysfunction for no other reason than to assert that sexual disorders can be caused by medical conditions.

The final classification system we will review is entitled "A New View of Women's Sexual Problems."[111] This framework is considerably different from the DSM-IV and consensus panel's criteria, and it purports to create a system based on women's needs and sexual realities. In particular, these researchers sought to avoid the three central shortcomings of other classification systems: an assumed sexual equivalency between men and women, a failure to acknowledge the role of relationships in sexuality, and the leveling of differences among women.[112] Furthermore, in light of the consensus panel's efforts to focus on physical causes of female sexual dysfunction, the working group hoped to shift concentration from the physiological back to the psychosocial causes of sexual disorders.[113]

The working group defines sexual problems "as discontent or dissatisfaction with any emotional, physical, or relational aspect of sexual experience."[114] These problems are thought to arise, for the most part, out of distress and inhibition that result from cultural and relational factors.[115] The working group's framework is as follows:

[109] American Psychiatric Association, *supra* note 67.
[110] *Id.*
[111] The Working Group on A New View of Women's Sexual Problems, *supra* note 69.
[112] *Id.*
[113] *Id.*
[114] *Id.*
[115] *Id.*

Sexual problems due to socio-cultural, political, or economic factors:[116]

A.

Ignorance and anxiety due to inadequate sex education, lack of access to health services, or other social constraints:

1.

Lack of vocabulary to describe subjective or physical experience.

2.

Lack of information about human sexual biology and life-stage changes.

3. Lack of information about how gender roles influence men's and women's sexual expectations, beliefs, and behaviors.

4. Inadequate access to information and services for contraception and abortion, STD prevention and treatment, sexual trauma, and domestic violence.

B.

Sexual avoidance or distress due to perceived inability to meet cultural norms regarding correct or ideal sexuality, including:

1.

Anxiety or shame about one's body, sexual attractiveness, or sexual responses.

2. Confusion or shame about one's sexual orientation or identity, or about sexual fantasies and desires.

C.

[116] *Id.*

Inhibitions due to conflict between the sexual norms of one's subculture or culture of origin and those of the dominant culture.

D. Lack of interest, fatigue, or lack of time due to family and work obligations.

Sexual problems relating to partner and relationship:[117]

A.

Inhibition, avoidance, or distress arising from betrayal, dislike, or fear of partner, partner's abuse or couple's unequal power, or arising from partner's negative patterns of communication.

B. Discrepancies in desire for sexual activity or in preferences for various sexual activities.

C. Ignorance or inhibition about communicating preferences or initiating, pacing, or shaping sexual activities.

D. Loss of sexual interest and reciprocity as a result of conflicts over commonplace issues such as money, schedules, or relatives, or resulting from traumatic experiences, e.g., infertility or the death of a child.

E. Inhibitions in arousal or spontaneity due to partner's health status or sexual problems.

Sexual problems due to psychological factors:[118]

A.

Sexual aversion, mistrust, or inhibition of sexual pleasure due to:

1.

Past experiences of physical, sexual, or emotional abuse.

2.

General personality problems with attachment, rejection, co-operation, or entitlement.

3. Depression or anxiety.

B.

> Sexual inhibition due to fear of sexual acts or of their possible consequences, e.g., pain during intercourse, pregnancy, sexually transmitted disease, loss of partner, loss of reputation. ?

Sexual problems due to medical factors:[119]

> Pain or lack of physical response during sexual activity despite a supportive and safe interpersonal situation, adequate sexual knowledge, and positive sexual attitudes. Such problems can arise from:

A.

> Numerous local or systemic medical conditions affecting neurological, neurovascular, circulatory, endocrine or other systems of the body.

B. Pregnancy, sexually transmitted diseases, or other sex-related conditions.

C. Side effects of many drugs, medications, or medical treatments.

D. Iatrogenic conditions.

This model attributes sexual dysfunction largely to psychosocial concerns, rather than physical conditions, and its inclusion of these psychosocial causes is extensive. With respect to socio-cultural factors, the model recognizes, for example, that in some societies women may remain subordinated to men and that this sexual inequality may result in sexual inhibition. In other societies, women might not have access to sexuality education or health services, and they may not understand or feel comfortable with their bodies and their sexuality. Alternatively, women's relational concerns may be at the root of their sexual difficulties. Women may be unable to communicate with their partners, may be dissatisfied with them, or may have different sexual preferences. The model also refers to psychological causes for sexual problems: women who suffer from

sexual abuse, attachment disorders, or depression may have difficulty with their sexual lives. Finally, in some cases, medical conditions may result in sexual dysfunction. These may include neurological or circulatory problems as well as the side effects of numerous medications.

Though the working group's model provides insight into the social, relational, and psychological contexts in which sexual dysfunction takes place, it is, in practice, difficult to operationalize. That is, we have a sense of what causes sexual dysfunction, but we are not told how the sexual problems manifest themselves. There are no variables and no end points that can be examined, measured, and compared. This effectively limits research and scholarship on sexual problems.

At this point, we have reviewed three models of female sexual dysfunction, which focus to varying degrees on physiological and psychosocial aspects of sexual concerns. We now consider the prevalence and patterns of sexual dysfunction in women.

Prevalence and Patterns

Prevalence

In this section, we review several studies that examine the prevalence of sexual dysfunction symptoms in women, paying particular attention to the National Health and Social Life Survey.[120] We also consider a few studies that inquire into the prevalence of sexual dysfunction in a different way: namely, by looking into women's levels of distress associated with their sexuality and supposed sexual problems.

[120]Laumann et al., *supra* note 32, at 537.

The National Health and Social Life Survey (the "NHSLS") is the most widely cited study on the prevalence of sexual dysfunction.[121] Conducted in 1992, the NHSLS was the first population-based assessment to examine adult sexual behavior in the United States since Kinsey's work. The NHSLS surveyed 1410 men and 1749 women between the ages of 18 and 59 and living in households in the U.S.[122] Each participant was interviewed in person for approximately 90 minutes.[123] Researchers examined sexual dysfunction by inquiring into 1) lack of desire for sex, 2) arousal difficulties (erection problems in men and lubrication problems in women, for example), 3) inability achieving climax, 4) anxiety about sexual performance, 5) climaxing too early, 6) physical pain during sex, and 7) not finding sex pleasurable.[124] The researchers found the total prevalence of sexual dysfunction in women to be 43%, notably higher than the 31% prevalence in men.[125] Specifically, 22% of women surveyed were affected by low sexual desire, 14% by arousal problems, and 7% by sexual pain.[126]

Other studies have produced different prevalence percentages. Goldmeier et al. asked 100 female and 103 male attendees at a genitourinary clinic whether they had experienced dissatisfaction with their sex lives or sexual problems over the last year.[127] Those who answered yes underwent a clinical interview to determine the specifics of the problem.[128] In this study, 20% of women reported sexual dysfunction.[129] Of the 20%, 50% had anorgasmia, 35% had decreased sexual desire, 20% had arousal problems, and 10% were generally dissatisfied with their sex lives.[130] In another study, questionnaires were mailed to women at military medical clinics.[131] Of the 1584 women who responded, 98% reported one or more sexual concerns, such as lack of

[121] *Id.*
[122] *Id.*
[123] *Id.* at 538.
[124] *Id.*
[125] *Id.* at 541.
[126] *Id.*
[127] David Goldmeier, Ali Judd, &, Kate Schroeder, *Prevalence of Sexual Dysfunction in New Heterosexual Attenders at a Central London Genitourinary Medicine Clinic in 1998*, 76(3) Sexually Transmitted Infections, 208, 209 (2000).
[128] *Id.*
[129] *Id.*
[130] *Id.*
[131] M.R. Nusbaum, *The Changing Nature of Women's Sexual Health Concerns Through the Midlife Years*, 49 Maturitas 283,

interest, sexual aversion, and difficulty with orgasm and intercourse.[132] The authors noted, however, that the prevalence of sexual dysfunction might have been inflated because women with sexual difficulties might have been more likely to send back the questionnaires.[133] Indeed, the prevalence of sexual dysfunction appears to vary considerably from study to study.

The NHSLS, as well as other typical prevalence studies, examine the prevalence of sexual dysfunction by inquiring about the presence of clinical symptoms of the various dysfunctions. These studies, however, have been criticized as being overinclusive because they fail to consider women's feelings about their supposed dysfunctions.[134] In the NHSLS, for example, the presence of sexual dysfunction was based on yes/no answers to the following questions: "During the last 12 months has there ever been a period of several months or more when you, a) lacked interest in having sex, b) were unable to climax (experience an orgasm), c) came to climax too quickly, d) experienced physical pain during intercourse, e) did not find sex pleasurable (even if it was not painful), f) felt anxious just before having sex about your ability to perform sexually, or g) had trouble lubricating?"[135] If a woman answered yes to at least one of these questions, she was seen as having a sexual dysfunction.[136] First, it is questionable that the NHSLS authors allowed the presence of a sexual dysfunction to be based on the answer to one question. But even more, the authors did not ask whether such "dysfunctions" had ever caused distress or were considered problematic by the women themselves.[137] If a woman answered "yes" to lack of sexual interest for several months, for instance, she would be seen as having sexual desire disorder, even if her lack of desire did not trouble her. Implicit in this criticism

283 (2004).
[132] *Id.*
[133] *Id.*
[134] Leonore Tiefer, *The "Consensus" Conference on Female Sexual Dysfunction: Conflicts of Interest and Hidden Agendas*, 27 J. Sex & Marital Therapy 227, 230 (2001).
[135] John Bancroft, Jeni Loftus, & J. Scott Long, *Distress About Sex: A National Survey of Women in Heterosexual Relationships*, 32(3) Archives Sexual Behavior 193, 203 (2003).
[136] *Id.*
[137] *Id.*

is the notion that some inhibition of sexual interest or response might be adaptive: it might occur as an appropriate, or at least understandable, reaction to certain circumstances.[138] It is therefore important to assess women's perceptions of their so-called sexual dysfunctions, because these perceptions are arguably necessary to determine whether their experiences are actually problematic.

A study by Haavio-Mannila & Kontula, for example, inquired into women's satisfaction with their sex lives and reported considerably lower rates of sexual dissatisfaction than the NHSLS.[139] Interviews with 1146 women aged 18-74 revealed that 6% of women found their sex lives unsatisfying, 13% found their sex lives neither unsatisfying nor satisfying, 52% quite satisfying, and 29% very satisfying.[140] Fewer women appeared to have sexual problems when they were asked about their general happiness with respect to their sex lives, rather than about the presence of clinical symptoms of sexual dysfunction.

Bancroft et al. conducted a study that examined women's distress about their sexual experiences.[141] Researchers asked 987 women aged 20-65 detailed questions about their sexual experiences and responses over the preceding month and about whether their sex lives distressed or worried them.[142] Sexual distress was assessed with the following two questions: 1) During the past 4 weeks, how much distress or worry has your sexual relationship caused you? 2) During the past 4 weeks, how much distress or worry has your own sexuality caused you? [143] Answers were categorized as no distress, slight distress, and marked distress.[144] The authors hoped to distinguish between distress that was a reaction to problems with the partner or sexual relationship and distress that was a reaction to concerns about the woman's capacity for sexual response.[145] The results indicated that 19.8% of women had marked distress about their relationship, and 14.7% had

[138] *Id.* at 194.
[139] Elina Haavio-Mannila & Osmo Kontula, *Correlates of Increased Sexual Satisfaction*, 26(4) Archives Sexual Behavior 399, 407 (1997).
[140] *Id.*
[141] Bancroft et al., *supra* note 135, at 193.
[142] *Id.*
[143] *Id.* at 195-196.
[144] *Id.*
[145] *Id.* at 200.

marked distress about their own sexuality.[146] In total, 24.4% of the sample had marked distress about their sexual relationship or their own sexuality or both.[147] Furthermore, 31.4% had slight distress about either or both, and 44.2% reported no distress of either kind.[148] Focusing on the 14.7% of markedly distressed women, the authors reported that, when women's own conceptions of their sexual "problems" are assessed, only one-third to one-half of women operationally defined as having a sexual dysfunction (satisfying diagnostic criteria, that is) actually regarded themselves as having a problem or reported marked distress about the supposed problem.[149]

In light of Laumann et al.'s 43% prevalence statistic, these results raise several questions. With respect to calculating the prevalence of sexual dysfunction, is the presence of symptoms—a loss of sexual desire or an inability to climax, for example—sufficient to declare that a woman has a given dysfunction? Or is a measurement of a woman's distress about a particular sexual problem or about sexuality in general a better indicator of the presence of sexual dysfunction? Alternatively, given that DSM-IV diagnostic criteria require symptoms and marked distress for a diagnosis, are both elements necessary?

K. Öberg et al. examined the prevalence of sexual dysfunction symptoms (sexual dysfunction per se) as well as the prevalence of personal distress caused by sexual dysfunction in a sample of 1056 women aged 18-65.[150] Women were asked about problems with sexual desire, interest, lubrication, orgasm, genital pain, and vaginismus and were asked to describe their dysfunction, if any, as none, mild (sporadically occurring), or manifest (occurring often or all the time).[151] Each subject was also asked to rate her distress associated with each dysfunction as none, mild, or manifest.[152]

The results indicated that the prevalence of distress was generally lower than the prevalence of sexual

[146] *Id.* at 196.
[147] *Id.*
[148] *Id.*
[149] *Id.* at 204.
[150] K. Öberg, A. R. Fugl-Meyer, & K. S. Fugl-Meyer, *On Categorization and Quantification of Women's Sexual Dysfunctions: An Epidemiological Approach*, 16 Int'l J. Impotence Res. 261, 261 (2004).
[151] *Id.*
[152] *Id.*

dysfunction per se.[153] For example, 29% of women reported manifest decreased sexual interest, and 60% reported mild decreased sexual interest.[154] However, of the 29% with manifest decreased sexual interest, 47% had manifest personal distress, 40% had mild distress, and 13% had no distress.[155] Similarly, of the 60% with mild decreased sexual interest, 2% showed manifest distress, 54% mild distress, and 45% no distress.[156] It appeared that, though women perceived themselves as suffering from some sort of sexual dysfunction, they did not necessarily experience the corresponding level of personal distress. The authors suggested that, from a clinical point of view, distress associated with sexual problems appears more relevant than sexual dysfunction per se.[157]

The study also found that aggregated manifest and mild dysfunction per se of sexual interest, orgasm and vaginal lubrication were reported by about 60-90% of the sample, with mild dysfunctions accounting for considerably more of this percentage.[158] With respect to this figure, they authors stated that "the prevalence of mild dysfunction is so high that it can be contemplated whether mild dysfunction might be regarded as 'normal' variation and not a clinical condition. This is further underscored by the fact that no more than 1-2% of women reporting mild dysfunction experienced it as manifestly distressing."[159] This highlights, again, the relevance of women's feelings about their so-called sexual dysfunctions.

In summary, the most widely cited prevalence statistic for female sexual dysfunction is that reported by the NHSLS: 43%. However, it is important to remember that this study did not take into account whether women viewed their sexual problems as troublesome. Studies that do consider women's perceptions of their sexuality and sexual difficulties tend to suggest that one-third to one-half of women with sexual dysfunction symptoms actually view these as problematic. Furthermore, as illuminated by K. Öberg et al., it is possible

[153] *Id.* at 267.
[154] *Id.* at 264.
[155] *Id* at 265.
[156] *Id.*
[157] *Id.* at 267.
[158] *Id.* at 261.
[159] *Id.* at 267.

that sexual difficulties may be so prevalent that some level of dysfunction is normal.

Patterns

We move now to a brief discussion of the relationship between sexual dysfunction and various demographic variables. We also examine several risk factors and concomitants.

The NHSLS is, again, the seminal study on this subject. The NHSLS noted several demographic trends. First, married women were less likely to experience sexual dysfunction than premarital (never married) women and postmarital (divorced, widowed, or separated) women.[160] That is, pre and postmarital women were approximately 1.5 times as likely as married women to have problems climaxing and to experience sexual anxiety.[161] Second, higher educational attainment was negatively associated with sexual problems: women who had graduated from college were half as likely to suffer from low sexual desire, difficulties achieving orgasm, sexual pain, and sexual anxiety than women who had not graduated from high school.[162] Third, the authors reported a variable relationship between race and ethnicity and sexual dysfunction.[163] Black women reported more low sexual desire and less pleasure than did white women, but white women were more likely to experience sexual pain than black women.[164] Hispanic women reported lower rates of sexual problems in general.[165]

The NHSLS also found that the prevalence of sexual problems decreased with age, with the exception of lubrication problems, which appeared to increase with age.[166] Other studies have found the opposite,

[160] Laumann et al., *supra* note 32, at 540.
[161] *Id.*
[162] *Id.*
[163] *Id.*
[164] *Id.*
[165] *Id.*
[166] *Id.*

however. Nusbaum's research, for example, found that, when women were divided into age groups (younger than 44, 45-54, and 54 and older), sexual function concerns were similar across the age groups but were more intense in older women.[167]

The NHSLS also examined risk factors, including health, lifestyle, social status, and sexual experience, in relation to sexual dysfunction categories (unaffected, low sexual desire, arousal problems, and sexual pain). With respect to health and lifestyle risk factors, women with emotional and stress-related problems were more likely to report sexual dysfunctions in each category.[168] In contrast, poor health was related only to sexual pain for women.[169] Social status variables—variables that measure socioeconomic status and individuals' normative position relative to others—showed that a decline in a woman's economic position, as measured by falling household income, was associated with a modest increase in risk for all categories of sexual dysfunction.[170] When measuring sexual experience, the authors found that women who reported low sexual activity or interests had an elevated risk for low sexual desire and arousal disorders.[171] Sexual victimization, either through adult-child contact or forced sexual contact, was also highly associated with arousal problems.[172]

Finally, the NHSLS studied quality-of-life concomitants and sexual concerns. It found sexual dysfunction to be highly associated with unsatisfying personal experiences and relationships.[173] Specifically, low emotional satisfaction and low levels of happiness were strongly associated with sexual dysfunctions.[174] Bancroft et al.'s work confirmed this finding: they reported that a lack of emotional wellbeing and negative emotional feelings during sexual interactions were associated with sexual distress.[175] In fact, women's negative mental

[167] Nusbaum, *supra* note 131, at 283.
[168] Laumann et al., *supra* note 32, at 541.
[169] *Id.*
[170] *Id.*
[171] *Id.* at 541-542.
[172] *Id.* at 542.
[173] *Id.*
[174] *Id.*
[175] Bancroft et al., *supra* note 135, at 202.

states were more important determinants of sexual distress than their physiological sexual impairments.[176] In sum, the central trends appear to be as follows. There is an elevated risk of sexual dysfunction with low educational attainment and minority status—this may attest to the fact that better educated individuals generally live healthier, less stressful lives. In a related vein, psychological disturbance appears to affect sexual functioning: emotional and stress-related problems generate an elevated risk of experiencing all forms of sexual dysfunction. It is not clear, however, whether sexual dysfunction increases or decreases with age. The NHSLS found sexual problems to be more common in young women. The authors noted that young women's inexperience and instability (high partner turnover, periods of sexual inactivity) might result in stressful sexual encounters, which may provide the basis for sexual difficulties.[177] Conversely, Nusbaum found that older women were more affected by sexual difficulties than younger women.

Causes

In this section, we review potential causes of female sexual dysfunction. This discussion is not meant to be exhaustive, but is intended to provide an overview of the principal psychosocial and biological origins of sexual problems.

Psychosocial Causes

Psychosocial causes of sexual dysfunction can be divided into three categories: immediate causes, conflict within the self, and relationship concerns.[178]

[176] *Id.*
[177] Laumann et al., *supra* note 32, at 542.
[178] Strong et al., *supra* note 20, at 505-507.

Immediate causes include fatigue and stress, ineffective sexual behavior, sexual anxieties, and an excessive need to please a partner.[179] To begin, weariness from the demands of every day life may result in sexual apathy or disinterest.[180] Raising children, working, and worrying about finances, for example, may leave couples too tired to engage in sexual activity at the end of the day. Long-term stress, such as that associated with coping with chronic illness, can also result in lowered sexual drive and reduced responsiveness.[181]

A lack of information and ineffective sexual techniques may also prevent some couples from being successful sexually with each other. Masters & Johnson note that men and women may not know what their partners find arousing and/or what they themselves find arousing.[182] In particular, many couples are unaware of the importance of the clitoris in female sexual arousal and of the need for direct stimulation.[183] Alternatively, some individuals may know what arouses them, but may be unable to communicate this information to their partners and/or may not be aroused by the techniques their partners use.[184]

A number of sexual anxieties can also lead to sexual problems. Performance anxiety, for example, may cause individuals to become obsessed with performing adequately in a sexual encounter and may lead them to focus on their performance rather than on their own pleasure or satisfaction.[185] In a study of 198 adults with sexual dysfunction and 145 adults without sexual dysfunction, McCabe found that women with sexual dysfunction exhibited considerably higher levels of performance anxiety than controls.[186] Furthermore, a

[179] *Id.* at 505-506.
[180] *Id.* at 505.
[181] *Id.*
[182] Masters et al., *supra* note 14, at 591.
[183] *Id.*
[184] *Id.*
[185] Marita P. McCabe, *The Role of Performance Anxiety in the Development and Maintenance of Sexual Dysfunction in Men and Women*, 12(4) Int'l J. Stress Mgmt. 379, 380 (2005).
[186] *Id.* at 385.

multiple regression analysis identified performance anxiety as one of the central variables in predicting the extent of sexual dysfunction in women.[187]

In a related vein, an excessive desire to please a partner may contribute to sexual dysfunction in women. Darling & Davidson reported that approximately two-thirds of women pretend to have orgasms during sexual activity with their partners.[188] Women may pretend to have orgasms to avoid disappointing their partners or to present a certain image of themselves as sexual beings.[189] Ultimately, because women lead their partners to believe that they are sexually satisfied, their orgasmic difficulties are never addressed or resolved.[190]

A second set of psychosocial causes of female sexual dysfunction is conflict within the self. It is thought that conflicting feelings about sexual activity may lead to sentiments of confusion and guilt that may inhibit sexual drive and alienate a person from her sexuality.[191] Such conflict may arise for a number of reasons, including negative parental, personal, or religious attitudes toward sex as well as traumatic sexual experiences.[192] With respect to attitudes towards sexual activity, in a study of the relationships among childhood, adolescent, and adult factors and sexual dysfunction, McCabe & Deakin found that negative parental attitudes about sex were strongly associated with sexual dysfunction in adulthood.[193] Additionally, in her study on performance anxiety and sexual dysfunction, McCabe's multiple regression analysis determined that an individual's attitude toward sex, as well as her performance anxiety, predicted sexual dysfunction.[194]

Religious beliefs may also contribute to sexual dysfunction in women. Davidson et al.'s study of religiosity and sexuality found, for example, that women who attended religious services frequently were more likely

[187] *Id.*
[188] C.A. Darling & J.K. Davidson, *Enhancing Relationships: Understanding the Feminine Mystique of Pretending Orgasm*, 12(3) J. Sex & Marital Therapy 182, 182 (1986).
[189] Strong et al., *supra* note 20, at 506.
[190] *Id.*
[191] *Id.*
[192] Masters et al., *supra* note 14, at 590.
[193] Marita P. McCabe & U. Deakin, *Childhood, Adolescent, and Current Psychological Factors Associated with Sexual Dysfunction*, 9(3) Sexual & Marital Therapy 267, 267 (1994).
[194] McCabe, *supra* note 185, at 385.

to perceive masturbation as a sin and unhealthy practice than women who attended religious services less frequently.[195] Additionally, they were more likely to feel guilty about masturbating and to be ashamed to admit to engaging in masturbation.[196] These studies suggest that negative attitudes about sex, whether they are derived from parental beliefs, personal feelings, or religious views, may predispose individuals toward developing sexual dysfunctions.

Traumatic sexual experiences, including child abuse, incest, and rape, are also strongly linked to the development of sexual dysfunction. With respect to child sexual abuse, it is thought that sexual abuse during childhood impairs sexual development, sexual decision-making, and interpersonal functioning as well as psychological and biological processes.[197] This impairment, in turn, can lead to the development of sexual difficulties. In a review of studies on child sex abuse, Wyatt noted that survivors of child sexual abuse reported numerous sexual problems, such as avoidance of sex, difficulty in touching and caressing their partners or being caressed themselves, and experiencing feelings of disgust about their own or their partner's body.[198] Another review indicated that women with a history of child sexual abuse were more likely to report sexual desire, arousal, and orgasm disorders, particularly if they were victimized multiple times.[199] Survivors of rape and incest show similar problems. A study of sexual functioning in survivors of rape and incest revealed markedly higher rates of sexual problems in these survivors than in controls.[200] Specifically, 58.6% of the survivors had at least one sexual problem, whereas only 17.2% of nonassaulted women had a sexual problem.[201] The nature of the sexual problems also differed between the two groups: survivors of sexual abuse were more likely to report symptoms that would prevent them from being sexual altogether, such

[195] J. Kenneth Davidson, Carol Anderson Darling, & Laura Norton, *Religiosity and the Sexuality of Women: Sexual Behavior and Sexual Satisfaction Revisited*, 32(3) J. Sex Res. 235, 242 (1995).
[196] *Id.*
[197] Tamra Burns Loeb et al., *Child Sexual Abuse: Associations With the Sexual Functioning of Adolescents and Adults*, 13 Ann. Rev. Sex Res. 307, 312 (2002).
[198] Gail E. Wyatt, *Child Sexual Abuse and Its Effects on Sexual Functioning*, 2 Ann. Rev. Sex Res. 249, 257 (1991).
[199] Loeb et al., *supra* note 197, at 316.
[200] Judith V. Becker, *Level of Postassault Sexual Functioning in Rape and Incest Victims*, 15(1) Archives Sexual Behav. 37, 42 (1986).
[201] *Id.*

as fear of sex, desire dysfunctions, and arousal dysfunctions.[202] Nonassaulted women, however, were more likely to report symptoms that did not diminish their desire for sex or their arousability, such as boredom with a sexual partner and less intense orgasms.[203]

A third category of psychosocial causes of sexual dysfunction is relationship concerns. These may include fears of becoming intimate with a partner, problems in a relationship, differing sexual tastes, and unequal power dynamics. To elaborate, some women may enjoy sexual activity but may fear its accompanying vulnerability.[204] Other women and their partners may have unresolved feelings of disappointment, anger, and hurt that come to characterize their relationship and to impair their sex lives.[205] Masters & Johnson also note that partners' conflicting sex value systems or very different sexual preferences with respect to timing, frequency, or type of sexual activity can lead to sexual problems.[206] Finally, power dynamics may harm a couple's sexual relationship. Women have been subordinated socially and economically by men for centuries and, though they now occupy a relatively more equal position in society, this lingering inequality may make it difficult for women to feel comfortable and assertive with sexual partners.[207] Even more, domestic violence and other forms of abuse within a relationship may lead to sexual problems.

Physiological Causes

We now consider several physiological causes of sexual dysfunction in women. These causes may be rooted in the vascular, muscular, nervous, and endocrine systems.

Beginning with vasculogenic causes, any injury to or compromise of the central arteries in the pelvic region—the iliohypogastric/pudendal arterial bed—can decrease blood flow to the genitals.[208] Pelvic fracture,

[202] *Id.* at 47.
[203] *Id.* at 46.
[204] Strong et al., *supra* note 20, at 506.
[205] Masters et al., *supra* note 14, at 591.
[206] *Id.*
[207] Tiefer, *supra* note 22, at 19.
[208] Berman, *supra* note 60, at S47.

trauma, or arteriosclerosis (the hardening and thickening of the walls of the arteries), for example, can decrease genital blood flow, reduce vaginal and clitoral engorgement, and lead to fibrosis (the development of excess fibrous connective tissue) of the vaginal wall and clitoral smooth muscle.[209] This, in turn, causes disruptions in the normal vasocongestion and relaxation response to sexual stimulation and can result in symptoms of vaginal dryness and dyspareunia.[210] In a study of sexual function in women with metabolic syndrome—a syndrome that is characterized by type II diabetes, central obesity, high blood pressure, decreased HDL cholesterol, and elevated triglycerides—women with the syndrome had increased rates of sexual dysfunction as compared to controls.[211] Specifically, they reported lower levels of arousal, orgasm, and lubrication than controls.[212] Though correlation does not indicate causation, it is thought that the metabolic syndrome may compromise genital vasocongestion and subsequently impair sexual response.[213]

Damage to pelvic floor muscles, which contract during sexual activity, can also reduce sexual reactivity in women. Pelvic surgery, such as removal of the bladder (cystectomy), uterus (hysterectomy), ovaries (bilateral oophorectomy), or colorectal re-sectioning, may disrupt pelvic nerves and change the anatomical relationships of pelvic structures.[214] For example, surgery for uterine prolapse or urinary incontinence may result in damage to the anterior vaginal wall and clitoral region, which can cause arousal and orgasmic difficulties as well as sexual pain disorder.[215] Additionally, surgery to repair the vagina, known as colporrhaphy or colpoperineoplasty, can narrow the vaginal opening, which can lead to pain during penetration.[216]

[209] *Id.*
[210] *Id.*
[211] K. Esposito et al., *The Metabolic Syndrome: A Cause of Sexual Dysfunction in Women*, 17 Int'l J. Impotence Res. 224, 224-225 (2005).
[212] *Id.* at 225.
[213] *Id.* at 226.
[214] Craig D. Zippe et al., *Female Sexual Dysfunction After Pelvic Surgery: The Impact of Surgical Modifications*, 96 Brit. J. Urology Int'l 959, 959 (2005).
[215] Hari S. G. R. Tunuguntla & Angelo E. Gousse, *Female Sexual Dysfunction Following Vaginal Surgery: A Review*, 175(2) J. Urology 439, 442 (2006).
[216] *Id.* at 443.

Neurogenic problems can also cause sexual dysfunction. Injuries to the spinal cord or diseases of the central or peripheral nervous systems may compromise or prevent signal transduction from the brain to various muscles in response to sexual stimuli.[217] Spinal cord injuries, for example, have been shown to limit responsiveness to sexual stimulation, and multiple sclerosis has been shown to decrease both vaginal lubrication and sexual responsiveness in general.[218]

For some women, hormonal or endocrine problems are at the root of their sexual difficulties. Various hormones are thought to be involved in female sexual response, including estrogen and testosterone. Researchers posit that estrogen enhances blood flow to the vagina and clitoris and maintains female sexual response by preventing arteriosclerosis of the pelvic arteries and arterioles.[219] Testosterone and its role in female sexual dysfunction will be addressed in the next section of this paper, but, briefly, testosterone is thought to be involved in maintaining libido. Any condition, medication, or procedure that alters hormone levels in women, such as hypothalamic/pituitary axis dysfunction, oral contraceptives, or surgical castration, can affect sexual response.[220] Endocrine disease, diabetes in particular, has also been linked to sexual dysfunction. In a study of women with type 1 diabetes, for example, Salonia et al. found that type 1 diabetics had decreased sexual function and increased sexual distress compared to controls during the luteal phase of the menstrual cycle.[221] Specifically, subjects reported lower levels of arousal, lubrication, and orgasm and more pain during this period than did controls.[222] Though the mechanism by which diabetes affects sexual functioning remains unknown, the authors suggest it may be rooted in poor glycemic control.[223]

[217] Berman, *supra* note 60, at S47.
[218] Strong et al., *supra* note 20, at 504.
[219] Berman, *supra* note 60, at S46.
[220] Berman, *supra* note 60, at S47-S48.
[221] Andrea Salonia et al., *Sexual Function and Endocrine Profiles in Fertile Women with Type 1 Diabetes*, 29(2) Diabetes Care 312, 312 (2006).
[222] *Id.* at 313.
[223] *Id.* at 315.

We have thus far reviewed normal sexual functioning and sexual dysfunction in women. Specifically, we have discussed models of normal sexual response, classifications of sexual problems, the prevalence and presentation of these problems in women, and possible causes. We now consider one potential cause of sexual dysfunction in women: testosterone.

Testosterone

Though the specific determinants of sexual desire in women remain poorly understood, researchers have long theorized that androgens, specifically testosterone, play a role in female sexual response. To support a relationship between sexual desire and androgens, researchers have looked to early anecdotal observations that sexual desire correlates with endogenous androgen levels, that decreased sexual desire is observed in women who have undergone oophorectomy and adrenalectomy, and that sexual desire increases following administration of exogenous androgens.[224] These early findings have led some researchers to posit that low levels of androgens, testosterone in particular, may lead to sexual dysfunction in women.

This next section will explore such a proposition. It will begin with a discussion of basic biological information about androgens and testosterone in women. It will then consider the few studies that look at the relationship between testosterone levels and sexual desire in normal women. This will be followed by a detailed exploration of the instances in which testosterone levels might be depressed in women. Specifically, we will discuss androgen insufficiency, the relationships among testosterone, aging, and menopause, and the relationship between testosterone and oophorectomy to identify when and what women might be suffering

[224] Alan Riley & Elizabeth Riley, *Controlled Studies on Women Presenting with Sexual Drive Disorder: I: Endocrine Status,* 26 J. Sex & Marital Therapy 269, 270 (2000).

from decreased testosterone levels and, perhaps, sexual dysfunction. Finally, this section will close with a discussion of the association between testosterone levels and libido in surgically menopausal women (women who have undergone oophorectomy).

As will become clear, the data on the connection between testosterone levels and sexual desire in women are far from convincing. First, though there are studies that find a relationship between testosterone levels and libido in normal women, these studies have a number of methodological flaws. The most recent and most methodologically sound study fails to find a relationship between levels of testosterone and sexual desire in women. Nonetheless, even if we assume that low levels of testosterone are associated with decreased sexual drive in women, there are limited instances in which women appear to suffer from depressed testosterone levels. First, there is anecdotal evidence that women with hypothalamic-pituitary and adrenal conditions, among others, may suffer from an androgen insufficiency syndrome. Second, research has shown a considerably stronger connection between oophorectomy and decreased testosterone levels in women. However, though researchers have long stated that testosterone levels decrease in women as they age and/or go through menopause, the data do not support this proposition. In sum, the data suggest that the connection between testosterone and sexual dysfunction exists only in women who have undergone oophorectomy.

Background Information

We begin with general information about androgens and testosterone. The term "androgens" refers to 19-carbon steroid hormones. Though they are traditionally associated with maleness and the induction of secondary sex characteristics in men, they constitute the most plentiful sex steroids circulating in both men

and women.[225] They are thought to play an important role in maintaining reproductive function and hormone homeostasis in women.[226]

In women, androgens are made by the ovaries, the adrenal glands (endocrine glands that sit atop the kidneys), and peripheral tissues such as adipose tissue, muscle, and skin.[227] The pituitary gland regulates, in part, the production of androgens, because two of its secreted hormones, lutenizing hormone (LH) and adrenocorticotropic hormone (ACTH), stimulate the production of androgens by both the ovaries and the adrenal glands.[228] In descending order of serum concentrations, the five major androgens found in women are: dehydroepiandrosterone sulfate (DHEAS), dehydroepiandrosterone (DHEA), androstenedione (A), testosterone (T), and dihydrotestosterone (DHT).[229] Testosterone and DHT are the most potent: if testosterone is given a reference potency of 100, the relative potencies of the other androgens are: 300 for DHT, 10 for A, and 5 for DHEAS and DHEA.[230] Androgens act on numerous tissues and receptors in the central nervous system and peripheral sites in the body. These include the hypothalamus and limbic system as well as bone, breast, pilosebaceous unit (the sebaceous glands in the skin), skeletal muscle, adipose, and genital tissues.[231]

The relationships among the various androgens are complex. Briefly, in the ovaries, cholesterol is metabolized to pregnenolone, the primary precursor for sex steroid synthesis.[232] Testosterone, which is synthesized from pregnenolone, can be converted to DHT in target tissues.[233] DHEA and A are produced by both the ovaries and the adrenal glands, whereas DHEAS is produced almost entirely by the adrenals.[234] DHEAS,

[225] Susan R. Davis & Henry G. Burger, *The Role of Androgen Therapy*, 17(1) Best Prac. & Res. Clinical Endocrinology & Metabolism, 165, 165 (2003).
[226] Gloria Bachmann et al., *Female Androgen Insufficiency: The Princeton Consensus Statement on Definition, Classification, and Assessment*, 77(4) Fertility & Sterility 660, 660 (2002).
[227] Jan L. Shifren, *The Role of Androgens in Female Sexual Dysfunction*, 79 Mayo Clinic Proc. (Supp.) S19, S20 (2004).
[228] *Id.*
[229] Davis & Burger, *supra* note 225, at 166.
[230] *Id.*
[231] Bachmann et al., *supra* note 226, at 661.
[232] *Id.*
[233] *Id.*
[234] *Id.*

DHEA, and A all serve as precursors for testosterone, and DHEAS is converted into DHEA by steroid sulphatase.[235] Finally, testosterone, A, and DHEA are precursors for the biosynthesis of estrogens, including estrone, estradiol, and estriol.[236]

Before menopause, approximately 25% of testosterone is produced by the ovaries, 25% by the adrenal glands, and 50% from the conversion of androgen precursors—DHEAS, DHEA, and A—that are produced by the ovaries and adrenals.[237] After menopause, it is thought that the percentage production of testosterone changes: 50% is produced by the ovaries (assuming they remain present), 10% by the adrenal glands, and 40% from precursor conversion.[238] Like other hormones, testosterone moves through the body in free form or bound to carrier proteins such as sex hormone binding globulin (SHBG) and albumin.[239] SHBG has a high affinity for and binds tightly to testosterone, thus preventing it from being biologically active.[240] Albumin, however, has a much lower affinity for testosterone, and as a result, testosterone can easily dissociate from the protein and enter cells.[241] Bioavailable testosterone refers to testosterone that is free, or unbound to a carrier protein, as well as that which is bound to albumin.[242]

Testosterone's mechanism of activity is both direct and indirect. The hormone affects the brain directly via androgen receptors and indirectly through the aromatization, or conversion, of testosterone to estradiol.[243] It is also thought that testosterone directly affects women's genitalia: testosterone receptors have been located on the vulvar epithelium, the vaginal mucosa, submucosa, stroma, and smooth muscle, and the vascular endothelium, with the greatest degree of expression in the vaginal submucosa.[244] How these receptors function remains unknown, but they are thought to be involved in the relaxation of vaginal smooth

[235] *Id.*
[236] Davis & Burger, *supra* note 225, at 165.
[237] S. Bolour & G. Braunstein, *Testosterone Therapy in Women: A Review*, 17 Int'L J. Impotence Res. 399, 400 (2005).
[238] *Id.*
[239] *Id.*
[240] *Id.*
[241] *Id.*
[242] *Id.*
[243] *Id.*
[244] *Id.*

muscles.[245]

Researchers typically use the circulating level of testosterone in the blood as the main indicator of tissue exposure to the hormone. There are, however, numerous concerns about this mechanism of measurement. First, active androgens often exert their effects in the same cells that synthesized them.[246] Blood concentrations do not capture this intracellular androgen production and metabolism and, as a result, do not measure androgen tissue exposure or action with total accuracy.[247] Second, there are different ways of measuring serum concentrations of free testosterone, and the reliability and comparability of each measure varies. For example, Miller et al. conducted a study comparing three different common methods of measuring serum free testosterone: equilibrium dialysis, direct radioimmunoassay (RIA), and the law of mass action.[248] The study found that calculated free values of testosterone using equilibrium dialysis and the law of mass action correlated well, whereas RIA measurements did not and also exhibited unacceptably high systematic bias and random variability.[249] A third concern is that current assays show poor reliability at the lower end of the spectrum of circulating testosterone in females.[250]

Additionally, variations in testosterone levels among and even within women can make measuring these levels problematic. Specifically, what constitutes a "normal" level of an androgen may vary from woman to woman. In their study of circulating androgen levels in women, for example, Lasley et al. found that baseline levels of DHEAS, which correlate with testosterone levels, appear to vary across ethnic groups, with concentrations being highest among Chinese and Japanese and lowest among African Americans and Hispanics.[251] Furthermore, women's testosterone levels exhibit diurnal and monthly fluctuations. Each day, testosterone

[245] *Id.*

[246] Susan R. Davis et al., *Circulating Androgen Levels and Self-Reported Sexual Function in Women*, 294(1) JAMA 91, 95 (2005).

[247] *Id.* at 96.

[248] Karen K. Miller et al., *Measurement of Free Testosterone in Normal Women and Women with Androgen Deficiency: Comparison of Methods*, 89(2) J. Clinical Endocrinology & Metabolism 525, 525 (2004).

[249] *Id.* at 531.

[250] Davis & Burger, *supra* note 225, at 167.

[251] Bill L. Lasley et al., *The Relationship of Circulating Dehydroepiandrosterone, Testosterone, and Estradiol to Stages of the Menopausal Transition and Ethnicity*, 87(8) J. Clinical Endocrinology & Metabolism 3760, 3760 (2002).

levels peak early in the morning, and each month, testosterone levels fluctuate in accordance with the normal menstrual cycle.[252] In the early follicular phase, when menstruation occurs, testosterone concentrations are lowest.[253] They peak midcycle, around the same time that estrogen levels peak and ovulation occurs.[254] During the luteal phase, when the endometrial lining proliferates in preparation for pregnancy, testosterone levels are higher than they are during the early follicular phase.[255] These normal variations in concentrations among and within women can make it difficult to determine what constitutes a "normal" testosterone concentration (a measurement in the morning? At midcycle?) and to compare women's testosterone levels. (Can measurements taken during the follicular phase be compared to measurements taken during the luteal phase?) A recent consensus statement on female androgen insufficiency proposed standards for measuring androgen levels in women, and it recommended obtaining measures of free and total testosterone levels in the morning hours and in the middle third of the menstrual cycle (early luteal phase) when levels are high but not peaking.[256]

Testosterone and Sexual Function in Normal Women

We now consider the data examining the relationship between testosterone levels and sexual dysfunction in healthy women. As we will discuss, the data are mixed. There are several studies that find low levels of testosterone in women with sexual dysfunction, but these studies uniformly suffer from methodological flaws,

[252] Davis & Burger, *supra* note 225, at 167.
[253] *Id.*
[254] *Id.*
[255] *Id.*
[256] Bachmann et al., *supra* note 226, at 662.

including small subject pools and no control groups. The most recent, and most methodologically sound, study found no relationship between testosterone levels and sexual function in healthy women.

We begin with the studies that find a relationship. Riley & Riley compared hormone profiles of 15 women with sexual drive disorder (or absence of sexual drive) with those of 15 women without any sexual functioning problems.[257] The results indicated that, though patients and controls had hormone levels within normal ranges and though there was no difference in total testosterone levels between the groups, levels of free testosterone were significantly lower in the patient group than in the control group.[258] It is important to note, however, that the sample size was very small and that each woman provided only one blood sample.[259] Furthermore, though researchers tried to obtain each sample as close to mid-menstrual cycle as possible, the timing was neither precisely at mid-cycle nor uniform among the subjects.[260]

Guay examined total and free testosterone levels in 12 premenopausal women complaining of decreased libido.[261] Of the 12 women, 8 had low or immeasurable levels of total and free testosterone.[262] Again, this study contained few subjects and, because it did not include a control group, Guay was not able to compare the results to testosterone levels in healthy controls. In another study, Guay & Jacobson measured total testosterone, free testosterone, and DHEAS in 105 premenopausal and postmenopausal women with decreased sexual desire.[263] Of the 105 women, 74 (70%)—36 of which were premenopausal and 38 of which were postmenopausal—had decreased total testosterone, free testosterone, and DHEAS.[264] As in prior

[257] Riley & Riley, *supra* note 224, at 269.
[258] *Id.* at 271.
[259] *Id.* at 278.
[260] *Id. at 278.*
[261] André T. Guay, *Decreased Testosterone in Regularly Menstruating Women with Decreased Libido: A Clinical Observation*, 27 J. Sex & Marital Therapy 513, 515 (2001).
[262] *Id.* at 515.
[263] A.T. Guay & Jerilynn Jacobson, *Decreased Free Testosterone and Dehydroepiandrosterone-Sulfate (DHEA-S) Levels in Women with Decreased Libido*, 28 J. Sex & Marital Therapy (Supp. 1) 129, 129 (2002).
[264] *Id.* at 132.

research by Guay, this study included no controls.[265] Finally, Guay et al. examined ovarian and adrenal androgens in 32 healthy premenopausal women, 18 with one or more complaints of sexual dysfunction and 14 without any such complaints. [266] Women with complaints of sexual dysfunction had significantly lower levels of total and free testosterone when compared to women without sexual dysfunction.[267] Though this study did include controls, it, like Guay's other research, included very few subjects.

In contrast, some studies have failed to find a relationship between testosterone levels and sexual function. Nyunt et al., for example, measured androgen levels in 29 female volunteers with reduced libido and 12 controls.[268] The authors found no significant difference between subjects and controls with respect to serum testosterone or free testosterone levels.[269] However, significantly more women with loss of libido reported a history of depression or a low income than did women without sexual dysfunction.[270] The authors concluded that psychosocial factors and health status, rather than androgen status, appeared to be more important in differentiating between females with and without loss of libido.[271]

Davis et al. conducted the largest and most methodologically sound inquiry into the relationship between self-reported sexual function and circulating androgen levels.[272] The study assessed androgen concentrations and sexual desire, arousal, orgasm, pleasure, responsiveness, and self-image in 1021 women between the ages of 18 and 75.[273] The study found that there was no relationship between levels of total or free testosterone

[265] *Id.*
[266] A. Guay et al., *Serum Androgen Levels in Healthy Premenopausal Women With and Without Sexual Dysfunction: Part B: Reduced Serum Androgen Levels in Healthy Premenopausal Women With Complaints of Sexual Dysfunction*, 16 Int'l J. Impotence Res. 121, 121 (2004).
[267] *Id.*
[268] A. Nyunt et al., *Androgen Status in Healthy Premenopausal Women with Loss of Libido*, 31 J. Sex & Marital Therapy 73, 75 (2005).
[269] *Id.* at 77.
[270] *Id.* at 76.
[271] *Id.*
[272] Davis et al., *supra* note 246, at 91.
[273] *Id.* at 92.

and any of the domains of sexual functioning, including sexual desire, arousal, and responsiveness.[274] Thus, there appears to be data for and against the proposition that low levels of testosterone may be associated with sexual dysfunction in women. However, all the studies that find a relationship have either very few subjects or no controls, so it is unclear whether the association is statistically significant. Furthermore, with the exception of Riley & Riley's study, Guay conducted all the studies. In light of the lack of methodological breadth and rigor, it is difficult to take this research as much more than anecdotal evidence that women with low libido might have low testosterone levels. On the other hand, there are fewer studies that find no relationship between testosterone and sexual dysfunction. Though Davis et al. is an impressive and more credible study—with 1021 women and published in JAMA—it has not yet been replicated. In conclusion, the relationship between testosterone and sexual dysfunction in women remains unclear and needs to be researched further.

Changes in Testosterone Levels

In this section, we assume that there is a relationship between low levels of testosterone in women and libido, and we seek to identify when women might be suffering from depressed testosterone concentrations. This, in turn, can help determine for which populations of women testosterone might be the cause of sexual dysfunction. We examine three cases: female androgen insufficiency, the effects of aging and menopause on testosterone, and oophorectomy and testosterone.

Female Androgen Insufficiency

[274] *Id.* at 93.

In recent years, researchers have posited the existence of a female androgen insufficiency syndrome that is distinguished by a pattern of clinical signs and symptoms accompanied by decreased levels of bioavailable testosterone and normal estrogen levels.[275] Though clinical observations and intervention trials have provided some evidence of an androgen insufficiency syndrome in women, there have yet to be large-scale epidemiological studies that confirm its existence.

Despite the shaky evidence, a recent consensus statement proposed a definition of androgen insufficiency in women.[276] First, the following clinical symptoms must be present: a diminished sense of wellbeing or dysphoric mood, persistent and unexplained fatigue, and sexual function changes, including decreased libido, sexual receptivity, and pleasure.[277] Other symptoms include vasomotor instability, decreased vaginal lubrication, bone loss, decreased muscle strength, and changes in cognition or memory.[278] Second, estrogen levels must be normal, as estrogen can also be involved in mood, psychological wellbeing, and sexual function and must therefore be ruled out as a cause.[279] Third, free testosterone levels must be at or below the lowest quartile of the normal range for women in their reproductive years.[280]

The potential causes of female androgen insufficiency are numerous. They include hypothalamic-pituitary, ovarian, and adrenal conditions as well as drug-use and various diseases.[281] Specifically, pituitary insufficiency from adenomas (benign tumors) or hypophysitis (inflammation) or other forms of destruction can block the production of LH and ACTH, which can then result in insufficient androgen production by the

[275] L.M. Rivera-Woll et al., *Androgen Insufficiency in Women: Diagnostic and Therapeutic Implications*, 10(5) Hum. Reprod. Update 421, 424 (2004).
[276] Bachmann et al., *supra* note 226, at 665.
[277] *Id.* at 662-663.
[278] *Id.* at 663.
[279] *Id.* at 663.
[280] *Id.* at 663.
[281] *Id.* at 663.

ovaries and adrenals.[282] Ovarian destruction by chemotherapy and radiation therapy can lead to reduced androgen production, as can adrenal insufficiency and adrenalectomy.[283] Certain drugs, such as corticosteroids, antiandrogenic agents, oral contraceptives, and oral estrogen replacement therapies, can block ovarian and adrenal function and thereby decrease androgen output.[284] Finally, other diseases have been implicated in reducing androgen production, including anorexia nervosa and immunologic disorders such as rheumatoid arthritis, systemic lupus erythematosus, and HIV-AIDS.[285]

Few studies have actually examined androgen levels in patients with conditions associated with androgen insufficiency. A 1959 study by Waxenberg et al. found sexual problems the researchers deemed characteristic of androgen insufficiency in a group of 29 women who had undergone adrenalectomy and bilateral oophorectomy for metastatic breast cancer.[286] After their operations, the women reported decreases in sexual desire, sexual activity, and responsiveness, which the authors stated were consequences of decreased androgen levels.[287] However, the study never actually measured androgen levels to confirm androgen insufficiency, and its subject were all fatally ill with cancer. These flaws limit the study's generalizability. Kaplan & Owett replicated Waxenberg et al.'s study, though they did measure subjects' androgen levels.[288] The authors examined 11 women who had undergone chemotherapy and/or bilateral oophorectomy for carcinomas or other medical conditions, and they found that 10 of the 11 patients exhibited low levels of circulating testosterone levels in comparison to normal controls.[289] In their study, ovarian destruction was associated with androgen deficiency.

[282] André T. Guay, *Screening for Androgen Deficiency in Women: Methodological and Interpretive Issues*, 77(4) Fertility & Sterility (Supp. 4) S83, S84 (2002).
[283] *Id.*
[284] Bachmann et al., *supra* note 226, at 663; Guay, *supra* note 282, at S84.
[285] Bachmann et al., *supra* note 226, at 663.
[286] Sheldon E. Waxenberg, Marvin G. Drellich, & Arthur M. Sutherland, *The Role of Hormones in Human Behavior I: Changes in Female Sexuality After Adrenalectomy*, 19 J. Clinical Endocrinology & Metabolism 193, 193 (1959).
[287] *Id.* at 194-195.
[288] Helen Singer Kaplan & Trude Owett, *The Female Androgen Deficiency Syndrome*, 19(1) J. Sex & Martial Therapy 3, 8 (1993).
[289] *Id.*

An additional study by Miller et al. inquired into the androgen concentrations of 55 women with acquired hypopituitarism (the majority of which were from pituitary adenomas) characterized by hypogonadism and/or hypoadrenalism.[290] The study found that, regardless of age and treatment with estrogen, all subjects had markedly reduced levels of serum testosterone, free testosterone, androstenedione, and DHEAS when compared to controls.[291] Furthermore, levels of serum testosterone, free testosterone, and androstenedione were lower in women with both hypogonadism and hypoadrenalism than in women with hypogonadism or hypoadrenalism alone.[292] Though there are limited data on the topic, it appears that certain conditions, such as hypopituitarism and hypoadrenalism, may result in androgen insufficiency and in decreased concentrations of testosterone in women.

Testosterone, Aging, and Menopause

The exact progression of testosterone levels over the course of a woman's lifetime remains unclear. The majority of review articles state that testosterone levels decrease over time[293] and that this decline is the result of natural aging rather than menopause.[294] However, the data are far from uniform on this subject, and the precise nature of the relationships among testosterone, menopause, and aging remains unresolved. Specifically, there is research that indicates that testosterone levels fall over time, that testosterone levels fall before or at menopause but begin to increase shortly after the climacteric, that levels remain unchanged over the lifespan, and that levels increase slightly late in women's lives. We consider all this data in turn.

[290]Karen K. Miller et al., *Androgen Deficiency in Women with Hypopituitarism*, 86(2) J. Clinical Endocrinology & Metabolism 561, 561 (2001).
[291]*Id.* at 565.
[292]*Id.* at 565.
[293]*See* Bolour & Braunstein, *supra* note 237, at 400; H.M. Buckler, W.R. Robertson, & F.C.W. Wu, *Which Androgen Replacement Therapy for Women*, 83(11) J. Clinical Endocrinology & Metabolism 3920, 3920 (1998); Susan Davis, *Androgen Replacement in Women: A Commentary*, 84(6) J. Clinical Endocrinology & Metabolism 1886, 1886 (1999).
[294]It was originally thought that testosterone levels decreased as a result of the climacteric and the corresponding decline in ovarian functioning. *See* Susan Davis, *Testosterone and Sexual Desire in Women*, 25(1) J. Sex Educ. & Therapy 25, 27 (2000).

Many researchers posit that testosterone levels decrease over time as a function of age. For example, Zumoff et al. examined testosterone levels in a cross-sectional study of 33 healthy, regularly cycling, nonobese women between the ages of 21 and 51.[295] The data indicated that mean plasma concentration of testosterone declined steeply with age, such that women in their 40's had half the testosterone concentration as women in their 20's.[296] Lasley et al. conducted a considerably larger prospective study in which they measured androgen levels over 2 years in 3,000 women aged 42 to 54.[297] This study found a 26% decline in mean testosterone levels between 42 and 50 years of age, with the majority of the drop occurring in the early 40's.[298] However, testosterone levels began to increase slightly in late perimenopausal women between the ages of 50 and 52.[299] Other longitudinal research has suggested that, though levels of testosterone may decrease at middle age, this decline is temporary. An early study by Chakravarti et al. inquired into endocrine changes in 60 postmenopausal women between the ages of 49 and 91.[300] The results indicated that, five years after menopause, testosterone levels fell.[301] However, in the next three decades, testosterone levels increased.[302] Another study by Laughlin et al. examined the hysterectomy and oophorectomy status and androgen levels of women between the ages of 50 and 89.[303] The results indicated that, in the 438 women who had not undergone hysterectomy or oophorectomy, testosterone levels decreased around the time of menopause.[304] However, for women who were 20 years past menopause or who were 70 years of age or older, levels of

[295] Barnett Zumoff et al., *Twenty-Four-Hour Mean Plasma Testosterone Concentration Declines with Age in Normal Premenopausal Women*, 80(4) J. Clinical Endocrinology & Metabolism 1429, 1429 (1995).
[296] *Id.*
[297] Lasley et al., *supra* note 251, at 3760.
[298] *Id.* at 3764.
[299] *Id.*
[300] S. Chakravarti et al., *Hormonal Profiles After the Menopause*, 2 Brit. Med. J. 784, 784 (1976).
[301] *Id.* at 785.
[302] *Id.* at 786.
[303] Gail A. Laughlin et al., *Hysterectomy, Oophorectomy, and Endogenous Sex Hormone Levels in Older Women: The Rancho Bernardo Study*, 85(2) J. Clinical Endocrinology & Metabolism 645, 645 (2000).
[304] *Id.* at 649.

testosterone were comparable to premenopausal levels, indicating that decreases in testosterone levels around the time of menopause may be transient.[305] Overlie et al. also found an increase in ovarian testosterone production after menopause and a movement towards premenopausal levels.[306] Specifically, testosterone levels dropped 20% during perimenopause but increased the following two years.[307]

The majority of data indicates that testosterone levels are unrelated to aging and menopause and do not change over time. In a cross-sectional study of 155 women between the ages of 34 to 83, all of whom had been postmenopausal for at least one year (the younger women had experienced premature ovarian failure), Meldrum et al. found that testosterone levels did not change with age.[308] Another cross-sectional study by Labrie et al. examined 60 women between the ages of 20 and 80 and, again, found no significant or consistent change in serum testosterone levels over time.[309]

Cauley et al. examined the effects of certain environmental factors, including obesity, physical activity, muscle strength, and alcohol consumption as well as age and menopausal status, on androgen levels in a cross-sectional sample of 176 healthy postmenopausal women.[310] Univariate analyses failed to show a relationship between testosterone levels and age and between testosterone levels and time since menopause.[311] Multiple regression analysis also failed to find such relationships, though there was a borderline significant positive correlation between obesity and testosterone levels.[312] Bancroft & Cawood also conducted a cross-sectional study of 141 women aged 40 to 60 that examined the relative contributions of environmental factors,

[305] *Id.* at 650.
[306] Overlie et al., *The Endocrine Transition Around Menopause: A Five Year Prospective Study with Profiles of Gonadotropins, Estrogen, Androgens and SHGB Among Healthy Women*, 78 Obstetrics & Gynecology Scandanavia 642, 642 (1999).
[307] *Id.*
[308] David R. Meldrum et al., *Changes in Circulating Steroids with Aging in Postmenopausal Women*, 57 Obstetrics & Gynecology 624, 627 (1981).
[309] Fernand Labrie et al., Marked Decline in Serum Concentrations of Adrenal C19 Sex Steroid Precursors and Conjugated Androgen Metabolites During Aging, 82 J. Clinical Endocrinology & Metabolism 2396, 2397 (1997).
[310] Jane A. Cauley et al., *The Epidemiology of Serum Sex Hormones in Postmenopausal Women*, 129 Am. J. Epidemiology 1120, 1121 (1989).
[311] *Id.* at 1122.
[312] *Id.* at 1127.

age, and menopausal status on androgen levels.[313] Though univariate analyses suggested that testosterone decreased with age, this relationship disappeared when other variables were introduced in a multivariate regression.[314] Specifically, testosterone levels were positively correlated with levels of androstenedione and lutenizing hormone as well as body-mass index.[315] Finally, Burger et al. studied average androgen levels in a population of 172 women over a period of seven years.[316] Mean testosterone levels did not vary across the time period, indicating that testosterone levels were unrelated to both menopausal status and age.[317]

Finally, some research suggests that testosterone levels may actually increase over time. Judd et al., an early study, found testosterone concentrations in the ovarian veins of 10 postmenopausal women to be twice the magnitude of those in premenopausal women.[318] The authors interpreted this data as suggesting that ovarian testosterone secretions may be larger in postmenopausal women than in premenopausal women.[319] A more recent study by Jiroutek et al. examined changes in circulating hormones in 32 postmenopausal women for approximately 10 years.[320] The study found a significant increase in the concentration of testosterone over time, the majority of which occurred during the later years of the follow-up.[321]

As shown by the numerous contradictory studies, whether and how testosterone levels change over time is far from clear. To further complicate the matter, most of the aforementioned studies suffer from methodological

[313] John Bancroft & Elizabeth H. Cawood, *Androgens and the Menopause: A Study of 40-60-Year-Old Women*, 45 Clinical Endocrinology 577, 578 (1996).
[314] *Id.* at 584.
[315] *Id.*
[316] Henry G. Burger et al., *A Prospective Longitudinal Study of Serum Testosterone, Dehydroepiandrosterone Sulfate, and Sex Hormone-Binding Globulin Levels Through the Menopause Transition*, 85(8) J. Clinical Endocrinology & Metabolism 2832, 2833 (2000).
[317] *Id.* at 2838.
[318] Howard L. Judd et al., *Endocrine Function of the Postmenopausal Ovary: Concentration of Androgens and Estrogens in Ovarian and Peripheral Vein Blood*, 39(6) J. Clinical Endocrinology & Metabolism 1020, 1022 (1974).
[319] *Id.*
[320] Michael R. Jiroutek et al., *Changes in Reproductive Hormones and Sex Hormone-Binding Globulin in a Group of Post-menopausal Women Measured Over 10 Years*, 5(2) J. N. Am. Menopause Soc'y 90, 90 (1998).
[321] *Id.* at 92.

flaws.[322] The majority are cross-sectional and, rather than observing testosterone levels in a sample of women over time, they compare levels of testosterone in women of different ages. For example, Meldrum et al. compared the testosterone levels of women between the ages of 34 and 83,[323] and Labrie et al. compared the testosterone levels of women between the ages of 20 and 80.[324] This is potentially problematic because individual physiology varies: what constitutes a "normal" level of testosterone in one woman may be a "low" level of testosterone in another. Additionally, many studies are based on small convenience or clinic samples with inherent biases, which makes it difficult to generalize the findings.[325] For example, the study by Zumoff et al. is the most widely cited study for the proposition that testosterone levels decrease as a result of aging in women, and yet this finding was based on testosterone samples from only 33 women.[326] Judd et al., another frequently cited study, included only 10 women.[327] As a final point, there are no comprehensive studies of a single cohort of women throughout their lives. Burger et al. examined the same women over a period of seven years,[328] but seven years does not constitute a lifetime.

Methodological considerations notwithstanding, it is difficult to synthesize the data in a coherent, meaningful way. However, taken together, the data suggest that it is far from patent that testosterone levels decrease with age and that, on the contrary, the bulk of studies point towards no change over time. The studies that are the most methodologically sound—Lasley et al.[329] and Laughlin et al.[330] (both of which included relatively more subjects, 3,000 and 438 respectively, compared to other studies), Cauley et al.[331] and Bancroft & Cawood[332] (which considered mediating environmental factors and conducted multivariate as

[322] *See* Lorraine Dennerstein et al., *Hormones, Mood, Sexuality, and the Menopause Transition*, 77(4) Fertility & Sterility (Supp. 4) S42, S42 (2002) for commentary on methodological flaws in studies examining hormone levels in women across the lifespan.
[323] Meldrum et al., *supra* note 308, at 627.
[324] Labrie et al., *supra* note 309, at 2397
[325] Dennerstein et al., *supra* note 322, at S42.
[326] Zumoff et al., *supra* note 295, at 1429.
[327] Judd et al., *supra* note 318, at 1022.
[328] Burger et al., *supra* note 316, at 2833.
[329] Lasley et al., *supra* note 251, at 3760.
[330] Laughlin et al., *supra* note 303, at 645.
[331] Cauley et al., *supra* note 310, at 1122, 1127.
[332] Bancroft & Cawood, *supra* note 313, at 584.

well as univariate analyses), and Burger et al.[333] (which was a longitudinal study rather than a cross-sectional study)—tend to suggest that testosterone levels remain relatively stable over time and that any age related decreases are short-lived.

Testosterone and Oophorectomy

In contrast to the mixed data on testosterone, aging, and menopause, the data on the effect of bilateral oophorectomy,[334] or the surgical removal of both ovaries, on testosterone levels in women are relatively clear. Specifically, the data indicate that the removal of both ovaries results in a decrease in testosterone levels. This section will begin with background data on oophorectomy and hysterectomy and will then describe several studies that illustrate the relationship between oophorectomy and testosterone levels.

When both ovaries are removed, a hysterectomy, or the removal of the uterus, is almost always performed at the same time.[335] Hysterectomy with and without oophorectomy is one of the most common procedures performed on women in the United States. Wilcox et al. reported that, between 1988-1990, 1.7 million women (or 600,000 a year) had a hysterectomy.[336] The highest rate—100.5 hysterectomies per 10,000 women—was for women between the ages of 30 and 54.[337] Of the women undergoing hysterectomies, 37% of women under the age of 45 and 68% over the age of 45 underwent concomitant bilateral oophorectomy.[338] In total, approximately 50% of women having a hysterectomy also have their ovaries removed.[339] A more recent study by Farquhar & Steiner found that the rates of hysterectomy did not change significantly over the period of

[333] Burger et al., *supra* note 316, at 2833.
[334] Note that the terms bilateral oophorectomy and oophorectomy are used interchangeably to refer to the surgical removal of both ovaries.
[335] The Boston Women's Health Book Collective, Our Bodies, Ourselves For the New Century 666-667 (3rd. ed. 1998).
[336] L.S. Wilcox et al., *Hysterectomy in the United States, 1988-1990*, 83(4) Obstetrics & Gynecology 549, 549 (1994).
[337] *Id.*
[338] *Id.*
[339] *Id.*

1990-1997 and appear level at 500,000 to 600,000 women per year.[340]

Common reasons for the removal of the ovaries include endometriosis, pelvic inflammatory disease, ectopic pregnancy, and malignant tumors on the ovary.[341] Hysterectomies are performed in cases of pelvic inflammatory disease, severe and uncontrollable bleeding, and invasive cancer of the uterus, cervix, vagina, fallopian tubes and/or ovaries.[342] Hysterectomies are sometimes performed for endometriosis, fibroid tumors, pelvic relaxation (uterine prolapse), and precancerous changes of the endometrium.[343]

The effect of oophorectomy on circulating androgen levels has long been a subject of inquiry. An early study by Judd et al. measured testosterone and androstenedione levels in 5 premenopausal and 16 postmenopausal women before and 6 to 8 weeks after bilateral oophorectomy as treatment for endometrial cancer.[344] After surgery, testosterone levels fell 57% in premenopausal women and 54% in postmenopausal women.[345] Hughes et al. also found that women who had had their ovaries removed experienced a considerable decline in serum testosterone levels.[346] Hughes et al. examined reproductive hormones in 11 postmenopausal women who had undergone pelvic surgery that included bilateral oophorectomy and found that testosterone levels dropped by half in these patients.[347] Though the drop in testosterone levels after oophorectomy was unmistakable in these two studies, the generalizability of these results is questionable. Specifically, both used cancer patients

[340] Cynthia M. Farquhar & Claudia A. Steiner, *Hysterectomy Rates in the United States 1990-1997*, 99(2) Obstetrics & Gynecology 229, 230-231 (2002).
[341] The Boston Women's Health Book Collective, *supra* note 335, at 667.
[342] *Id.* at 663.
[343] *Id.*
[344] Howard L. Judd, William E. Lucas, & Samuel S. C. Yen, *Effect of Oophorectomy on Circulating Testosterone and Androstenedione Levels in Patients With Endometrial Cancer*, 118(6) Am. J. Obstetrics & Gynecology 793, 793 (1974).
[345] *Id.* at 795-796.
[346] Claude L. Hughes et al., *Reproductive Hormone Levels in Gynecologic Oncology Patients Undergoing Surgical Castration After Spontaneous Menopause*, 40(1) Gynecologic Oncology 42, 42 (1991).
[347] *Id.*

as subjects, and hormone production and hormone levels may be abnormal in individuals with cancer.[348] Laughlin et al., a more recent population-based longitudinal study, examined endogenous sex hormone levels for a period of 4 years in 684 older women, some of whom had undergone hysterectomy and/or oophorectomy many years earlier and some of whom had not ("intact" women).[349] The results indicated that women who had undergone hysterectomy with bilateral oophorectomy had a substantial and sustained reduction in total and bioavailable testosterone levels: these levels were reduced by more than 40% in comparison to levels in intact women.[350] Women who had undergone hysterectomy but retained their ovaries had total and bioavailable testosterone levels that were lower than levels in intact women but higher than levels in women who had had a hysterectomy and oophorectomy.[351] Presumably, given that these women had retained their ovaries, their testosterone levels should have been comparable to those of intact women.[352] The authors suggest that damage to the ovarian artery during surgery might have led to functional impairment or failure of one or both ovaries and subsequent reduced production of testosterone.[353]

Testosterone and Sexual Function in Oophorectomized Women

Thus far, we have seen that the evidence for a relationship between testosterone and sexual function in normal women is slim. We have also seen that there appears to be evidence for depressed testosterone levels only in women who have undergone oophorectomy, as opposed to women with androgen deficiency

[348] Judd et al., *supra* note 344, at 795.
[349] Laughlin et al., *supra* note 303, at 645.
[350] *Id.* at 648-649.
[351] *Id.* at 649.
[352] *Id.*
[353] *Id.*

or older/menopausal women. In this section, we consider whether depressed testosterone levels are related to a decline in sexual functioning in oophorectomized women. We first consider studies that look at sexual function in women after they have undergone oophorectomy, and we then consider studies that treat oophorectomized women with sexual dysfunction with testosterone.

The data indicate that women who have undergone oophorectomy can experience concurrent declines in testosterone levels and sexual function. Early research by Waxenberg et al. found adrenalectomy and bilateral oophorectomy to be associated with impairment in sexual function.[354] Specifically, the majority of subjects who reported preoperative sexual desire, sexual activity, and sexual responsiveness experienced a loss of desire, a decrease in sexual activity, and a loss of responsiveness after surgery.[355] As mentioned earlier, problems with this study include the small sample (29 women), the lack of controls, the failure to measure testosterone, and the presence of cancer. In a similar study, Kaplan & Owett examined 11 women who had undergone chemotherapy and/or bilateral oophorectomy and who had normal sexual functioning prior to cancer treatment.[356] After treatment, all the women exhibited low levels of circulating testosterone in comparison to normal controls as well as markedly decreased or absent sexual desire and orgasm.[357] Again, the study had methodological problems—the small sample size, the presence of cancer, and the fact that testosterone levels and sexual function were not assessed before treatment—but it nonetheless pointed to an association between decreased testosterone and depressed sexual function in women without their ovaries.

Another study compared sexual function in women who had undergone hysterectomy and oophorectomy to sexual function in women who had undergone hysterectomy with ovary preservation.[358] The results indicated that women who had their ovaries removed reported less pleasure from intercourse and impaired libido

[354] Waxenberg et al., *supra* note 286, at 194-195.
[355] *Id.*
[356] Kaplan & Owett, *supra* note 288, at 3.
[357] *Id.* at 10.
[358] J. Nathorst-Boos, B. von Schoultz, & K. Carlström, *Elective Ovarian Removal and Estrogen Replacement Therapy—Effects on Sexual Life, Psychological Well-Being, and Androgen Status*, 14 J. Psychosomatic Obstetrics & Gynaecology 283, 286 (1993).

and lubrication in comparison to women who retained their ovaries, suggesting that ovary removal and the concurrent drop in testosterone levels are associated with sexual impairment.[359] Shifren et al. examined 75 women who had undergone hysterectomy and bilateral oophorectomy and who felt that their sex lives were active and satisfying before undergoing surgery.[360] After their operations, these women had markedly impaired sexual function in comparison to normal women of similar age.[361] Specifically, they reported lower levels of desire, arousal, frequency of sexual activity, and pleasure/orgasm.[362]

These studies indicate that oophorectomy, which appears to cause a drop in testosterone levels, can be associated with decreases in sexual functioning. This also suggests that in women without their ovaries, depressed testosterone levels may result in sexual problems. In response to this data, researchers have treated oophorectomized women with sexual dysfunction with testosterone and have seen improvements in sexual functioning. Several of these studies are discussed below.

Sherwin et al. put a group of women who had undergone hysterectomy and bilateral oophorectomy on estrogen and/or androgen replacement therapy.[363] The results indicated that sexual desire, sexual fantasy, and sexual arousal were significantly higher in women on androgen and estrogen-androgen replacement therapy than in women on estrogen or placebo.[364] However, androgen treatment had no effect on physiologic response (frequency of intercourse or orgasm) or interpersonal aspects of sexual behavior; its primary impact appeared to be on sexual motivation—fantasies, desire, and arousal—rather than on sexual activity.[365]

In another study, Sherwin & Gelfand examined whether androgenic effects on sexual behavior would be

[359] *Id.* at 288.
[360] Jan L. Shifren et al., *Transdermal Testosterone Treatment in Women with Impaired Sexual Function After Oophorectomy*, 343 New Eng. J. Med. 682, 683 (2000).
[361] *Id.* at 686.
[362] *Id.* at 687.
[363] Barbara B. Sherwin, Morrie M. Gelfand, & William Brender, *Androgen Enhances Sexual Motivation in Females: A Prospective, Crossover Study of Sex Steroid Administration in the Surgical Menopause*, 47(4) Psychosomatic Med. 339, 340 (1985).
[364] *Id.* at 345.
[365] *Id.* at 349.

enduring.[366] In this study, the subjects had undergone hysterectomy and bilateral oophorectomy for benign disease approximately 4 years prior to the study and had been on an estrogen-androgen preparation (22 subjects), estrogen alone (11 subjects), or no treatment (11 subjects) for approximately 2 years.[367] The results indicated that women who received estrogen-androgen therapy had significantly more sexual desire, arousal, and sexual fantasies compared to women on estrogen alone or on no treatment.[368] Furthermore, changes in these behaviors covaried with levels of testosterone: sexual desire, arousal, and fantasy levels as well as testosterone levels were greatest the week following injection and decreased over the course of the following two weeks.[369] Additionally, for the first two weeks after injection, rates of intercourse and orgasm were higher in the estrogen-androgen treatment group than in the estrogen and no treatment groups.[370] This suggests that the researchers' prior finding that testosterone did not affect sexual activity may have been due to the fact that subjects had not yet recovered fully physically from having surgery.[371] It is important to note, however, that this study was not blind—both researchers and subjects knew what, if any, treatment subjects were receiving—and there was no use of placebo.

Shifren et al. also found testosterone treatment to be associated with increased sexual wellbeing in oophorectomized women.[372] This study examined 75 women who had undergone hysterectomy and bilateral oophorectomy and were suffering from sexual dysfunction.[373] Over three 12-week treatment periods, subjects were given, in random order, two placebo patches (no active drug), one active and one placebo patch (nominal

[366] Barbara B. Sherwin & Morrie M. Gelfand, *The Role of Androgen in the Maintenance of Sexual Functioning in Oophorectomized Women*, 49 Psychosomatic Medicine 397, 398 (1987).
[367] *Id.* at 399.
[368] *Id.* at 401-403.
[369] *Id.*
[370] *Id.* at 403.
[371] *Id.* at 406.
[372] Shifren et al., *supra* note 360, at 683.
[373] *Id.*

dose of testosterone—150μg per day), and two active patches (300μg per day).[374] Both the placebo and testosterone treatments improved sexual functioning.[375] Specifically, the authors noted a strong placebo response, with all indexes of sexual functioning increasing (composite score, thoughts/desire, arousal, frequency of sexual activity, receptivity/initiation, pleasure/orgasm, and relationship satisfaction).[376] Testosterone treatment resulted in further increases in each index, but the only statistically significant results were increases in the composite sexual functioning score, frequency of sexual activity, and pleasure/orgasm that were associated with 300μg testosterone treatment.[377]

These studies suggest that testosterone treatment improves sexual functioning in women who no longer have their ovaries. It is important to note, however, that the studies by Sherwin et al. and Sherwin & Gelfand were not blind and did not include placebo groups. This is especially significant in light of the considerable placebo effect found by Shifren et al. Furthermore, it is not clear whether some or all aspects of sexual functioning are improved by treatment with testosterone. Finally, the subjects in these studies knew they were involved in research on sexual functioning, and it is possible that this knowledge might have affected or improved their sexual relationships. Subjects may, for example, have communicated more with their partners or engaged in more sexual activity.[378]

We have thus far reviewed the relationship between female sexual dysfunction and testosterone. We have seen that there is little evidence for a causal relationship between decreased testosterone levels and sexual problems in normal women, and we have seen that few populations of women have depressed testosterone levels. Women who have undergone oophorectomy, however, appear to exhibit low levels of testosterone, and these depressed concentrations may result in sexual difficulties. At this point, we consider Intrinsa, a testosterone treatment for female sexual dysfunction, and the controversy surrounding its development and

[374] *Id.*
[375] *Id.* at 685.
[376] *Id.*
[377] *Id.*
[378] Shifren et al., *supra* note 360, at 687.

its rejection by the FDA.

Intrinsa

In 2004, Proctor & Gamble ("P&G") submitted its drug, Intrinsa, for approval by the FDA.[379] Intrinsa is a testosterone transdermal system ("TTS"), or a 28 cm^3 patch that contains 8.4 mg of testosterone.[380] It delivers approximately 300 mcg/day of testosterone when worn on the abdomen and changed twice a week.[381] P&G proposed Intrinsa as treatment for hypoactive sexual desire disorder in women without their ovaries ("surgically menopausal" women).[382]

Intrinsa was evaluated over a series of seven clinical trials, though the last two Phase 3 trials were the central studies submitted to support the drug's safety and efficacy. Each Phase 3 study was a 24-week, randomized, double-blind, placebo-controlled design that was followed by a 28-week open label period.[383] All subjects were between 20 and 70 years old, had undergone oophorectomy and hysterectomy at least 6 months prior to the study, were receiving estrogen, and had been in a stable, monogamous relationship for at least 1 year prior to entering the study.[384] Additionally, all subjects reported satisfying sex lives prior to surgery and had experienced postoperative decreases in sexual desire and activity that caused them distress.[385] However, unlike Phase 2 trial subjects, Phase 3 subjects were not required to have low levels of testosterone

[379] Proctor & Gamble Pharmaceuticals, Inc., *Advisory Committee Briefing Document: Intrinsa (Testosterone Transdermal System)* (Dec. 2, 2004), http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4082B1_01_A-P&G-Intrinsa.pdf.
[380] *Id.* at 15.
[381] *Id.*
[382] *Id.* at 4.
[383] *Id.* at 26.
[384] *Id.*
[385] *Id.* at 27.

to participate in the study.[386]

For the first Phase 3 trial, 283 women received 300 mcg/day TTS, and 279 received a placebo patch.[387] For the second, 266 women received 300 mcg/day TTS, and 266 received a placebo patch.[388] After 24 weeks, both placebo groups were switched to 300 mcg/day TTS, and both active groups remained on testosterone treatment for another 28 weeks.[389] Intrinsa's efficacy was measured by assessing the change in the 4-week frequency of total satisfying sexual episodes ("SSEs") from baseline to week 24.[390] The study also assessed changes in personal distress and sexual desire.[391]

Generally, the results indicated that the women receiving testosterone experienced a statistically significant increase in frequency of satisfying sexual episodes as well as a decrease in personal distress and an increase in sexual desire that were statistically significant.[392] Specifically, for the first Phase 3 trial, the placebo group experienced a mean increase of 0.98 SSEs per 4 weeks (from 3 to 4 events), and the treatment group experienced a 2.13 mean increase (from 3 to 5 events).[393] In the second Phase 3 trial, the placebo group reported an increase of 0.73 (from 3 to 4 events) and the treatment group an increase of 1.56 (from 3 to 4.5 events).[394] The increases experienced by the treatment groups (approximately 1 satisfying sexual event per 4 weeks more than the controls) reached statistical significance.[395] Additionally, though both placebo and treatment groups reported decreased personal distress and increased sexual desire, the changes the treatment groups experienced were significantly greater than those experienced by the placebo groups.[396]

[386] *Id.* at 37.
[387] *Id.* at 42. Note that this study was also published in a peer-reviewed journal. *See* James Simon et al., *Testosterone Patch Increases Sexual Activity and Desire in Surgically Menopausal Women with Hypoactive Sexual Desire Disorder*, 90(9) J. Clinical Endocrinology & Metabolism 5226 (2005).
[388] Proctor & Gamble Pharmaceuticals, Inc., *supra* note 379, at 42.
[389] *Id.* at 37.
[390] *Id.*
[391] *Id.*
[392] *Id.* at 41.
[393] *Id.* at 42.
[394] *Id.*
[395] *Id.*
[396] *Id.*

With respect to side effects, the researchers concluded that Intrinsa had a favorable safety profile. During the course of the trials, there was only one death: a woman in the placebo group died from a brain hemorrhage.[397] Additionally, three women in the treatment group and one woman in the placebo group were diagnosed with breast cancer, but the researchers noted that these numbers were consistent with breast cancer rates in middle-aged women.[398] Though there were no heart attacks during the studies, one woman in the treatment group suffered a transient ischemic attack and another experienced an "episode of tightness in the chest, diarrhea, flushing, increased heart rate, nausea, tingling in roof of mouth, and diaphoresis."[399] Both adverse events resolved while the women were still on testosterone.[400] Generally, the testosterone and placebo groups exhibited similar overall adverse events, with the most common being application site reactions.[401] In one study, subjects on testosterone reported slightly more acne and hirsutism (hair growth) than did controls, but these events were mild and did not cause subjects to discontinue treatment.[402]

In its instructions to the Advisory Committee on Reproductive and Urologic Drug Products, the FDA requested that the Committee consider three points.[403] First, the Committee was asked to determine whether the increase of one satisfying sexual event per 4 weeks more in the testosterone group than in the placebo group was clinically meaningful.[404] Second, the Committee was to examine the safety data on Intrinsa in light of the recently discovered risks of hormone replacement therapy.[405] Finally, the FDA asked the Committee to determine whether unanswered safety questions remained.[406]

[397] *Id.* at 71.
[398] *Id.* at 96.
[399] *Id.* at 71.
[400] *Id.*
[401] *Id.* at 64.
[402] *Id.*
[403] Food & Drug Administration, *FDA Intrinsa Advisory Committee Background Document Overview* (Dec. 2, 2004), http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4082B1_02_A-FDA-Intrinsa-Overview.htm.
[404] *Id.*
[405] *Id.*
[406] *Id.*

Ultimately, the FDA refused to approve Intrinsa. Though the Advisory Committee noted that the increase in satisfying sexual episodes in the treatment group was clinically meaningful, it concluded that P&G's safety data did not assuage its concerns about the long-term health effects of testosterone treatment in women.[407] The Committee was concerned that the sample sizes and duration of P&G's prior and future safety studies were insufficient to determine increases in adverse events (above background rates) that were caused by Intrinsa.[408] The Advisory Committee stated that only a prospective, long-term randomized, controlled study "of sufficient power" would provide meaningful answers about the long-term risks of Intrinsa.[409]

The Controversy

Intrinsa itself and the FDA's denial of approval caused considerable controversy among sexual health scholars and researchers. Some found fault with the development of the drug, arguing that Intrinsa was the result of the pharmaceutical industry's efforts to create a disease for pecuniary gain. Others criticized the FDA for basing its rejection of the drug on inappropriate grounds and for setting unattainable safety standards. The following section discusses both controversies. It concludes by considering Intrinsa and the FDA's decision in light of the issues discussed in the prior two sections of this paper.

The Making of a Disease

[407] *FDA Panel Rejects P&G's Intrinsa for Boosting Women's Sex Drive*, 3011 INFORMA 21, 21 (2004).
[408] Food & Drug Administration, *Intrinsa (Testosterone Transdermal System): Review by the Division of Reproductive and Urologic Drug Products* 66 (Nov. 3, 2004), http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4082B1_02_B-FDA-Intrinsa-Medical-Review.pdf.
[409] *Id.*

The pharmaceutical industry has long been accused of inventing diseases to promote drug development and sales, and many scholars viewed the creation of Intrinsa as the industry's latest effort to fashion and promote a disorder. After Viagra's considerable success, it is thought that the pharmaceutical industry sought to build a similar market for such drugs for women. Specifically, experts accused the industry of working to redefine female sexual dysfunction to create clearly described medical conditions with measurable characteristics such that it could develop and sell drugs as treatment.[410] Furthermore, once the industry had recharacterized sexual problems in women, it then marketed its new disorders and drugs without regard for the basic science of female sexual dysfunction.[411]

The pharmaceutical industry began with an attempt to redefine women's sexual problems. As discussed earlier, the most widely used classification of sexual dysfunctions has been the DSM-IV classification system. In 2000, a "consensus panel" of experts assembled to reassess this system and to propose new definitions.[412] This meeting, however, was hardly a consensus panel: it was funded by pharmaceutical companies and characterized by secrecy and cronyism. At the bottom of the consensus panel's report, it is noted that the panel was:

> Supported by the Sexual Function Health Council of the American Foundation for Urologic Disease through educational grants provided by Affiliated Research Centers, Eli Lilly/ICOS Pharmaceuticals, Pentech Pharmaceuticals, Pfizer Inc., Proctor & Gamble, Schering-Plough, Solway Pharmaceuticals, TAP Pharmaceuticals and Zonagen.[413]

Additionally, all 19 researchers present at the meeting were affiliated with and received funding from pharmaceutical companies. Asterisks next to the researchers' names indicated that they had:

[410] Ray Moynihan, *The Making of a Disease: Female Sexual Dysfunction*, 326 Brit. Med. J. 45, 45 (2006).
[411] Ray Moynihan, *The Marketing of a Disease: Female Sexual Dysfunction*, 330 Brit. Med. J. 192, 192 (2006).
[412] Basson et al., *supra* note 68, at 888.

> Financial interest and/or other relationship with Affiliated Research Centers, Astra, Bayer AG, Bristol-Myers Squibb, Eli Lilly, Fournier Group, Glaxo Wellcome, Lilly/ICOS, Matrix Pharma, NexMed, NitroMed, Pentech, Pfizer Inc., Pfizer Canada Ltd., Pfizer UK, Pharmacia & Upjohn, Proctor & Gamble, Schering-Plough, Senetek, Shwarz-Pharma, Solvay Pharmaceuticals, Syntec, Syntex, TAP Pharmaceuticals, Vivus and/or Zonagen.[414]

Unlike a veritable consensus panel, this group worked in an atmosphere that was closed to the public; it did not have formal scientific presentations; and it relied upon participation and support from pharmaceutical industry employees.[415] Unsurprisingly, the report it produced was declared "the work of a particular group with serious conflicts of interest."[416]

The substance of the panel's report provides further evidence that the pharmaceutical industry was working to create a disease so that it might develop treatments. As discussed earlier, the classification system the panel proposed was almost identical to the DSM-IV system.[417] The central difference, as stated by the panel, was that the newly proposed definitions were "based on physiological as well as psychological pathophysiologies," whereas the DSM-IV was purely a psychological model.[418] Again, as noted earlier, the DSM-IV is not exclusively a psychological model: it includes, for example, a category entitled "Sexual Dysfunction Due to a General Medical Condition."[419] Rather than making any meaningful scientific changes to the DSM-IV system, the consensus panel appeared to be working to shift female sexual dysfunction from the psychological realm to the physiological realm. In Tiefer's words, the panel wanted to "contribute to an atmosphere that legitimizes female sexual dysfunction as a common condition with substantial organic causes requiring treatment by urologists and new pharmaceutical products."[420] The panel worked to frame female sexual dysfunction as a physiological disorder so that pharmaceutical companies could then provide

[415] Tiefer, *supra* note 134, at 228.
[416] *Id.*
[417] Basson et al., *supra* note 68, at 888.
[418] *Id.*
[419] American Psychiatric Association, *supra* note 67.
[420] Tiefer, *supra* note 134, at 233.

medications as treatment. By shifting perceptions about female sexual dysfunction, the panel created a market for drugs.

The industry also worked to promote awareness of women's sexual problems and treatment and, in doing so, disregarded much relevant research and debate. As it developed Intrinsa, Proctor & Gamble targeted health professionals, the media, and the public: it funded medical education activities, published a guide on testosterone for reporters, and created a website.[421] Additionally, P&G worked with public relations companies and advertising firms to shape the public's perceptions of female sexual dysfunction and its treatment, setting aside an estimated $100 million for advertising.[422] In its effort to advertise female sexual problems and testosterone, the pharmaceutical industry disregarded scientific disagreement and uncertainty in the field.[423] The industry presented hypoactive sexual desire disorder as an accepted, uncontroversial condition, for example, though numerous scholars believe calculating "normal" levels of desire downplays the complexity of female sexual response and overlooks cultural and relational factors.[424] The industry also relied continuously on Laumann et al.'s figure that 43% of women suffer from sexual dysfunction.[425] However, as was discussed earlier, this figure is inflated because it fails to consider women's perceptions of their so-called dysfunctions and whether they view them as such.[426] In light of these facts, as well as the industry's role in reframing female sexual dysfunction as a physiological disorder, many scholars viewed Intrinsa with suspicion.

The FDA's Decision

The FDA's failure to approve Intrinsa also set off a flurry of criticism. Researchers accused the FDA of setting unattainable safety standards, of failing to approve the drug for inappropriate reasons, and of discriminating

[421] Moynihan, *supra* note 411, at 192.
[422] *Id.*
[423] *Id.* at 193.
[424] *Id.*
[425] Laumann et al., *supra* note 32, at 541.
[426] Bancroft et al., *supra* note 135, at 194.

against women.

First, researchers asserted that the FDA's demands for more safety data were unreasonable. Kingsberg, for example, argued that the Advisory Committee's safety requirements were both unrealistic and unclear.[427] He contended that committee member Dr. Nissen stated that P&G would need to conduct studies with 5,000-10,000 more subjects—3.5 to 7 times as many subjects as in P&G's original research, which P&G would be unable to afford—before the FDA's safety concerns would be addressed.[428] Numerous other suggestions were made: some committee members suggested that studies in high-risk populations would be necessary, others suggested animal studies to determine cardiovascular risk, and others proposed studies in premenopausal women.[429] As Kingsberg wrote, the FDA's comments left researchers wondering what and "how much data are sufficient to show that a new drug is 'safe enough'?"[430]

In light of the FDA's stringent demands for safety information, researchers also posited that its decision was unduly influenced by recent developments in the drug industry as well as concerns about off-label use. In particular, the FDA may have been influenced by the Women's Health Initiative study, which found that women taking estrogen-progesterone hormone replacement therapy had increased risks of breast cancer and heart attacks in comparison to women on a placebo.[431] The Committee may have been concerned that testosterone, another sex steroid, might cause similar, unanticipated adverse events in women and thus refused to approve the hormone without more safety information.[432] Furthermore, it is possible that the Vioxx debacle may have predisposed the FDA to reject Intrinsa: the increased cardiac risk associated with Vioxx was not discovered until millions of patients had taken the drug, and the FDA may have wanted to avoid another public health fiasco and publicity firestorm with Intrinsa.[433]

[427] S.A. Kingsberg, *The Testosterone Patch for Women*, 17 Int'l J. Impotence Res. 465, 465 (2005).
[428] *Id.*
[429] *Id.*
[430] *Id.*
[431] R.F. Spark, *Intrinsa Fails to Impress FDA Advisory Panel*, 17 Int'l J. Impotence Res. 283, 283 (2005).
[432] *Id.*
[433] A. Guay, *Commentary on Androgen Deficiency in Women and the FDA Advisory Board's Recent Decision to Request*

Still other experts have argued that the FDA refused to approve Intrinsa for fear of the consequences of its off-label use. P&G studied Intrinsa's efficacy and safety in one group of women: women who had undergone hysterectomy and oophorectomy and were suffering from hypoactive sexual desire disorder. However, premenopausal and naturally menopausal women also experience sexual dysfunction, and off-label use of Intrinsa in these populations was likely.[434] Indeed, as stated in P&G's Intrinsa Briefing Document, 114,000 prescriptions for testosterone products were written for women with sexual problems between 2000-2003.[435] The FDA may have wanted to prevent Intrinsa use by women for whom the efficacy and side effects remained unknown.

The FDA's decision has also been critiqued as being decidedly anti-woman. This criticism has taken numerous forms. Researchers have suggested that the FDA's decision reflected an unwillingness to recognize hypoactive sexual desire disorder as an important disorder and to acknowledge the significance of women's sexuality and sexual concerns.[436] One journalist, for example, cited the FDA's decision to reject Intrinsa as an example of the government's suppression of female sexuality, while she noted, in contrast, that Medicaid has given free Viagra to 198 sex criminals over the past 5 years.[437] Similarly, it has been argued that the FDA imposed different standards on men and women: the Advisory Committee required more long-term safety data for testosterone to be used in women despite the fact that there is no long-term safety data on the many uses of testosterone replacement therapy in men.[438]

More Safety Data, 17 Int'l J. Impotence Res. 375, 375 (2005).

[434]Lynn Crawford Cook, *Meeting Women's Desire for Desire; Testosterone Risky, Say Some Experts*, Wash. Post, Sept. 20, 2005, at F1.

[435]Proctor & Gamble Pharmaceuticals, Inc., *supra* note 379, at 15.

[436]Kingsberg, *supra* note 437, at 466; Spark, *supra* note 431, at 284.

[437]Katha Pollitt, *Burning Desire; Women Fed Up With the Double Standard in the Bedroom*, Seattle Post-Intelligencer, June 5, 2005, at C6.

[438]Guay, *supra* note 433, at 375.

Final Thoughts

Our prior discussions of female sexual dysfunction and the relationship between testosterone and sexual difficulties inform our evaluation of Intrinsa, the medicalization of sexual dysfunction in women, and the FDA's decision. Though it is difficult to decipher the precise motivations behind the pharmaceutical industry, the consensus panel, and the FDA's actions, we can conclude that testosterone is seldom the cause of sexual dysfunction in women and is therefore rarely an appropriate treatment.

Female sexual dysfunction is not primarily a physiological disorder, as the pharmaceutical industry would have the public believe. Rather, sexual problems in women can be psychosocial in origin and are often the result of multiple factors. As discussed earlier, much sexual difficulty is rooted in psychological causes, including fatigue and stress, inadequate information and ineffectual sexual techniques, and psychological conflicts within the self.[439] Additionally, it can be difficult to locate one specific cause of a woman's sexual problems: for many women, their sexual concerns result from a constellation of interconnected variables.

For the most part, women's sexual problems have been and continue to be viewed as predominantly psychosocial in origin. Despite recent developments, the American Psychiatric Association's framework, as articulated in the DSM-IV, remains the dominant classification of sexual dysfunctions. Additionally, the definitions presented by the Working Group on A New View of Women's Sexual Problems emphasize psychosocial causes: sexual difficulties are thought to arise primarily out of inhibition and distress brought about by cultural and relational factors.[440] Even the consensus panel, which worked to shift female sexual dysfunction from the psychosocial realm to the physiological realm, acknowledges that sexual problems are based on "physiological as well as psychological pathophysiologies."[441] The best treatments for sexual

[439] Strong et al., *supra* note 20, at 504-507.
[440] The Working Group on A New View of Women's Sexual Problems, *supra* note 69.
[441] Basson et al., *supra* note 68, at 888.

dysfunction target the underlying causes, and, given the numerous and complex reasons women suffer from sexual problems, Intrinsa is not the panacea the pharmaceutical industry would have us believe it to be.

Even if we assume that physiological problems are to blame for most sexual difficulties, there is little evidence for a causal relationship between low levels of testosterone and female sexual dysfunction. As we have discussed, studies that find an association between depressed testosterone levels and diminished libido in normal (physically intact) women are plagued by small sample sizes and a lack of controls.[442] If we nonetheless overlook these methodological flaws, we must remember that these studies show only an association between depressed testosterone levels and depressed libido. It is not clear that low testosterone levels caused the sexual dysfunction: it is possible that the reverse is true or that both were caused by some other condition. The most methodologically rigorous and compelling study—Davis et al.—found no relationship between testosterone levels and sexual problems in women.[443] These data illuminate, at the very least, the need for more research before we conclude that testosterone can cause as well as treat most women's sexual problems.

Additionally, were we to find a convincing causal link between depressed testosterone levels and sexual dysfunction, women would have to exhibit low testosterone levels to create a general need for a drug like Intrinsa. As we discussed, however, women rarely suffer from low levels of testosterone. Though researchers have long believed aging and/or menopause to be associated with a decline in testosterone, the data do not support this trend. Rather, the data suggest that testosterone levels do not change over time and, if they do decrease for some middle-aged women, the decline is temporary. The women who appear to suffer from low levels of testosterone are few. There is anecdotal evidence that women with hypothalamic-pituitary or adrenal conditions, among others, may suffer from androgen insufficiency, though few studies have actually examined androgen levels in these women. The most compelling evidence for reduced levels of testosterone is found

[442]Guay et al., *supra* note 266, at 121; Guay, *supra* note 261, at 515; Guay & Jacobson, *supra* note 263, at 132.
[443]Davis et al., *supra* note 246, at 93.

in studies of women who have undergone oophorectomy: ovary removal has been shown to be associated with a 40-50% decline in circulating testosterone levels[444] and, for some women, with a decline in sexual functioning.[445] Thus, taken together, the data on testosterone and sexual function indicate that there may be a causal link between low levels of testosterone and sexual dysfunction only in women who have had their ovaries removed. Testosterone supplements, like Intrinsa, are appropriate treatment for sexual problems in these women alone.

With these thoughts in mind, we conclude that Intrinsa, and testosterone generally, is not the solution for women's sexual problems. Of course, Proctor & Gamble purportedly developed Intrinsa for surgically menopausal women, a group that exhibits depressed testosterone levels. This population, however, is small—approximately 300,000 women undergo oophorectomy each year[446]—and P&G likely anticipated that normal women would use Intrinsa. (Certainly, its intended advertising budget of $100 million suggests that P&G was planning on reaching out to women in general.[447]) Indeed, given how few women have undergone oophorectomy, it is probable that the majority of women taking Intrinsa would have been physically intact, or normal, women. Thus, as it considered Intrinsa, the FDA confronted potential widespread use of testosterone in populations of women for whom the benefits and the risks of the drug remain, at best, unknown. Testosterone is neither the cause of nor the solution for most female sexual dysfunction, and the FDA exhibited appropriate caution in demanding more efficacy and safety data before approving its use in any population of women.

[444] Judd et al., *supra* note 344, at 795-796; Laughlin et al., *supra* note 303, at 648-649.
[445] Kaplan & Owett, *supra* note 288, at 10; Shifren et al., *supra* note 360, at 686; Waxenberg et al., *supra* note 286, at 194-195.
[446] Wilcox et al., *supra* note 336, at 549.
[447] Moynihan, *supra* note 411, at 192.