CHAPTER 19

Committee 7

Physiology of Female Sexual Function and Pathophysiology of Female Sexual Dysfunction

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CONTENTS

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A. INTRODUCTION

The Sexual Response Cycle

The sexual response cycle in men and women includes the basic stages of sexual desire, arousal and orgasm. Understanding of the neurobiology and psychophysiology of these fundamental phases or aspects of sexual response has advanced dramatically since the early studies of Masters and Johnson (1966, 1970). A review of the early studies is beyond the scope of the present volume. This chapter will address recent studies of the physiological and pathophysiological processes in women's sexual dysfunction; the corresponding mechanisms and physiological processes in men are described in Chapters XX, XX Dramatic advances have occurred in our understanding of the neurochemical and hormonal meachanisms of sexual response. Many of these advances are based on animal models, although human studies are being reported with increasing frequency. The latter portion of the chapter includes an overview of these new and exciting areas of reasearch. Following the principles of the International Consultation, criteria of evidence-based medicine were applied rigorously in the evaluation of all experimental literature in this new area of study. It is noteworthy that the committee identified over 600 references of relevance to the topic.

Scientific advances in women's sexual health have lagged somewhat behind those of men's sexual health. This is despite the fact that numerous epidemiologic studies show a higher prevalence of sexual complaints and problems in women than in men. Therapies for women with sexual dysfunction have not been developed in accordance with current physiologic understanding of women's sexual function. This chapter addresses the contemporary evidence-based knowledge of the physiology of desire, arousal and orgasm in female sexual function and pathophysiology of disorders of desire, arousal and orgasm in female sexual dysfunction. The basic principles of evidence-based medicine were systematically applied in evaluating a large and growing body of research.

Due to ethical constraints and practical limitations, much of the current knowledge-base in sexual physiology is derived from studies in non-human species. These studies are reviewed first, prior to the studies in normal volunteers and clinical samples in the latter portion of the chapter.

B. NON-HUMAN STUDIES

I. DESIRE

While it is difficult to study the neurobiology of human sexual behavior experimentally, real progress in the past decade has been realized in understanding the neuroanatomical and neurochemical mechanisms that underlie sexual desire, and how sexual stimulation and reward impact on attractiveness and mate choice.

1. Conceiving of commonalities

All organisms that engage in sexual behavior share a common set of principles and end-points that define

the behavior, along with particular neural mechanisms that make it successful. All organisms must be able to respond to hormonal and neurochemical changes that signal sexual desire and arousal. This ability underlies our moment-to-moment level of sexual arousability (as conceived by Whalen [1]), and defines a large part of the internal state that is commonly referred to as "sex drive". The rest requires a complex mix of instinct, learning, and feedback; a neural organization that allows us to interact with external sexual incentives. All organisms must be able to identify external stimuli that predict where potential sex partners can be found, to seek out, solicit, court, or otherwise work to obtain sex partners, distinguish external cues and behavioral patterns of potential sex partners from those that are not sexually receptive, and to pursue sex partners once sexual contact has been made. Neural mechanisms exist that allow sexual responding to become habitual or automated with practice, and such processes may underlie the ability of sexually experienced animals to be less affected by treatments that disrupt sexual responding in sexually naive animals [2]. Similarly, neural mechanisms exist that allow the stimulation received during sexual contact to be perceived as rewarding. Such reward alters subsequent behavior, for example, by contributing to the formation of preferences for salient stimuli associated with positive sexual reinforcement [3].

With regard to models of human behavior, something performed by an animal may not appear similar to its human counterpart, despite serving a similar endpoint and being dependent on identical neural systems. Solicitation in female rats is a good example. During copulation, female rats control the initiation and pacing of copulation by soliciting mounts from males. Females make a headwise orientation to the male and then run away, forcing the male to chase them [4]. If the male is sluggish or non-responsive, the female may increase the strength of her solicitations, to the point of kicking the male in the head before the runaway or even mounting the male if he does not respond to previous enticements [5, 6]. Of course, such behavior would not be interpreted as sexual solicitation in most human cultures. However, solicitation in all species indicates a willingness or desire to copulate, and high levels of solicitation in females, or analogous courtship behaviors in males, suggest that the animals are highly motivated to copulate. At a strictly behavioral level of analysis, it does not matter whether the motivation to do so is driven by a primary desire for sexual gratification, offspring, conflict resolution, or other social rewards. Contrast solicitation with lordosis, the arching of the back characteristic of sexual receptivity in many mammalian females. There is no human counterpart to this behavior. Thus, solicitation in rats, and not necessarily lordosis, might be the most "analogous rat model" of sexual desire in women.

2. What Animals Make Good Models?

Any animal "system" in which the homology or analogy has predictive validity to human responses or physiological processes (and can be replicated) is a good model. Rats continue to be the most frequently-used animals in the study of sexual behavior, the most obvious reasons being that they are practical (e.g., small, easy to handle, and quite social) and they have a large literature associated with them. Rats also resemble humans in many analogous and homologous ways. Certain tissues and neuroendocrine systems in rats are strikingly similar to our own (e.g., the physiological control of erection or uterine tissue growth following estrogen treatment). As a social animal, rats have evolved a level of behavioral plasticity that allows them to adapt to a variety of ecological niches [7,8,9]. Like humans, their patterns of copulatory behavior can be described as "opportunistic", and they will copulate in a variety of circumstances, in dyads, triads, or large groups [4,9-12]. Beach [10] noted that male and female rats will copulate in virtually any type of testing chamber. Rat sexual behavior has thus been examined experimentally in groups (4), in mate-choice paradigms (13, 14), and in traditional dyadic mating situations in a variety of unilevel or bilevel chambers (15-18). The use of different testing situations sometimes results in different patterns of copulatory behavior. Rather than such differences being considered an experimental annoyance, they stand as examples of the profound behavioral plasticity of rats in different circumstances, examples of the way that rats are able to alter their behavior to meet the demands of different contexts, much like humans do.

a) Models of sexual arousal

Physiological sexual arousal in both humans and other animals can be defined as increased autonomic activation that prepares the body for sexual activity. This includes both parasympathetic blood flow to genital and erectile tissues, in particular the clitoris, labia, vaginal epithelium, and sympathetic blood flow from the heart to striated and smooth muscle that participate in sexual responses. Sexual arousal also includes a central component that increases neu-

ral "tone" or preparedness to respond to sexual incentives. This latter concept was defined as "arousability" by Whalen (1), and may form around an intricate interaction of hormone priming and noradrenergic activity in different regions of the brain. Both peripheral and central arousal may be detected as part of the perception of subjective sexual arousal, and both clearly lead to changes in responsiveness in genital tissues and control certain copulatory responses, such as the latency to orgasm or ejaculation (with shorter latencies indicating an increase in arousal).

b) Female sexual arousal

Physiological sexual arousal in women has received experimental attention. Drugs or stressful circumstances block vaginal and possibly clitoral blood volume in women. Clinical results with sildenafil in women with sexual arousal disorders have been inconclusive [19-21]. There may be real differences between men and women in patterns of sexual arousal and in the types of psychogenic stimuli that elicit genital blood flow [22-23]. For example, women are reported to experience cyclic fluctuations in arousability and desire, with peak incidents of female-initiated sexual activity coinciding with ovulation [24]. Indeed, event related potentials (ERPs) that correspond to attention and stimulus processing for working memory (e.g., the P3 amplitude) increase following the presentation of sexually arousing pictures, but not pictures of babies or body care products, to women during the ovulatory phase [25]. The same pictures do not activate those ERP components during other phases of the menstrual cycle, or in women taking oral contraceptives [26]. Timing may thus be extremely important when studying sexual arousal in women relative to men. Such a relationship has been established for rats and other species. Female rats display sexual "heat" only during the periovulatory period of their estrous cycle, a state that can be induced in ovariectomized rats by sequential administration of estrogen and progesterone [27].

In vivo experimental models of genital arousal in female New Zealand White rabbits have been developed by Traish, Goldstein, and their colleagues [28-33]. In these models, electrical stimulation of the pelvic nerve is applied that mimics the type of stimulation normally received by females during vaginal intromission and results in increased vaginal blood flow, vaginal wall pressure, vaginal length, clitoral intracavernosal pressure and blood flow, and decreased vaginal luminal pressure. Similar effects have been reported following pelvic nerve stimulation in female rats [34, 35]. In addition to vaginal and clitoral blood flow responses, vaginal smooth muscle preparations have been developed to examine the ability of different neurotransmitters to induce muscle contraction and relaxation. These studies have shown that ovariectomy diminishes vaginal blood flow, lubrication, and epithelial cell morphology, and that treatment with estradiol restores these measures of vaginal response. Moreover, the nitric oxide-cyclic GMP pathway appears to be critical for vaginal blood flow, as it is for penile blood flow. Treatment with androgens facilitates vaginal nitric oxide synthase activity, along with vaginal smooth muscle relaxation. Although it is not yet known how these vaginal responses are integrated with behavioral responses, Whalen and Lauber [36] hypothesized that cyclic GMP was a common target for drugs that substitute for progesterone in the facilitation of lordosis in rats. Inhibition of the ability of nitric oxide to stimulate cyclic GMP in the rat brain results in a profound disruption of lordosis [37] suggesting that the brain is an important target for nitric oxide/GMP stimulated activation of lordosis. However, it remains an intriguing possibility that increased vaginal blood flow could be perceived by females and help stimulate behavioral measures of sexual arousal. Such a relationship could be examined following inhibition of peripheral nitric oxide-cyclic GMP.

c) Models of sexual desire

Desire has always been difficult to define [38-39]. In the DSM-IV-TR [40], the diagnosis of Hypoactive Sexual Desire Disorder is given when "desire for and fantasy about sexual activity are chronically or recurrently deficient or absent." By converse logic, then, sexual desire is the presence of desire for, and fantasy about, sexual activity. This definition appears coherent but is circular. How does desire manifest itself?

Many clinicians and motivational theorists alike view desire as distinct from arousal in both animals and humans. This is apparent in the DSM's categorization of arousal disorders distinct from desire disorders, a distinction that generally reflects blood flow to the genitals and erectile tissues versus a "psychological" sexual interest in which individuals "want" or "crave" sex (with wanting and craving defined here as in Robinson & Berridge, [41] for drugs of abuse). In practice, however, desire may well be informed or even confirmed by the presence of auto-

nomic and central responses that define arousal, and there is growing evidence that people regard desire and arousal as parts of one another, despite being given distinct definitions [19, 42]. When an individual expresses sexual desire behaviorally, it follows that attention and behavior focus on obtaining some form of positive sexual reinforcement.

Like people, animals manifest sexual excitement behaviorally. They will increase their motor output in anticipation of copulation and work for the opportunity to copulate or to obtain primary or secondary (conditioned) sexual rewards associated with copulation. Animals will also choose between two or more sexual incentives based on the strength of the incentive cues and the animal's own internal drive state. What characterizes these behaviors is that they occur before copulation: Courtship, operant responses, conditioned locomotion in anticipation of sex, time spent near a particular sexual incentive, or choices made between two or more incentives, can all be considered analogies of anticipatory sexual desire. Simply put, animals with more "desire" will display more robust behavior than animals with less desire. Desire can also be inferred from certain appetitive behaviors that occur during copulation. A growing body of evidence indicates that these aspects of sexual behavior are altered in a relatively selective fashion by certain drugs that are known to alter desire in humans.

All animals will work to obtain sexual rewards, and such behavior can be viewed as analogous to desire. Sexual rewards may come in the form of primary reinforcers (e.g., orgasm in humans, or pacing in female rats), or secondary reinforcers, such as stimuli associated with sexual gratification (e.g., certain facial features, clothes, or smells in humans; certain odors or place cues in rats).

Bermant [43] and Bermant and Westbrook, (44) reported that female rats would bar-press for access to gonadally-intact, sexually active males. More recently, Matthews et al. [45] reported that access to intromissions from a male that were made contingent on poking a lever with the nose increased the incidents of nose-poking in sexually receptive female rats. Contingent access to male bedding or emulsified preputial gland did not support increases in behavior, indicating that the copulatory stimulation was rewarding. The paradigm used by Matthews et al. ensured that females could control or "pace" the rate of copulation, a characteristic of copulatory interaction that female rats find rewarding (see below). Becker and colleagues [46-48] found increased dopamine release in the striatum and nucleus accumbens of females that had to press a lever to gain access to a male, or run back and forth from behind an opaque barrier, relative to females that did not. Indeed, lesions of the striatum reduced the efficiency of females to pace the copulatory interactions, whereas lesions of the nucleus accumbens resulted in females that avoided sexual contact [49].

1. Sexual preference paradigms

Sexual desire can be inferred from the strength of preference made toward particular features of a person or conspecific, or toward a place in which potential sex partners have been found in the past. As with other instrumental responses, preferences are typically displayed prior to sexual interaction so that animals and people can focus their forward trajectories toward sexual incentives. In humans, preferences exist for gender, and within gender for certain individually-defined physical features, scents, for certain types of clothing, even for fetish objects. The role of such preferences is to focus the attention of individuals on other individuals so that sexual interactions can occur. Some preferences are determined by particular cultures or epochs within a culture, whereas others are learned during a critical period of sexual behavior development, especially during an individual's first sexual experiences. Some may be genetic. However, what is clear is that the association of particular features with sexual gratification entices people to seek out those features in future sexual interactions, even if those interactions are made at a distance or are part of a rich fantasy life. Preferences exist in humans that are conditioned by experience; yet arguments continue to be made that the sexual preferences of animals (and even humans) are hard-wired for ultimate reproductive success and fitness, rather than more proximate rewards, such as sexual pleasure [50, 51]. Certainly animals do not exist within a social organization that approximates human culture, and therefore are not subject to moral restrictions or the whims of advertising executives. However, recent evidence indicates that animals do show preferences for specific features, many of which are learned during experience with sexual reward, rather than driven instinctually to maximize reproductive fitness. This latter dimension represents an exciting new foray into a level of animal behavior that approximates our own.

Some preferences in animals seem instinctual and hard-wired by hormonal influences on the brain. For example, sexually receptive females spend more time near gonadally intact, sexually active males versus castrated, sexually inactive males [52]. However,

other preferences are conditioned by experience with sexual reward. Female rats find the ability to pace or control their copulatory contact with males rewarding [53], and will display conditioned place and partner preferences for cues associated with such reinforcement (see below). For example, in female rats, a neutral odor (almond) was paired with the ability of females to pace [54]. This is was done using a pacing chamber similar to that described by Erskine [15] and Paredes and Alonso [53] in which a Plexiglas divider is placed in the middle of the chamber. The bottom of the divider has one or more holes cut out that are small enough for the female to pass through, but too small for the male, thus the female can regulate her contact with the male simply by running from side to side. During training, females in the paired group received sequential access to scented males on one side of the divider or unscented males with no divider, on alternate testing days. Females in the explicitly unpaired group received the opposite order of experience. On the final test, each female was placed into an open field with two intact, sexually experienced males, both tethered to opposite sides of the open field. One male was scented and the other was not. Females in both groups were significantly more likely to solicit and receive their first intromissions from the male paired with pacing. However, only females in the paired group show a significant preference to stay with that male for their first ejaculation; females in the unpaired group did not show a conditioned ejaculatory preference. The selective copulation and mating behavior on the part of females in the paired group would be expected to assure paternity [55].

2. Desire in copulatory measures

Sexual desire can also be inferred from certain unconditioned copulatory measures. For example, the rate at which female rats will solicit and pace their copulatory contact with males can be considered analogues of desire (and possibly subjective arousal). These measures can be recorded unambiguously in bilevel chambers, pacing chambers, mazes, or choice boxes [56]. Solicitations by the female usually result in mounts and intromissions by the male. Following intromission, the female runs away in order to "pace" the rate of copulation. In an open field or in bilevel chambers, the male typically chases her until she stops again and holds a lordosis crouch, allowing him to mount. If the male stops chasing, she will have to solicit to initiate another bout of copulation. Essentially, pacing refers to the amount of temporal distance the female keeps from the male between bouts of copulatory activity. This measure is inversely related to her degree of sexual interest; for example the timing between intromissions increases with successive intromissions, and increases dramatically following several ejaculations [18]. Rates of pacing are also much larger in ovariectomized female rats primed with estrogen but no progesterone, relative to females primed with both hormones. To the extent that solicitation and pacing reflect inversely a general desire for sexual contact, then experimental treatments that increase solicitations and/or keep pacing durations short, may increase desire in women. For example, ovariectomized female rats primed with estrogen and progesterone, or estrogen alone, and administered the melanocortin agonist PT-141, display a dramatic and selective increase in solicitations. Although in recent Phase I clinical trials, this drug was shown to increase vaginal arousal in women viewing a female-centric erotic film [57], it remains to be tested whether this drug will increase their desire for sex in appropriate circumstances, or as measured by paper-and-pencil tests of sexual arousal and desire. If so, then solicitation in female rats can be considered an analogue of sexual desire in women.

Another feminine copulatory behavior that is taken as a measure of the willingness to have sex is lordosis, the arching of the back displayed by female rats (and other species) that indicates their sexual "receptivity" [58]. More is known about the hormonal, neurochemical, and neuroanatomical control of lordosis than any other mammalian sexual behavior [59, 60]. This reflex is dependent on estrogen, although treating ovariectomized females with estrogen alone produces only a moderate activation of the reflex in response to flank stimulation by the male. Full receptivity depends on additional activation by progesterone. Indeed, so does the full expression of proceptive behaviors like solicitation, and the normally low expression of pacing [58, 18]. Drugs that bind to D1 dopamine receptors, adrenergic receptors, oxytocin receptors, opioid receptors, or GABA receptors in certain hypothalamic brain regions can increase lordosis in ovariectomized rats primed with estrogen alone [61, 62]. These substances may work on neurochemical substrates normally activated by progesterone, or could work via cell-signaling cascades that activate progesterone receptors (e.g., as has been described by Mani et al. [63], for dopamine in the ventromedial hypothalamus). If these drugs also enhance solicitations and delay the increase in pacing normally observed at the beginning of estrus

termination, they might stand as suitable candidates for the treatment of hypoactive sexual desire disorder.

d) Models of sexual reward

Like the expression of sexual desire, sexual reward has many faces and states of being. This alone makes it difficult to define what is and is not rewarding for any person or within a culture. Moreover, sexual behavior may occur for reasons that have nothing to do with sexual gratification per se. But sexual reward as a general concept has a more pervasive problem: its association in psychology with positive reinforcement. Positive reinforcers are traditionally considered events or stimuli that increase the probability of subsequent behavior [64]. Small food pellets to a hungry rat are positive reinforcers because they increase instrumental responding for them. Playing with one's hair or sideways glances during a bout of flirting would also be considered positive reinforcers if they increase the degree of responding between the flirting pair [65].

All behaviors have a beginning, middle, and end, and satiety mechanisms place negative feedback on behavior by activating inhibitory neural pathways. Satiety mechanisms are absolutely critical for any regulatory behavior [66]. In the short term, consuming a large meal or copulating to sexual exhaustion decreases responding for food or sexual incentives. Fortunately, meals can be broken up into small bits that maintain operant responding for them. Sex partners cannot. This was the reason that Everitt et al. [67] used a stimulus light that predicted the arrival of a sex partner. The light acted as a conditioned reinforcer that could be presented for brief periods, and doing so supported relatively high rates of operant responding. If positive reinforcement equals reward, then satiety cannot be rewarding because it suppresses ongoing behavior. It is easy to see how theories of human sexual reward can be hindered by conflicting definitions of reward, reinforcement, and satiety: flirtations which are unambiguously rewarding if they lead to more behavioral output. However, orgasms would be rewarding only if they lead to more sexual activity; they could not be considered rewarding if they induce a period of sexual refractoriness.

In any motivational system, reward should be considered a dynamic function with an inverted U-shaped relationship to ongoing behavior: Low rewards do not sustain behavior, moderate to ideal rewards do, and high rewards induce the inhibitory feedback that characterizes satiety. With regard to sexual behavior, rewards that sustain sexual arousal and desire might be considered low-to-moderate, whereas high rewards like orgasm might be those that induce a period of sexual refractoriness. The reward value of satiety may also depend on the time frame. Although sexual satiety decreases sexual responding in the short term, the reward associated with it in female rats is necessary for the conditioning of sexual preferences in the long term.

1. Responding for sexual reinforcers

How do we infer sexual reward in animals? One involves assessments of operant or instrumental responding for a particular sexual reinforcer. Anything an animal must do to get closer to, or obtain, the reward can be assessed in this manner. in rats, this would include behaviors like nose-poking through a wire-mesh screen, navigating obstruction boxes or complex mazes, or bar-pressing for first- or second-order reinforcers. The inference here is simple (albeit circular): if the animal will work for it, it must be reinforcing. But Meisel and Sachs' [68] caveat for understanding preference without copulation also applies here: without knowing what animals will actually do with the reinforcer once they obtain it. It is difficult to know exactly what the motivation was behind the responding and hence difficult to specify what was rewarding about the stimulus in the first place.

2. Reward in copulatory measures

Another way to infer sexual reward is based on copulatory activity. Indeed, solicitation and pacing in female rats can all be construed as indices of the reward value of the stimulus animal. These behaviors are also operants in the sense that animals must perform them in order to achieve the goal of copulatory interaction/sexual stimulation.

3. Conditioned place preference

Contextual factors such as settings are important components of positive sexual experiences for women [69-73]. Salient cues in the environment may be associated with sexual reward in such a way that they increase arousal or desire directly in their presence. Accordingly, one way to infer sexual reward is to examine responses made toward contextual cues paired with sexual reward. With animals, this can be done using the conditioned place preference (CPP) paradigm. Animals often display a preference to remain in a context that has been paired consistently with access to a reward (e.g., drugs of abuse, highly

palatable foods, a mate) over a context that has not. This type of CPP is typically demonstrated in an apparatus with two distinctive compartments that are connected to either side of a third neutral compartment. During training, the compartments are paired differentially with unconditional stimuli, (e.g., one side is paired with a sex partner, food, or a rewarding drug, and the other side is paired with either nothing or a control manipulation). On the final test, the subject is placed into the neutral compartment with the two doors on either side opened to allow free access to either compartment. CPP is said to have developed if the subject spends significantly more time in the reward-paired compartment than the other compartment. Stimuli or events that are capable of supporting CPP are referred to as "rewards" rather than "reinforcers", because the subject has never been required to move into the paired compartment to experience them. Thus, CPP is not reinforced, per se, because it is displayed spontaneously on the final test. However, the increased time spent in the side paired with reward is clearly conditional upon the Pavlovian association of those contextual cues with the reward state.

CPPs have been demonstrated in female rats and hamsters. Oldenburger et al. [74] found that when copulation occurred within one of the distinctive compartments of a CPP apparatus, female rats showed only a weak CPP. Conversely, Paredes and Alonso [53] and Paredes and Vazquez [75] demonstrated a robust CPP in female rats that depended on whether the females were able to pace the rate of copulation without having to employ defensive behaviors. This was accomplished using the pacing chambers described above, in which a Plexiglas divider bisects the chamber. The divider contains one or more holes that only the female can pass through. This allows her to pace the rate of copulation by moving freely from side to side. Like males, females acquired a strong preference for a distinctive environment only if they were placed into the CPP box immediately after paced copulation. No preference was found if the copulation was unpaced prior to placement in the CPP box (meaning that it had occurred in the same pacing chamber but without the divider). Thus, for a female rat, CPP develops only if she has been able to control the initiation and rate of copulation freely without having to use defensive behaviors. Although a sexually vigorous male rat is a clear unconditioned stimulus for approach and solicitation in female rats [76], contextual cues associated with pacing elicit a conditioned sexual reward state in those females. However, these results may also indicate the presence of an unconditional aversive state during unpaced copulation. To examine this possibility, Afonso, Woehrling, and Pfaus [77] allowed female rats to copulate in two paced conditions using Plexiglas dividers that had either 4 holes or 1 hole. This was done to eliminate the possibility of an "aversive" state resulting from unpaced copulation. Trials were conducted sequentially at 4-day intervals, and each pacing condition was paired with one of the distinctive sides of a CPP apparatus, in a counterbalanced fashion. Control groups contrasted the 4-hole condition with no divider, or the 1-hole condition with no divider (as was done by Paredes and colleagues). Control females developed significant CPP for either the 1-hole or 4-hole condition, relative to unpaced copulation with no divider. Those control data replicate the findings of Paredes and colleagues, and indicate that both the 4-hole and 1-hole condition are rewarding relative to the unpaced (no divider) condition. However, they do not rule out the possibility that the real distinction being made is between an aversive condition (unpaced copulation) and a rewarding condition (paced copulation). This was addressed in the group allowed to contrast the 4-hole versus 1-hole condition. In this group, females developed significant CPP for the 4-hole condition, relative to the 1-hole condition, suggesting strongly that copulatory CPP reflects a true sexual reward state in females. Similarly, Jenkins and Becker [47] found that female rats developed significant CPP for paced relative to unpaced mating, but also for unpaced mating in which the experimenter removed the male for a period that approximated the female's imposed interintromission interval, relative to unpaced mating in which male removal did not occur. Thus, female rats develop CPP for sex at their own preferred intervals. Taken together with the results of Matthews et al. [45] (1997), these data suggest that reward comes from the sexual stimulation that females receive, namely mounts with intromission, so long as that stimulation occurs at the desired time intervals.

In females, naloxone blocked the acquisition of a pacing-related CPP, suggesting that opioid systems in the brain of female rats are activated by sex-related cues [78]. Dopamine antagonists have not been reported to alter the development or expression of copulatory CPPs in female rats. In contrast, Meisel, Joppa, and Rowe [79] found that the development of a copulatory CPP in female hamsters was blocked by injections of the D2-receptor antagonists sulpiride or

raclopride prior to each training session. To summarize, sexual reward appears to involve the activation of brain opioid systems. In some cases, odor or contextual stimuli associated with sexual reward activate mesolimbic dopamine pathways (either to increase attention or drive goal-directed behaviors). **(Figures 1 and 2)**

e) Animal Models: A Synthesis

Animals possess appetitive and consummatory aspects of sexual behavior that are homologous and analogous to our own and that are controlled by similar or identical neurochemical and hormonal systems. They experience sexual arousal, desire, reward, and inhibition. Females like to control the initiation and rate of sexual contact. Sexual behavior in females is strengthened with experience, making them less vulnerable to treatments that disrupt sexual responding. From an evolutionary perspective, sexual behavior appears to have similar processes and endpoints for all mammals, and perhaps for all species that engage in it.

If the process and endpoints of sexual response are the same (even if the outward expression of appetitive behaviors or copulation is species-specific), then animals can indeed be used as models of human sexual response provided the homology or analogy is specified unambiguously, and that treatments or experiences have similar effects between the species, giving the animal model predictive validity. This requires that we understand the particular behaviors of both species as best we can, which in turn requires that we be careful and creative in how we ask our scientific questions. It was believed that female rats didn't "enjoy" copulation because it took them longer to return to a male following intromission or ejaculation, relative to precopulatory interaction or mounts without intromission. However, Paredes and colleagues provided an important glimpse of what female rats really like about sex: their ability to control its occurrence and rate. If they have control over the initiation and rate of sexual interaction, then female rats will develop copulatory CPPs; if not, then CPPs do not develop despite the fact that females still copulate and are sexually receptive. Control is an important aspect of sexual function in women, and problems with locus of control may form an important part of the etiology of different sexual disorders [80]. Female rats display proceptive and receptive sexual behaviors only during their periovulatory period, or if they are ovariectomized and given appropriate replacement with estrogen and progesterone. Although female primates, including humans, can have sex throughout their ovulatory cycles, they display increased female-initiated solicitation and sexual activity during their periovulatory periods [24, 81]. Making the conceptual connection between animal and human sexual behaviors is the primary challenge for researchers. Subsequent testing of those connections is easier, but equally important.

Animal models will continue to be indispensable for studies of the neurobiology of sexual behavior. The knowledge that lesion and drug studies, neurochemical and neuroanatomical analyses and molecular approaches provided in animals guide our emerging work in the neuroanatomy of sexual responding in humans using functional magnetic resonance imaging or positron emission tomography. Animal models are needed to further understand the hormonal processes that lead to changes in sexual arousability (e.g., following hormone therapy in postmenopausal or hypogonadal individuals). The kind of invasive and direct studies of brain or organ function in animals simply cannot be conducted in human subjects.

II. AROUSAL: PHYSIOLOGY OF GENITAL AROUSAL IN FEMALES

1. Innervation of female genital arousal response

The neural control regulating the female genital response is poorly investigated, and is therefore less understood than the male counterpart. The majority of investigations elucidating the neural control have been done in animal studies, primarily rodents, and only few human studies exist. The use of animal studies has clear advantages, as they are easily performed, but the obvious drawback is the lack of evidence of comparability between human and animal structures. As such, animal data primarily generate ideas for future human studies and conclusions from animal studies must be made with reservations.

Studies on regulation of genital arousal include those on regulation of vaginal blood flow, clitoral, labial and vestibular bulb engorgement, and vaginal smooth muscle wall. The role of contraction and relaxation of the vaginal smooth muscle wall in the genital arousal response is still debatable. Many *in vitro* studies have focused on vaginal tone and its regulation. Most likely this is because it is an easy end organ to study and exert basal smooth muscle properties,

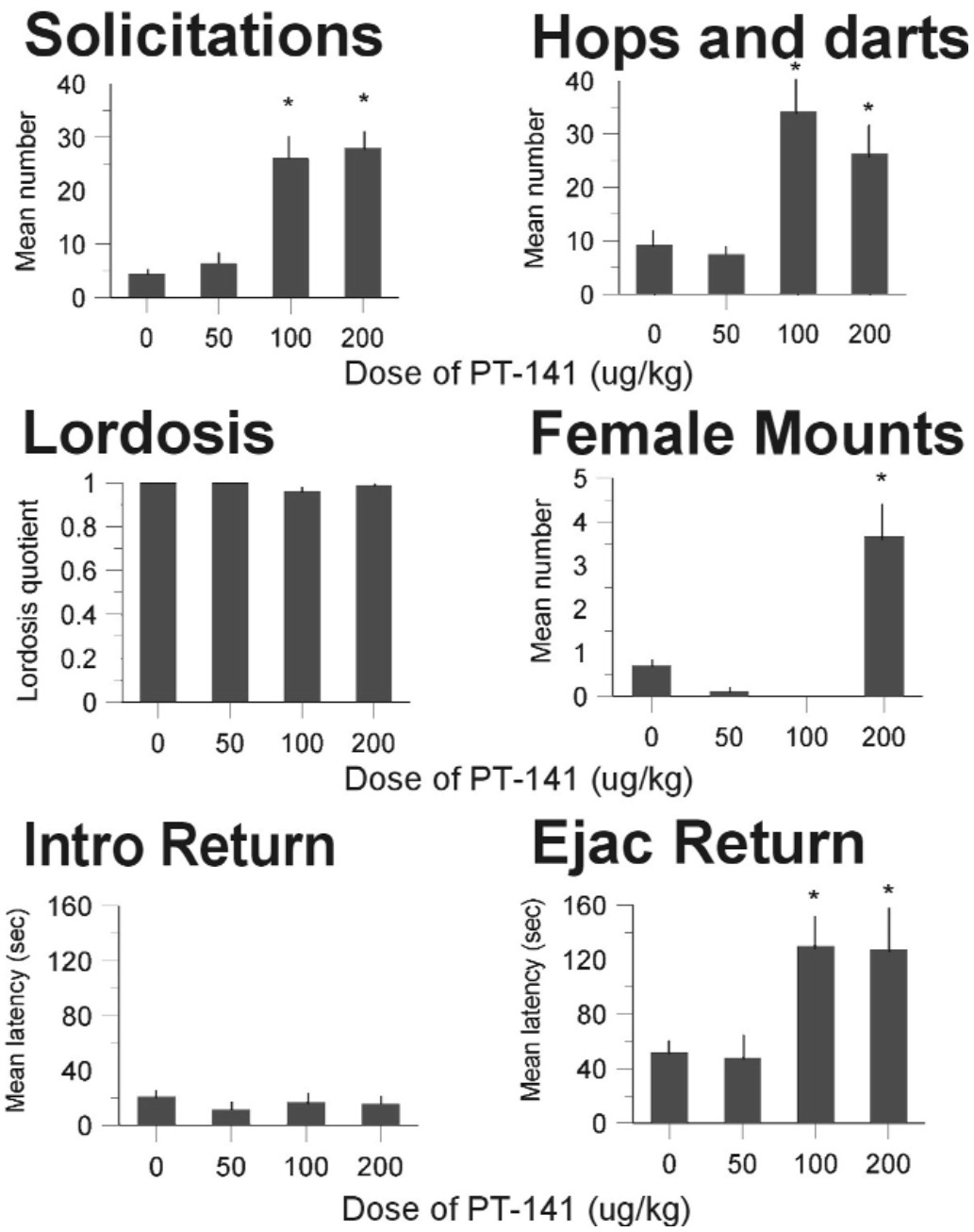

Figure 1: TOP: Effects of the dopamine agonist apomorphine on solicitation and pacing behavior in ovariectomized female rats without hormone replacement (O), primed with estrogen alone (E+O), or primed with estrogen and progesterone (E+P). Data are means + SEM. Tests were conducted in bilevel chambers. Apomorphine increased solicitations and decreased pacing in females primed with estrogen alone, but not without estrogen. Apomorphine did not affect solicitation or pacing in females primed with estrogen and progesterone. Females solicit sexual contact with males by orienting their heads toward the males, and then running away to another level. Pacing in bilevel chambers is defined as the number of level changes displayed by females prior to each mount by the male. Females with high sexual interest display a large number of solicitations and low number of level changes between mounts. This pattern of behavior increases their sexual contact with males.

BOTTOM: Dopamine release in the nucleus accumbens and dorsal striatum of sexually experienced female rats during sexual contact with males. Dopamine in extracellular fluid was extracted using microdialysis and analyzed by electrochemical detection after separation with HPLC. Samples were taken at 10-min intervals. To rule out general locomotion, females were first placed onto an elevated rotating drum for 20 min, followed by the drum rotating at a speed of 6 meters/min for another 20 min. Females were then placed into a clean testing chamber. This was followed by exposure to an increasing succession of stimulus intensities. First the bedding was replaced with clean bedding, then with bedding soiled by sexually active male rats. Then a male was placed behind a wire-mesh screen, after which the screen was removed to allow sexual contact for 20 min. The male was removed after this copulatory period. Nosepokes through the wire mesh were counted prior to copulation as a measure of the female's precopulatory interest.

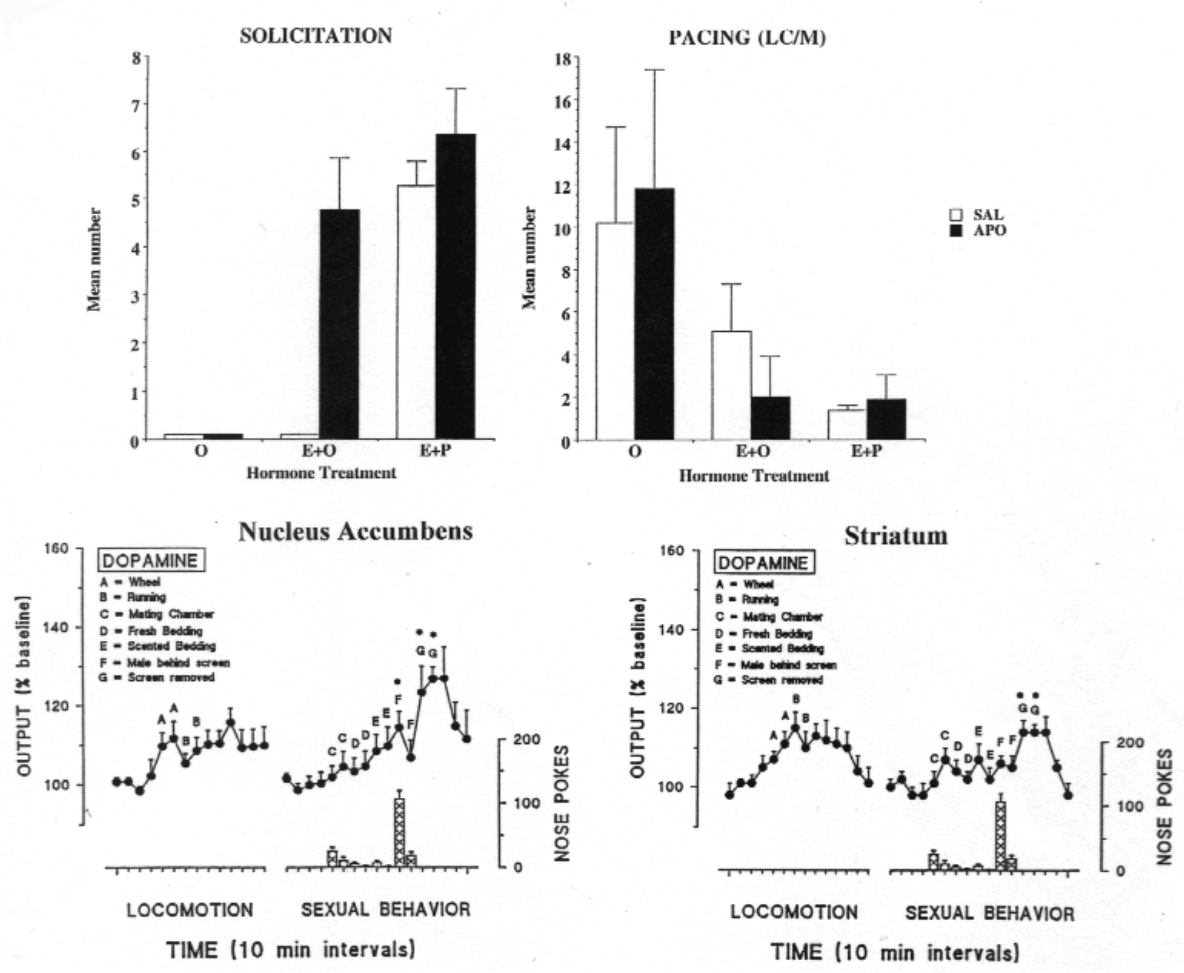

Figure 2: Dose-response effects of the melanocortin agonist PT-141 on the sexual behavior of ovariectomized female rats primed with E+P. Data are means + SEM. Tests were conducted in unilevel pacing chambers bisected by a Plexiglas screen with four holes at the bottom small enough to allow the female, but not the male, free access from one side to the other. Females in these chambers pace their copulatory contact by running back and forth from the side containing the male. PT-141 increased solicitations, hops and darts, but did not affect pacing or lordosis. Interestingly, although PT-141 did not alter the latency to return to the side containing the male after an intromission, it increased the latency to return after an ejaculation. This pattern of data suggests that PT-141 increased the desire of female rats to initiate sexual contact, and further increased the intensity of stimulation received following ejaculation.

which may be comparable to that of the smooth muscles in the genital vasculature and clitoris.

a) Autonomic neurotransmitters in the female genital arousal response.

Adrenergic and cholinergic neurotransmitters have been identified in the postganglionic fibers to the vagina and the clitoris, primarily in animal models [82-88], as well as alpha-adrenergic receptors which have been demonstrated biochemically and functionally in the rabbit vagina [85, 86]. Little data exists on the presumed inhibitory effect of adrenergic stimulation on the female sexual genital response. In vitro experiments on the smooth musculature of the rat and rabbit vagina and rabbit clitoris show contractile response to adrenergic stimulation [89-91].

In a pilot study, oral phentholamine was administered to postmenopausal women with Female Sexual Arousal Disorder. The results indicated a moderate effect on subjective and objective parameters of sexual arousal. [92]. Unfortunately it was impossible to discriminate between preferential and central effects in the study. Meston and colleagues provided evidence for ***an excitatory*** role of peripheral adrenergic activation on sexual arousal in women. Ephedrine (50mg), an alpha and beta adrenergic agonist, facilitated vaginal photoplethysmograph measures of sexual arousal in a randomized controlled trial of 20 women [93].

The role of noradrenaline in the control of clitoral erection is indirect and only elucidated by case reports on treatment of clitoral priapism with injection of adrenergic agonists [94, 95]. Despite the rich cholinergic innervation, the role of acetylcholine is uncertain. In the *in vivo* animal model described by Giuliano et al, intravenous injection of ***atropine*** only decreased the vaginal blood engorgement induced by stimulation of the pelvic nerve (PNS) slightly. In the same model, intravenous atropine decreased vaginal smooth muscle contractions also induced by PNS. In a small, uncontrolled study of six women, intravenous injection of atropine had no effect on the vaginal blood flow during masturbation [96].

b) Non-adrenergic, non-cholinergic (NANC) neurotransmitters/ mediators:

A great variety of NANC neurotransmitters/mediators have been identified in the female genital tract, mainly in animal models. In animal studies on the vagina and its vasculature, vasoactive intestinal polypeptide (VIP), nitric oxide synthase (NOS; producing nitric oxide, NO), neuropeptide Y (NPY), calcitonin gene-related peptide (CGRP) substance P (SP), pituitary adenylate cyclase-activating polypeptide (PCAP), helospectine and peptide histidine methionine (PHM) have been demonstrated [84, 85, 88, 90, 97-104].

In humans, nerves that contain VIP, NPY, PACAP, NOS, and ***CGRP, have been demonstrated*** in the vagina [105-109]. Hoyle et al demonstrated a dense innervation of the vaginal vasculature (arteries, veins and subepithelial plexuses). Most abundant were NPY and VIP immunoreactive fibers, less abundant were NOS, CGRP and SP fibers [108]. Human studies are crucial, however the major drawback is that the tissue studied comes from women undergoing hysterectomy. This is tissue from the proximal part of the vagina, less innervated and of different embryological origin than the denser innervated distal part [110] that may be of more importance in the physiological sexual arousal response. An exception is the study of Jorgensen et al who demonstrated NPY-immunoreactivity in both the proximal and distal parts of the human vagina as plexuses of nerve fibers beneath the vaginal epithelium in relationship to the small vessels [107].

In the human clitoris, limited immunohistochemical studies have demonstrated that the clitoris is innervated by VIP, PHM, NPY, CGRP and substance P immunoreactive nerves [111]. ***Signal transduction systems have also been investigated***. In cell cultures from human and rabbit vaginal smooth muscle, the signal transduction molecules cAMP and cGMP have been studied. In the vaginal smooth muscle cells cAMP was stimulated by PGE_1 and isoproterenol and cGMP by the NO donor; sodium nitroprusside, suggesting that these signal transduction pathways are of importance for regulation of vaginal smooth muscle tone. Furthermore, sildenafil enhanced the intracellular cGMP accumulation in the human and rabbit vaginal smooth muscle cells [112]. In the human vagina, PDE5 expression has been demonstrated in the anterosuperior vaginal wall [113].

c) The role of NANC transmitters in the arousal response.

Very little is known about the role of these neurotramsmitters/mediators in the regulation of the genital arousal response in females. While their existence in the genital tract can be demonstrated, their functional role in the physiology and pathophysiology of genital arousal is unknown.

VIP has traditionally been considered to be the most important neurotransmitter in the regulation of human vaginal blood flow in the sexual arousal response. This assumption is based on 1) the high concentration of VIP in the tissue of the genital tract, 2) the close association of the genital vasculature and VIP containing nerve fibers, 3) the increase in the level of VIP in women from sexual arousal and 4) the increase of vaginal blood-flow in women from IV and subepitheal administration of VIP [109, 114-118]. This is only indirect evidence: further clinical studies must be performed in order to obtain more information. The role of VIP in the physiological arousal response needs to be investigated further.

During the last ***few*** years the role of NO in the arousal phase have been studied with more interest, partly based on the knowledge from males where NO is known to play a crucial role in the erectile response. New *in vivo* models on rats, rabbits and dogs have made it possible to investigate vaginal and clitoral blood flow, vaginal oxygen tension, vaginal temperature and vaginal luminal pressure as markers of sexual arousal. [31, 119-123].

In the *in vivo* animal models, pelvic nerve stimulation (PNS) increases vaginal blood flow and temperature as well as clitoral blood flow [34, 120, 122]. Stimulation of the pavertebral sympathetic chain reverses the PNS induced effect in the rat [34]. In both the rabbit and the dog model, the PDE5-inhibitors sildenafil and vardenafil respectively enhanced the PNS induced vaginal and clitoral blood flow indicating that the NO/cGMP pathway is involved in

the physiological mechanism of female genital arousal [123, 124].

A role of the NO/cGMP system on clitoral erection is further indicated by *in vitro* animal experiments. In rabbit, clitoral corpus cavernosum inhibition of NOS dramatically abolishes electrically stimulated relaxation, whereas sildenafil augments the relaxation [89, 125, 126]. In human clitoral tissue, sildenafil has been demonstrated to inhibit PDE5 [127], and immunohistochemical studies have identified NOS immunoreactive nerve bundles within the glans and corpora cavernosa of the clitoris [128].

Clinically, sildenafil has been shown to enhance vaginal engorgement during erotic stimulus in healthy women without sexual dysfunction [129]. Several trials are being performed investigating sildenafil as a treatment for arousal disorders [130,131]. There are indications that the NO/cGMP system plays a role in the genital arousal response, but the exact role in the normal arousal response still needs to be investigated.

2. Pathophysiological factors that may influence the physiological genital arousal response

a) Diabetes

In rat models, diabetes mellitus (Type 1) induces vaginal fibrosis, measured as TGF-beta expression in collagen connective tissue, fibroblasts and smooth muscle fibers [132]. The nitrergic dependent relaxation of vaginal tissue is impaired during the diabetic state [90]. Park and colleagues also have demonstrated that type 1 diabetes mellitus in the *in vivo* rabbit model produces significant adverse effects on the hemodynamic mechanism of clitoral engorgement and leads to diffuse clitoral cavernous fibrosis [133].

b) Hypertension

In the rabbit, experimentally induced arteriosclerosis results in decreased PNS induced vaginal blood flow and vaginal wall pressure [31].

c) Conclusions and future directions.

The understanding of peripheral mechanisms and neurotransmitters regulating the female genital sexual arousal response is limited. Modulation of vaginal and clitoral engorgement, vasocongestion and vaginal lubrication may be antagonistic, regulated by parasympathetic and sympathetic components of the autonomic nervous system of the female genitalia. VIP and NO may be the primary facilitators with ***noradrenaline*** and NPY the primary inhibitors of the genital arousal response. There is a need to expand our current understanding of the physiological mechanisms responsible for the arousal response. Better understanding of the physiology and pathophysiology of genital arousal is necessary for improved clinical management of arousal disorders in women.

3. Arousal: nervous system in genital arousal

Our knowledge regarding human female sexual function is at its initial stages, and many important unanswered questions in this area still need to be investigated. Most of the information available is derived from animal studies or drawn by analogy from studies in males. The female animal studies have been predominantly focused on behavioral studies and on the central nervous control of genital responses. Data regarding the peripheral nervous system and in particular the genital somatic sensory information pathways are very limited, especially vis-à-vis arousal and orgasmic functions. Neurogenic female sexual dysfunction can result from disease of the central or peripheral nervous system. The effects of specific spinal or peripheral neural injuries on female sexual response is under investigation and will hopefully lead to improved understanding of the neurophysiology of orgasm and arousal in normal as well as women with sexual difficulties.

a) Peripheral innervations involved in female genital response

Innervations of the pelvic organs have been previously reviewed by several authors [134, 135], but most of the information available today has been extensively studied in the rat. [136, 137]. In general, innervations of the genitals are comparable between human males and females. Sexual arousal is a vascular and neuromuscular event controlled by facilitatory parasympathetic and inhibitory sympathetic inputs. Autonomic preganglionic parasympathetic fibers to the vagina and clitoris originate in the sacral parasympathetic nucleus at the spinal cord, and the sympathetic fibers at the thoracolumbar level. Parasympathetic fibers are conveyed by the pelvic nerve, sympathetic fibers by the hypogastric nerve and the paravertebral sympathetic chain. In addition, both the somatic pudendal nerve and, very likely, the afferent and efferent fibers of the vagus nerve contribute to the genital sexual response.

b) Autonomic innervation

Both the hypogastric (sympathetic) and pelvic (para-

sympathetic) nerves innervate the pelvic ganglion. Postganglionic fibers innervate the pelvic organs, including the bladder, urethra, accessory sex glands, vagina, uterus and clitoris. The cavernous nerve provides the vasodilatatory innervation to the clitoris.[138]. Identification of nerve fibers in the human vagina showed that there are significantly more fibers in the more distal part than in the proximal area. Moreover, the anterior vaginal wall that probably is the most sensitive part of the vagina displays a denser innervation than the posterior one [139]. The sacral parasympathetic nucleus neurons represent the main parasympathetic outflow to the genitalia in females. Preganglionic neurons of the hypogastric nerve emerge from the T12-L3 spinal segments from two separate nuclei, the dorsal gray commissure and the intermediolateral cell column, and represent the sympathetic outflow to the genital tract [140-142].

c) Somatic innervation

Anatomical studies show sensory fibers from the pudendal, pelvic and hypogastric nerves innervate the female pelvic organs. The pudendal nerve, which originates from the pelvic splanchnic branches of the sacral plexus, provides sensory innervation to the perineum, clitoris, and urethra. The motor axons originate in the spinal cord from two motor-neuron nuclei in the L5 segment of the spinal cord (dorsomedial and dorsolateral nuclei) [143]. Moreover, the motor innervation to the perineal striated muscle may be involved in the female sexual response, through voluntary contraction of the perineal muscle that can enhance arousal and play a role in the feeling of pleasure during intercourse [144].

Pelvic nerve sensory fibers innervate the vagina, cervix, and body of the uterus, with the greatest concentration in the fornix of the vagina [138]. The hypogastric nerve contains relatively few axons of afferent neurons, however, these neurons are important for conveying pain sensation from the uterus [142]. There is also some evidence that vagal fibers may convey sensory information from the female pelvic organs. This pathway remains functional after spinal cord transection and may account for the menstrual cramping and orgasm reported in women with complete spinal cord injury. [145, 146].

d) Spinal reflexes

Sexual arousal responses are mainly the product of spinal reflex mechanisms, and are under descending excitatory and inhibitory control from supraspinal sites. The afferent arm is primarily through the pudendal nerve. The efferent arm consists of coordinated somatic and autonomic activity. One spinal sexual reflex is the bulbocavernous reflex involving sacral cord segments S2-S4. Another reflex involves vaginal and clitoral cavernosal autonomic nerve stimulation, resulting in clitoral, labial and vaginal engorgement. [147].

The control of sexual function is based upon spinal mechanisms. The spinal cord provides the autonomic and somatic innervation of the sexual organs. Sensory information from the sexual organs project to interneurons in the lower spinal cord. These interneurons likely generate the coordinated activity of sexual responses.

III. AROUSAL: ROLE OF SEX STEROIDS MODULATING PHYSIOLOGY OF GENITAL AROUSAL IN FEMALES

1. Steroid biosynthesis and metabolism in women

Androgen hormones are a class of C-19 steroids, produced by the gonads and the adrenals [148, 149]. Steroids with androgenic activity include testosterone (T), α-dihydrotestosterone (5 DHT), Δ4-androstenedione, Δ5-androstenediol, 5α-androstane 3β 17β diol, dehydroepiandrosterone (DHEA) and 3 α-hydroxy androsterone (**Figure 3**).

a) Physiology of Androgen Hormones in Women

Androgens modulate the function of many organs and tissues in women including the pituitary, bone, adipose tissue, kidney, skeletal muscle, blood, ovaries, uterus, vagina, oviduct, clitoris and mammary gland and regulate secondary sex characteristics [150]. Androgens are not only essential for the development of reproductive function in women and hormonal homeostasis, but also represent the immediate precursors for the biosynthesis of estrogens. Androgens affect sexual desire, bone density, adipose tissue distribution, mood, energy and well-being. Consequently, imbalance in androgen biosynthesis or metabolism in women may have undesirable effects on female general health as well as sexual and reproductive functions [151].

b) Biosynthesis of Androgens in Women

Approximately 25% of androgen biosynthesis takes place in the ovaries, 25% is produced by the adrenal gland and the remaining is produced in the periphery [148, 149, 152]. In women, essentially all of the

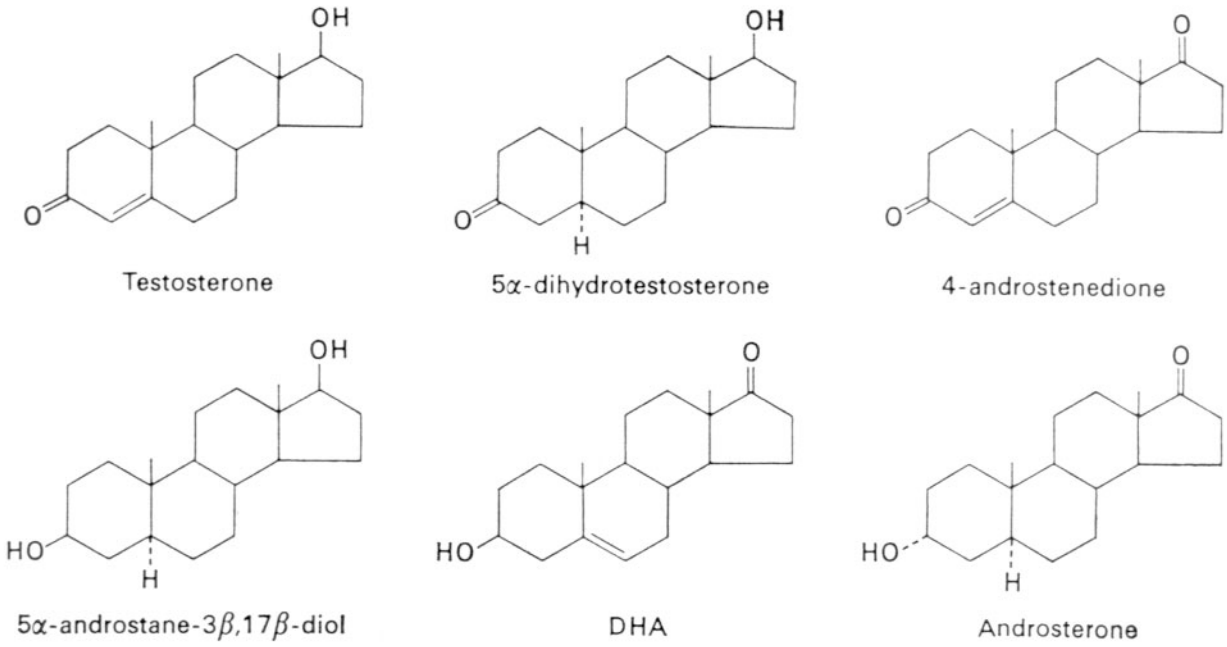

Figure 3 : Structures of some C19 steroids that possess androgenic activity.

androgens detected in the urine are of adrenal origin [150]. In Addison's disease, the output of urine androgens in the female approaches zero.

In the ovaries, cholesterol is metabolized to pregnenolone, which serves as the precursor for the synthesis of sex steroids. Biosynthesis of testosterone from pregnenolone proceeds via participation of several key enzymes in two interrelated pathways (*i.e.* Δ5or Δ4 pathways). In the Δ5 pathway, hydroxylation of pregnenolone by 17 α-hydroxylase and subsequent cleavage of the C-17,20 side chain by the C-17,20-lyase produces dehydroepiandrosterone (DHEA). The latter is converted to Δ5-androstenediol via 17β-hydroxysteroid dehydrogenase (17βHSD). This derivative is converted into testosterone by the enzyme complex, 3β-hydroxy Δ5 steroid dehydrogenase (3βHSD), Δ4,5 isomerase. In the Δ4 pathway, pregnenolone is converted first into progesterone by 3βHSD, Δ4,5 isomerase. Progesterone is then hydroxylated at the C17 position by the 17α-hydroxylase and becomes the substrate for the C-17,20-lyase, which converts 17α-hydroxyprogesterone to Δ4 androstenedione. The latter product is metabolized to testosterone by the action of the 17βHSD.

Synthesis of estrogen from androgens in the ovary is believed to involve both the thecal layer and the granulosa. The theca cells have a rich blood supply and steroids synthesized in the theca can readily pass into the circulation. In contrast, the granulosa cell layer is relatively avascular and steroids formed in these cells cross into the theca interna in order to enter the circulation. Both the theca and the granulosa express the aromatase enzyme systems for synthesis of estrogens. In the theca cells androstenedione and estradiol are derived from 17-hydroxypregnenolone (Δ5 pathway). In the granulosa, pregnenolone is readily converted into progesterone suggesting a Δ4 pathway. Estradiol is the major steroid detected in ovarian venous blood. The estrogen yield is approximately 10 fold greater from 4-androstenedione than from testosterone.

The synthesis of estrogens from androgens is regulated by gonadotropic hormones, LH and FSH. FSH acts mainly on the granulosa cells while LH acts on multiple sites including the theca, stroma, luteal and granulosa. The theca interna expresses LH receptors which regulate androgen biosynthesis, mainly androstenedione and testosterone. Androgens (Δ 4-androstenedione and testosterone) produced by the thecal compartment diffuse into the follicular fluid where they are converted into estrogens by the granulosa cells or released into the ovarian vein. The granulosa cells express FSH receptors and increased FSH levels increase the number of FSH receptors

due to increased granulosa cell number. Furthermore, FSH upregulates the aromatase activity in the granulosa increasing the conversion of androgens to estrogens. Estradiol via autocrine or paracrine mechanisms increases the mitogenic activity, independent of that of FSH. Estradiol augments the activity of FSH in increasing aromatase activity and increasing the conversion of androgens to estrogens.

c) Androgen Biosynthesis in the Adrenal Gland

In the adrenal gland, cholesterol is metabolized to pregnenolone, which serves as the precursor for the synthesis of glucocorticoids and androgens. Biosynthesis of androstenedione from pregnenolone proceeds via participation of several key enzymes. Hydroxylation of pregnenolone by 17α-hydroxylase and subsequent cleavage of the C-17,20 side chain by the C-17,20-lyase produces dehydroepiandrosterone (DHEA). The latter is converted to Δ4-androstenedine via the enzyme complex, 3β-hydroxy Δ5 steroid dehydrogenase (3βHSD), Δ4,5 isomerase. The latter product is metabolized to testosterone by the action of the 17βHSD (**Figure 4**).

d) Peripheral Conversion of Androgens in Target Tissues

Conversion of precursor steroids, derived from adrenal or ovarian origin, into active androgens in peripheral tissues is an important pathway of androgen metabolism [149, 153]. Thus, DHEA and Δ4-androstenedione may be converted into testosterone and 5α-DHT in target tissues [149, 150, 152]. Labrie and his colleagues [153] suggested that in post-menopausal women almost 100% of active sex hormones are derived from peripheral conversion of the steroid precursor DHEA and DHEA-S into active estrogens and androgen hormones. This concept suggests that active androgen hormones could be made on demand by the target tissues from precursors of ovarian or adrenal origin. This would also suggest that in many tissues conversion of DHEA and Δ4-androstenedione from adrenal or ovarian origin to testosterone and estradiol may take place.

The conversion of DHEA and Δ4-androstenedione into specific metabolites in the peripheral target tissues is catalyzed by tissue-specific, unidirectional 17β-HSDs [152]. A family of several enzymes have been cloned and characterized to date. These enzymes may play an important role in providing target tissues with active sex steroid hormones, via a well-controlled intracellular pathway. Thus, local conversion of DHEA or DHEA-s into 4-androstenediol (via 3 β-HSD) or Δ5 androstenediol (via 17 β-HSD) leads to production of testosterone. Testosterone may be converted locally into 5α-DHT (via 5 α-reductase) or into estradiol (via the aromatase). Δ4-androstenedione may be converted locally into estrone via the aromatase and into estradiol via 17 β-HSD [152]. Since specific target tissues express specific and selective isoforms of 17 β-HSD, it is likely that conversion of the adrenal androgen precursor into active androgen derivative is regulated by the tissues' specific physiological requirements.

e) Alterations in Ovarian or Adrenal Androgen Biosynthesis and Metabolism may lead to Androgen Insufficiency in Women

The concept of androgen insufficiency in women, in particular in pre-menopausal women, is controversial. Nevertheless, potential metabolic alteration in steroid biosynthesis in the ovaries or the adrenal may lead to reduced synthesis of androgens. In the ovaries, conversion of Δ4- androstenedione into estradiol is the predominant pathway.

It is possible that under certain pathophysiological conditions the ovaries continue to produce Δ4-androstenedione as an androgen precursor for estrogen biosynthesis but an inadequate production of androgen results, due to shunting of the Δ4-androstenedione to the aromatase or lack of 17β-HSD. Thus, in pre-menopausal women, sufficient estrogen levels may be reached with concomitant reduced levels of androgens. In addition, if reduced output of androgens from the adrenal due to other pathophysiological conditions is coupled with inadequate synthesis of androgen in the ovaries, then it is expected that the pre-menopausal woman would continue to have a menstrual cycle but with androgen insufficiency.

Data on serum androgen levels in healthy, pre-menopausal women without any symptoms of androgen insufficiency is lacking. It is necessary to establish normal and low serum androgen values in healthy subjects. Methodological differences in measurements of serum androgen levels further contribute to the difficulty in defining reduced levels of serum androgens in women. The fact that androgens are derived from multiple endocrine (ovaries and adrenals) and non-endocrine (peripheral) sources contributes further to the difficulty in defining the pathophysiology of androgen insufficiency in women. Testosterone and Δ4-androstenedione synthesized by the ovaries are utilized as substrates by the aromatase in the theca and granulosa cells. Thus, diffusion, compartmentalization, and expression of target-specific enzymes involved in the metabolism of andro-

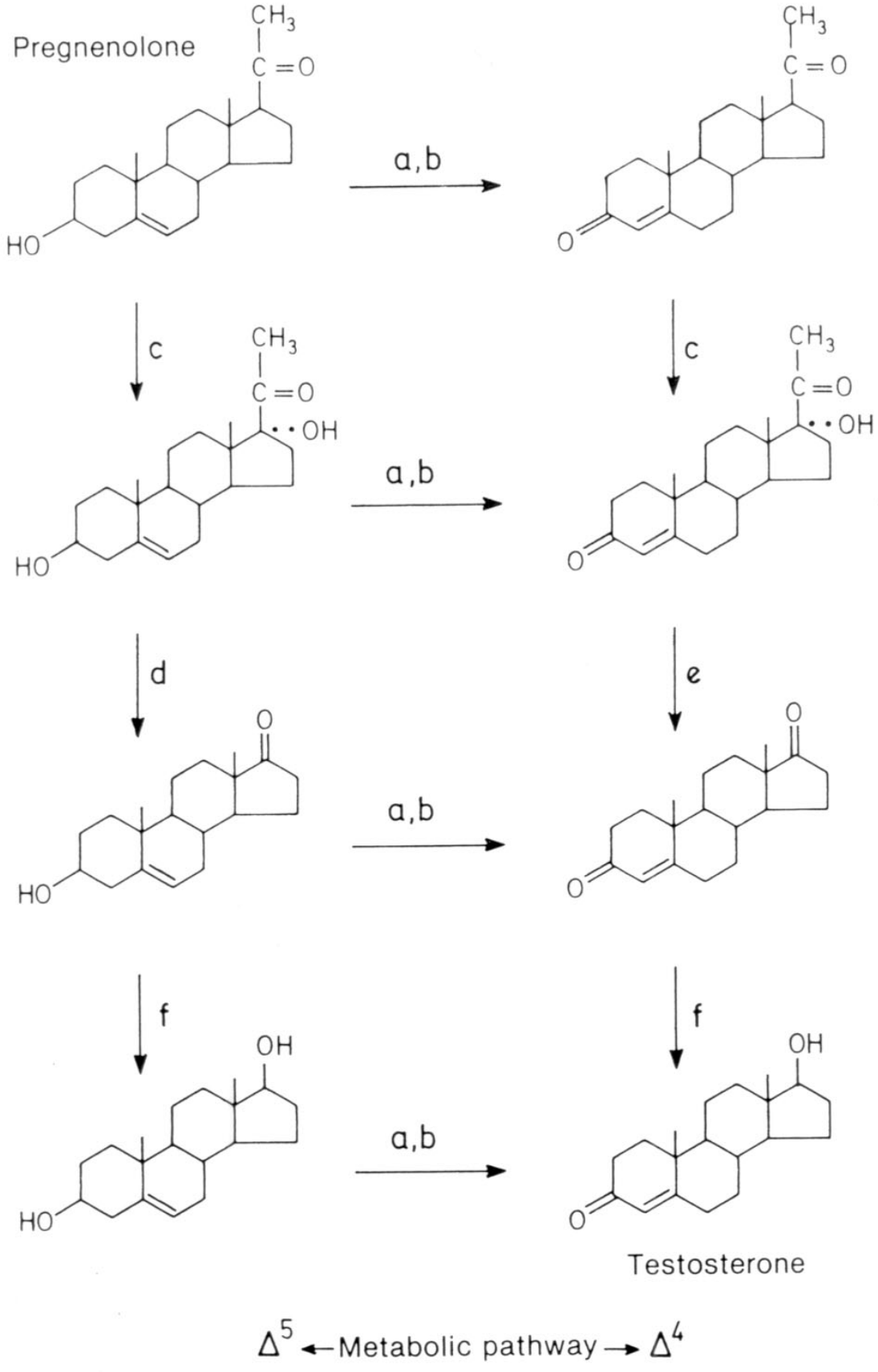

Figure 4 : iogenesis of testosterone from pregnenolone.

gens may determine the amount of androgens utilized by the aromatase and that available to enter into the circulation. It has been shown that in the early follicular and late follicular phases, the levels of Δ4-androstenedione are far greater than that of testosterone in the ovarian venous plasma. Another possible reason for reduced plasma androgen levels is the potential increase in peripheral catabolism of testosterone.

f) Effects of Plasma Binding Proteins on Availability of Bioactive Androgens

Sex hormone binding globulin (SHBG) binds testosterone and estradiol with high affinity but does not bind androstenedione or estrone. The concentrations of SHBG increase in response to estrogens, and during pregnancy increase five fold. SHBG synthesis is influenced not only by estrogens but also by thyroid hormones.

It is presumed that the free fraction of sex steroid hormone that enters the cells elicits the biological response. Thus the availability of bioactive hormone is dependent on the level of plasma binding proteins and the affinity of these steroids for the protein. Since the free hormone also acts on the pituitary to regulate further synthesis of steroids, and the free hormone is preferentially inactivated by the hepatic metabolism, one would suggest that plasma proteins play an important role in regulating the bioavailable steroids in the plasma. It is unclear, however, what role the plasma binding proteins play in physiological response. Thus, plasma sex steroid binding proteins may act as depot storage and transportation of sex steroids from the site of synthesis to the target tissue. It is difficult to speculate that changes in the levels of SHBG may contribute to androgen insufficiency in women. This needs further investigation.

2. Modulation of female genital sexual arousal by sex steroid hormones

Pre-clinical and clinical studies suggest that estrogens modulate genital hemodynamics and are critical for maintaining structural and functional integrity of vaginal tissues [29, 155-157]. Estrogen-depletion resulted in a significant reduction in vaginal blood flow following pelvic nerve stimulation, when compared to controls. Estrogen replacement increased genital blood flow and lubrication [29, 157, 158]. Evidence suggests that estrogens may modulate blood flow by regulating the activity of neural and endothelial NO synthase and VIP in the vagina [104, 159-162]. In estrogen-deprived animals, vaginal lubrication was markedly decreased compared to controls and was restored by estrogen treatment [29]. Vaginal mucification was reduced by estrogen administration in ovariectomized animals [163]. There are limited studies examining the effects of estrogens on vaginal smooth muscle contractility. Recently, Kim et al. [164] demonstrated that electric field stimulation and VIP caused frequency- and dose-dependent relaxation of vaginal tissue strips. These responses were slightly attenuated in ovariectomized animals and significantly inhibited in estrogen treated animals.

Although clinical studies have indicated that androgens modulate sexual arousal responses [165-170], no investigations have addressed the mechanism by which androgens facilitate such responses. Preliminary studies from our laboratory have shown that androgen treatment of ovariectomized animals enhanced vaginal smooth muscle relaxation in response to electrical field stimulation [164]. In addition, androgen treatment normalized VIP-induced smooth muscle relaxation, suggesting that androgens modulate neurotransmitter function. Kennedy and Armstrong [171,172] have shown that androgens increase vaginal mucification in the rat. Treatment of ovariectomized rats with topical DHEA resulted in complete reversal of vaginal atrophy and stimulated proliferation and mucification of the vaginal epithelium [149]. Furthermore, preliminary data from work by Traish and Kim suggests that androgens maintain vaginal mucification in rabbits. Recent work has suggested that progesterone is an important signaling molecule in peripheral nerves, where it promotes myelin sheath formation by activating expression of specific hormone sensitive genes [173]. However, the role of progesterone on peripheral vaginal arousal is poorly understood. In the following section is a brief discussion of the experimental data on sex steroid hormones in modulating the physiological process of arousal. Specifically discussed is the role of steroid hormones in modulation of i) blood flow, ii) lubrication, iii) neurotransmitter function, iv) smooth muscle contractility), v) mucification, and vi) sex steroid receptor expression in genital tissues.

a) Modulation of Genital Blood Flow by Estrogens and Androgens

Although sexual receptivity in the female of lower animals is controlled by estrogens, sex drive in women is not stimulated by estrogen, as experienced in clinical studies. However, administration of androgens in females intensifies sexual interest

[149]. Clinical and pre-clinical studies strongly support a role of estrogens in modulating genital blood flow [29, 157,158]. In an animal model, it has been shown that treatment of ovariectomized animals with estradiol or estradiol plus testosterone increased pelvic nerve-stimulated genital blood flow when compared to controls [29, 154, 158]. Treatment of ovariectomized animals with testosterone alone did not result in increased genital blood flow [158]. These observations suggest that estrogens regulate the vascular components of genital tissues and androgens markedly facilitate genital blood flow in estrogenized animals

b) Modulation of Vaginal Lubrication by Estrogens and Androgens

Vaginal lubrication is an indicator of tissue health and genital sexual arousal and facilitates sexual intercourse. The decline in circulating estrogen levels associated with menopause is thought to be responsible for many of the sexual complaints seen in post-menopausal women [157, 174]. Estrogen deprivation may lead to decreased pelvic blood flow resulting in diminished vaginal lubrication, clitoral fibrosis, thinning of the vaginal wall and decreased vaginal submucosal vasculature [155]. In addition, estrogen deficiency leads to involution and atrophy of the genital organs, adversely affecting cervical, endocervical, and glandular mucin production. In contrast, estrogen therapy in post-menopausal women increases pelvic blood flow, re-establishing vaginal integrity and lubrication.

The effects of ovariectomy and estrogen replacement on vaginal lubrication were investigated in an animal model. Ovariectomy markedly diminished vaginal lubrication, suggesting that genital atrophy and diminished genital blood flow, secondary to estrogen deprivation, may bring about structural and functional changes in the genital tissues that negatively affect lubrication. Treatment of ovariectomized animals with estradiol significantly increased vaginal lubrication. Interestingly, treatment with testosterone alone did not improve vaginal lubrication [29]. The data in this study demonstrate that estrogen replacement in ovariectomized animals normalized vaginal lubrication to levels observed in control animals. These observations suggest that estrogen therapy in post-menopausal women with complaints of diminished vaginal lubrication and genital atrophy may restore vaginal lubrication and health.

c) Regulation of Vaginal NOS Activity by Estrogens and Androgens

The role of NOS/cGMP pathway in regulating genital blood flow has been under investigation. Traish et al and others have demonstrated the expression of phosphodiesterase type 5 in the vagina [112, 113], suggesting a role for this enzyme in regulating the second messenger cGMP. Cellek and Moncada [89] have shown that the clitoral corpus cavernosum relaxes in response to NO and that this response is facilitated by PDE type 5 inhibitors. Kim et al. reported that NOS plays an important role in stimulating blood flow in an animal model [28] and that inhibition of NOS by administration of LNAME resulted in reduced vaginal blood flow. The effects of androgen and estrogen deprivation and replacement on the expression and activity of NOS in rabbit vaginal tissue were investigated [175]. Androgens enhanced and estradiol down-regulated NOS activity and protein in the vagina of ovariectomized rabbits.

Observations were in agreement with those reported by Batra and his colleagues with estrogen and progesterone in the rabbit model [104, 159- 161, 175, 176]. The significance of down-regulation of NOS by estrogens and its up-regulation by androgens on vaginal hemodynamic parameters remains to be determined. Several clinical studies with sildenafil in women produced contradictory results [130-132, 177, 178]. It remains to be determined, however, if the endocrine status of the patient may play an important role in determining whether PDE type 5 inhibitor will be effective in facilitating genital arousal response.

d) Effects of androgens and estrogens on vaginal smooth muscle contractility

In the female animal model, pelvic nerve stimulation induces a coordinated peripheral genital swelling and lubrication response, increased clitoral and vaginal blood flow, increased length and diameter of the vaginal canal and clitoral corpus cavernosum, increased tissue pressure and engorgement of the vaginal wall and clitoris, and development of a transudate of lubricating fluid from the vaginal vasculature.

The changes in the tissue properties of the vaginal canal are in part regulated by smooth muscle contractility. It has been demonstrated that ovariectomy reduces smooth muscle relaxation to electric field stimulation and to VIP in organ bath studies [164]. Estrogen treatment of ovariectomized animals reduced the relaxation response. In contrast, androgen treatment facilitated VIP-induced relaxation. These observations suggest that androgens facilitate vaginal smooth muscle relaxation while estrogens attenuate this response [164].

e) Effects of ovariectomy and estrogen replacement on vaginal sialic acid content (mucification)

It has been suggested that mucin production in the vagina is stimulated by low doses of estrogen and is reduced by high doses of estrogen [163, 179, 180]. The effects of estradiol on production of sialic acid in the rabbit vagina were investigated by Traish and Kim (unpublished data). One group of animals remained intact and four groups underwent bilateral ovariectomy. Two weeks post-ovariectomy, animals were treated with vehicle, estradiol or testosterone. The ovariectomized, vehicle treated group showed a significant decrease in vaginal sialic acid concentration compared to the control group. Animals treated with estradiol demonstrated further decreases in vaginal sialic acid concentration, whereas no changes were observed with testosterone treatment, relative to the vehicle treated group. These observations suggest that estrogens regulate mucin production in the vagina, as demonstrated by reduced sialic acid content.

f) Effects of steroid hormones on estrogen and androgen receptors in the vagina

The vagina is a target tissue for sex steroid hormones. Several studies have shown the presence of steroid receptors by biochemical and immunochemical assays [181-188]. While the effects of steroid hormones on regulation of estrogen and progesterone receptor in reproductive organs have been extensively investigated [189], there are limited studies on the regulation of expression of sex steroid hormone receptors in the vagina. Steroid receptors are regulated differentially in different target tissues by sex steroid hormones. For example, estrogens increase expression of estrogen and progesterone receptors in uterine tissue [190]. However, in preliminary studies, we have observed that ovariectomy increased vaginal tissue content of ER alpha (Kim et al., unpublished observation). Further, estrogen treatment of ovariectomized animals reduced ER alpha expression in the vagina, as assessed by ligand binding studies and western blot analyses, suggesting tissue specific regulation of ER isoforms by estradiol. Androgen receptor expression is decreased by ovariectomy and was increased by estradiol or estradiol plus testosterone treatment, suggesting cross-regulation of AR by estrogens.

It has recently been reported that ERα expression is diminished or lost in the vagina of postmenopausal women, suggesting loss of physiological response mediated by this receptor isoform [188].

Since hormone therapy is utilized for management of post-menopausal women, it would be important to determine how sex steroids regulate the expression of vaginal steroid hormone receptors. Moreover, these studies will be invaluable to correlate the changes in receptor expression with changes in neurotransmitter function in modulating the physiological parameters of vaginal arousal (vaginal blood flow, lubrication, mucification and smooth muscle contractility).

3. SUMMARY

The important role sex steroids play in modulating sexual function in women has been recognized for many years. Receptors for sex steroid hormones (estrogens, progestins and androgens) are widely expressed in the brain and genital tissues suggesting that steroid hormones may modulate sexual function at the central level (desire and arousal) as well as the peripheral level (genital, arousal,). Sex steroid hormones are critical in maintaining structural and functional activity of genital tissue and therefore may be critical for genital arousal physiology (genital blood flow, lubrication, mucification, and sensation). (**Figure 5**) While the effect of androgens on sexual desire is fairly established, the role of sex steroid hormones on genital sexual arousal is not well understood. Sex steroid hormones' modulation of genital tissue hemodynamics and genital arousal responses is an area that had received limited attention. Decreased circulating levels of estrogen following bilateral oophorectomy in the rabbit altered nerve-mediated vaginal blood flow and vaginal structure [157] and lubrication [158].

Administration of estrogen to ovariectomized animals increased genital blood flow [157, 158] and restored vaginal lubrication [29, 158]. Nevertheless, the cellular and molecular mechanisms by which estrogens regulate vaginal blood flow and lubrication remains poorly defined. Frequency- and dose-dependent relaxation of vaginal tissue strips caused by electric field stimulation and VIP were attenuated in ovariectomized animals, enhanced by androgen treatment and significantly inhibited in estrogen treated animals [164]. Androgens increase vaginal mucification in the rat [171, 172]. Estrogens reduced vaginal mucification [163].

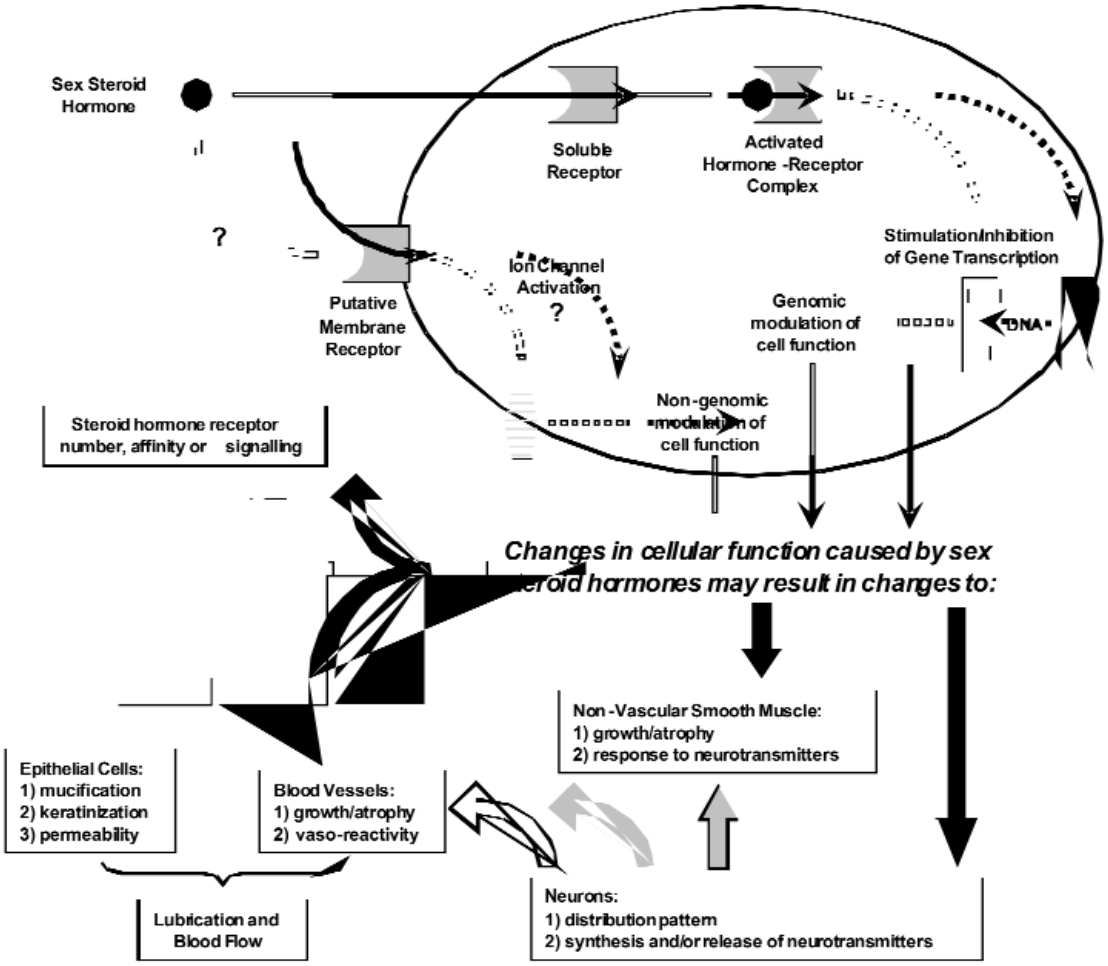

Figure 5 : Working model: Cellular mechanisms by which sex steroid hormones regulate vaginal arousal.

IV. PHYSIOLOGY OF ORGASM IN FEMALES

1. Animal models of female sexual function

Few animal models have attempted to mimic the physiological changes that occur during orgasm in women since one cannot determine whether an animal 'experiences orgasm', unlike men where orgasm and ejaculation are related and relatively easily measured. Therefore, an appropriate model for orgasm in females has to rely on mimicking the physiological changes that occur during orgasm. Models developed to date to study female sexual function include lordosis, a hormone dependant behavior that examines the receptivity of the females [191, 192], pacing and proceptive behavior [15, 193], vaginocervical stimulation [194-197], and urethrogenital reflex [198, 199]. Other researchers have measured changes in vaginal and clitoral blood flow, temperature and secretions [34, 123, 126]. Due to delayed development of an appropriate model for female orgasmic reflexes and its implications, most studies to date have been performed in males with only a few studies in the last decade in females.

a) Urethrogenital reflex – a model of 'climax'

The urethrogenital (UG) reflex model mimics the genital changes seen during 'climactic' responses. The UG reflex is a sexual response generated by a multisegmental spinal pattern generator involving the coordination of sympathetic, parasympathetic and somatic efferents innervating the genital organs. The neural responses are similar in males and females; the reflex is a spinal reflex, similar to the

orgasmic reflex described in spinal cord injured patients [200, 201]. In the acutely spinalized female rat, genital stimulation evoking the UG reflex results in rhythmic contractions of the striated perineal muscles as well as vaginal, anal and uterine contractions [198, 202]. Recordings in women during orgasm have shown coordinated rhythmic contractions of the vagina and anal sphincter that are virtually identical to recordings obtained during the UG reflex in the female rat [198, 199, 203, 204]. The UG reflex model has been used to examine the CNS control of genital reflexes (**Figures 6 and 7**).

b) Peripheral regulation of orgasmic reflexes

Orgasmic reflexes are regulated by both the somatic and autonomic nervous systems. The pudendal (somatic) nerve relays sensory stimuli from the external genitals, the perineum, clitoris and urethra, and the pelvic floor musculature. These sensory signals are essential for the urethrogenital (UG) reflex, [198, 205] and lordosis behavior [192]. The pelvic and hypogastric nerves mediate sensory information from the internal pelvic organs. Light touch, noxious or chemical stimuli of the vagina, cervix, and uterus are primarily mediated via the pelvic nerve [206-208]. The pelvic nerve is also vital for pregnancy or pseudopregnancy induced by mating or cervical stimulation [209-211]. The hypogastric nerve afferents that innervate the uterus, cervix, and ovaries may be important in the transmission of noxious stimuli from the uterus and genital vasocongestion [200, 201, 212-214].

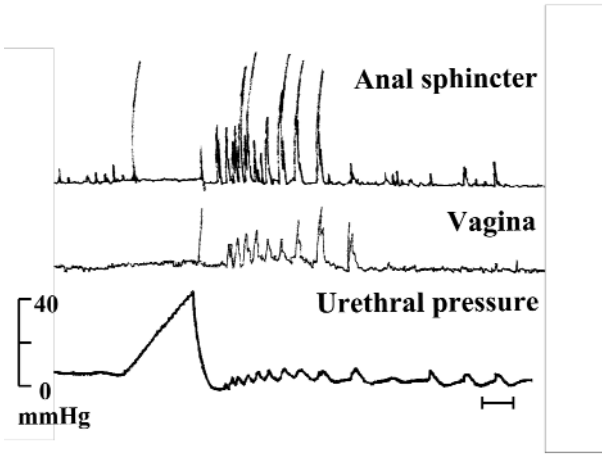

Figure 6 : The UG reflex in a female rat

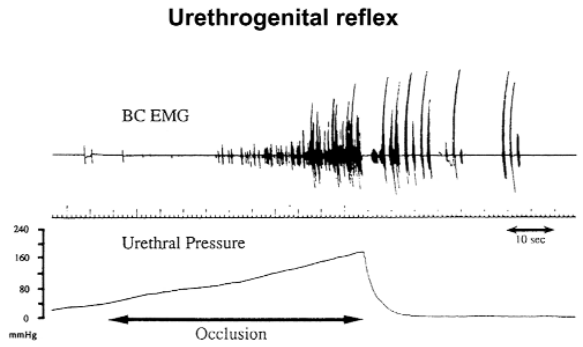

Figure 7 : The UG reflex in a female rat

While the pelvic and hypogastric afferents are not essential for evoking the UG reflex, their role in mediation of other sensory inputs during orgasm is unknown. Neural activity in the pelvic, pudendal and hypogastric nerve afferents are sensitive to the level of gonadal steroid hormones [206. 212. 213, 215-217], therefore these nerves may be important in hormone sensitive reflexes.

c) Non-spinal pathway (vagus nerve)

Evidence suggests that the vagus nerve conveys sensory information from female pelvic organs to nuclei in the brainstem [145, 218-220]. The vagal pathway appears to remain functional after spinal cord transection and has been implicated in menstrual cramping, analgesia, and the psychological feeling of orgasm in women with complete spinal cord transection. Electrophysiological studies in the rat support the idea of a vagal-genital pathway, but clear evidence for a direct pathway involved in genital organ responses remains to be clarified. Recordings of neurons in the nucleus tractus solitarius respond to mechanical stimulation of the vagina, uterine horn and cervix [221]. These responses were eliminated by spinal cord transection suggesting an essential spinal pathway. However, evidence for a direct link between the nucleus tractus solitarius and uterus was also provided. These authors concluded that the vagal nerve may act in a facilitatory role supplemental to the spinal pathways. The UG reflex is not abolished by vagal nerve cuts in the acutely spinalized, anesthetized female rat [222] and therefore is not dependant on vagal pathways. It is unclear whether the vagal pathway is supplemental to the spinal systems, or whether this pathway is activated after spinal damage. Further animal studies and verification of this hypothesis in clinical studies is required.

d) Peripheral nerve inputs to the spinal cord

Animal studies (primarily performed in rats) have examined the neuroanatomical pathways of the nerves involved in sexual function. The pudendal nerve afferents enter the spinal cord through the superficial dorsal horn of segments L6-S1 (human - S2-S4) and travel through the medial dorsal horn to the dorsal gray commissure, which is located in the medial cord [143, 223, 224]. Pelvic afferents terminate primarily in spinal segments L6-S1 (sacral cord in humans). The fibers course through the lateral dorsal horn and extend toward the intermediolateral cell column. In addition, some fibers course through the medial dorsal horn and enter the medial gray [140, 225, 226]. The hypogastric nerve afferents terminate in the medial dorsal horn and medial gray of spinal segments T13-L3 [227].

e) Ascending and Descending Spinal Pathways

The spinothalamic and spinoreticular pathways relay sensory information to the brain. Primarily these pathways travel in the dorsal columns and dorsal lateral quadrant and consist of fast myelinated fibers which terminate in the thalamus [228-230]. Most of the spinoreticular fibers cross to the opposite side of the cord (below T8) and travel in the lateral spinal columns terminating in brainstem reticular formation [230]. Descending information from the brain also passes through the dorsal and dorsolateral white matter before entering the spinal gray; the majority of the fibers of these pathways are crossed.

Recent studies in the rat have identified a group of spinothalamic neurons that may be involved in ejaculation [231, 232]. These neurons, located in the lumbar cord, contain galanin, cholecystokinin and enkephalin [231-233]. C-fos is an immediate early gene that can be visualized in activated CNS neurons using immunocytochemistry [234, 235]. Using double labeling of fos and galanin, it was reported that galanin containing cells in L3-L4 of the spinal cord were activated with ejaculation and the UG reflex in the male but were not activated with vaginocervical stimulation in the female. Further studies examining the role of these neurons are required to clarify whether or not they have a role in female orgasmic responses.

2. EFFERENTS MEDIATING GENITAL RESPONSES

Orgasmic responses of the genital organs are mediated through autonomic and somatic efferents. These responses are regulated in a coordinated fashion. The efferent fibers of the pudendal nerve provide innervation of the pelvic floor and anal and urethral sphincters [143, 236]. The pudendal motoneurons are located in the ventral horn of the lumbar spinal cord in Onuf's nucleus, which in the rat is divided anatomically into the dorsomedial and dorsolateral nuclei [143, 237]. Application of neuroanatomical tracers to the rat pelvic nerve resulted in labeling of the parasympathetic preganglionic neurons (the sacral parasympathetic nucleus), primarily in the lumbosacral spinal cord [226, 238]. Application of tracers to the hypogastric nerve resulted in labeling of the sympathetic preganglionic neurons in the upper lumbar spinal cord [141, 238, 239]. The preganglionic neurons were found in the medial gray and intermediolateral cell column.

a) Spinal Interneurons/ spinal pattern generator

The genital afferent input to the spinal cord relays through spinal interneurons, which eventually send signals to the efferent neurons that control the pelvic organs. The sensory information is also sent to other spinal segments and to the brain. Sexual reflexes occur in a coordinated fashion, therefore important spinal interneurons that transverse multiple spinal segments must regulate this coordination. A number of electrophysiological, anatomical, and functional studies have provided some information concerning the location of these spinal interneurons.

Anatomical transneuronal tracing studies using the neurotrophic virus, pseudorabies virus (PRV), have demonstrated the spinal neurons that innervate the pelvic organs. PRV was injected into the clitoris and uterus of female rats [142, 240, 241]. Postganglionic neurons were found in the major pelvic ganglia. Sympathetic and parasympathetic preganglionic neurons were also labeled. Spinal interneurons were located in and around the intermediolateral cell column and in the medial gray forming a column of neurons through segments T13-S1. These studies suggest that spinal interneurons involved in sexual function course through the lower thoracic lumbosacral cord in the lateral and medial gray. These cells may be important in the integration of pelvic responses seen during sexual behavior.

Electrophysiological recordings in the cat have also suggested that interneurons in the medial gray are important in mediation of pelvic visceral and perineal stimulation [242-244].

Activation of c-fos, an immediate early gene, has been used to identify spinal and brain neurons that are activated during sexual function [202, 245-247]. Activation of the UG reflex led to increased activity

in spinal circuits that span multiple segments. The spinal circuits involve an afferent arc via the pudendal nerve and efferent outputs via the parasympathetic and sympathetic nerves (pelvic and hypogastric). In addition, fos positive nuclei were found throughout the dorsal horn suggesting that the dorsal horn neurons form connections within the superficial laminae and these cells may be important in coordinating intraspinal and supraspinal information. Local interneurons in the lateral, intermediate and medial gray were associated with the preganglionic neurons [202]. These cells may represent components of the spinal pattern generator that regulates the UG reflex.

3. Pharmacological control of orgasm

Little is known about the pharmacological control of orgasmic reflexes in females. Similar pharmacological control in males and females is suggested due to the similar orgasmic dysfunctions in both sexes with the same class of drugs (e.g. SSRI, antihypertensive). While some information is known about the local neurotransmitters subserving blood flow to the penis and clitoris (e.g. NO, adrenergic etc) there is little known about the CNS neurotransmitters involved in mediating sensory and motor output during orgasm (see below). In male rats some evidence for a role for acetylcholine in erections, ejaculation and the UG reflex has been suggested [248, 249]. Since preganglionic and pudendal motor neurons contain acetylcholine, both spinal and peripheral mechanisms are possible. However, no studies have been done in females.

a) Supraspinal control: Inhibitory Control

The brain exerts an inhibitory and facilitatory influence on the spinal cord pathways involved in orgasmic reflexes. The nucleus paragigantocellularis (nPGi) exerts an inhibition of spinal sexual reflexes in males and females [250, Marson personal communication). Bilateral lesions of this nucleus release the inhibition of the UG reflex and facilitate ex copula sexual reflexes and ejaculation [250-252]. The nucleus paragigantocellularis projects directly to pelvic efferent neurons and interneurons in the lumbosacral spinal cord [202, 250, 253-255] and directly innervates spinal neurons activated with the UG reflex [202]. Neurons in this area are transneuronally labeled following virus injection of a variety of pelvic organs including the clitoris, uterus, penis, prostate and perineal muscles [142, 241, 251, 256, 257]. In addition, the nucleus paragigantocellularis receives genital sensory information in males and females [191, 258, 259]. Many bulbospinal neurons in this region stain for multiple neurotransmitters, including serotonin, and serotonin fibers are found in the spinal cord [260, 261]. Application of serotonin to the lumbosacral cord inhibits sexual reflexes in males [261]. Serotonin levels increase with the use of SSRI antidepressants and a higher incidence of orgasmic dysfunction is seen in both men and women using SSRI [262, 263]. This may be one mechanism of action. In addition, peripheral serotonin modulates the chemosensory pathways from the urethra [264]. However, other neurotransmitters such as thyrotropin-releasing hormones may be involved in the inhibition of penile erections in males, although its role in orgasmic reflexes in females has not been examined [265].

b) Supraspinal control: Facilitatory control

Brain regions also facilitate sexual behavior. This is evident from psychogenic and nocturnal erections and arousal. It is well established that the medial preoptic area (MPOA) plays an important role in sexual behavior, especially in males. Lesions of this region severely attenuate or abolish male copulatory behavior in multiple species [68]. The MPOA does not appear to specifically regulate erections or sexual motivation, since medial preoptic lesions do not abolish erections caused by exposure to volatile odors from estrus females and masturbation [266-268]. However, stimulation of the MPOA induces the UG reflex and vaginal vasocongestion, and injection of galanin into the MPOA facilitates some female sexual behaviors [34, 269-272]. The MPOA does not directly innervate spinal circuits involved in sexual reflexes, therefore neurons in this region may relay various aspects of sexual behavior through other hypothalamic or brainstem nuclei [273-275]. Cells are activated in response to female sexual behavior in the MPOA [276-278]. Dopaminergic mechanism in the forebrain mediate some aspects of male and female sexual behavior [279-281], but the role of dopamine in orgasmic function in the female has not been studied.

The ventromedial nucleus of the hypothalamus is critical for the expression of lordosis behavior and neurons in this region are labeled following virus injection into the uterus and vagina [192, 241, Marson personal communication]. However, the relevance of lordosis to human sexual behavior has not been ascertained. Other brain regions may be involved in orgasmic reflexes such as the raphe magnus, Barrington's nucleus, periaqueductal gray, ventral teg-

mental area, paraventricular nucleus, medial amygdala, bed nucleus of the stria terminalis and the cerebral cortex. Most of these regions are labeled after transneuronal tracing of the genital organs and/or are activated with sexual behavior or project to the lumbosacral spinal circuits mediating orgasmic reflexes [142, 191 196, 241, 253, 254, 277, 278, 282-285], however their specific contribution to female orgasmic responses has yet to be determined.

C. HUMAN PHYSIOLOGY

I. AROUSAL

Arousal: Evidence-based data on genital blood flow and sexual arousal in women

Sex steroids play a crucial role in maintaining the anatomical and functional integrity of all the structures involved in women's sexual function [286, 287]. However, given the variety of physical, emotional and cognitive issues influencing women's sexual health [288-290], direct involvement of sex steroids in female sexual dysfunction (FSD) remains controversial. FSD may appear in all stages of the reproductive life cycle even though an age-dependent decline, which is particularly evident at the time of menopause, is highly present [291, 292]. Reproductive-related events (menstrual cycle alterations, infertility, pregnancy and lactation, etc.) and hormonal manipulations (hormonal contraception, use of antiandrogens and ovariostatic treatments such as GnRH analogues, exogenous oral estrogens, etc.) are associated with consistent changes in desire, arousal and orgasm in women [293]. Menopause may be considered a good clinical paradigm for studying the effects of sex steroid deprivation on women's sexual function [294, 295].

1. Sex steroids and women's sexual function

Sex steroids exert both organizational and activational effects which are relevant to sexual function, and their actions are mediated by nongenomic as well as direct and indirect genomic pathways [296-297]. Androgens are essential for the development of reproductive function and the growth and maintenance of secondary sex characteristics directly or through their conversion to estrogens [298]. Estrogens, as well, play a critical role in maintaining the physiological function of many tissues, including the central nervous system, the genital apparatus, and organs relevant to general health [299]. Sex steroids modulate cortical coordinating and controlling centers interpreting what sensations are to be perceived as sexual, and issue appropriate commands to the rest of the nervous system. In addition, sex steroids affect the sensitivity of both genital organs and hypothalamic-limbic structures where they elicit conscious perception and pleasurable reactions by influencing the release of specific neurotransmitters and neuromodulators [300]. Therefore sex steroids influence desire, arousal and orgasm throughout neuroendocrine and trophic actions in women.

a) Estrogens and women's sexual function

The importance of adequate estrogen levels in preserving vaginal receptivity and preventing dyspareunia has long been established. At a level of estradiol (E_2) less than 50 pg/ml, women reported vaginal dryness, increased frequency and intensity of dyspareunia, pain with penetration and deep insertion, and burning [301]. Women with higher E_2 levels had no complaints related to sexual desire, response or satisfaction. Indeed, E_2 levels below 35 pg/ml are associated with reduced coital frequency [302] and decline in estradiol is related to a decline in sexual functioning [303]. Vaginal dryness has been confirmed as the most important later consequence of hormonal changes during menopause [304], but pain during sexual intercourse seemed to reflect sexual arousal problems rather than be a pure consequence of vaginal atrophy [305]. Coitally active post-menopausal women were noted to have less genital atrophy in comparison to abstinent women and pre-menopausal sexual satisfaction was significantly associated with coital activity in elderly women [294]. The positive effect of E_2on mental well-being [306] may highly contribute to the maintenance of an active sexual life throughout the aging process.

b) Androgens in women

The major androgens in women include dehydroepiandrosterone sulphate (DHEAS), dehydroepiandrosterone (DHEA), androstenedione (A), testosterone (T) and dihydrotestosterone (DHT). However, DHEAS, DHEA and androstenedione are considered as pro-androgens because they require conversion to testosterone to express their effects. Androgen biosynthesis occurs both in the ovary and the adrenal under the stimulation by LH and ACTH, respectively, together with intraglandular paracrine and auto-

crine regulatory mechanisms. Two key enzymes are involved in androgen biosynthesis: P450 SCC and P450 c17, required for DHEA and androstenedione production from pregnenolone and progesterone, respectively. Substantial androgen production originates from circulating DHEAS, which is a unique secretory steroid of the adrenal zona reticularis, in target tissues [307]. The most potent androgen, testosterone, is secreted by the adrenal zona fasciculata (25%) and the ovarian stroma (25%), while the remaining amount (50%) derives from peripheral conversion of circulating androstenedione (308]. Plasma tesosterone levels are in the range 0.2 e 0.7 ng/mL (0.6-2.5 nmol/L), with significant fluctuations related to the phase of the menstrual cycle, being highest at ovulation, lowest during the early follicular phase and higher during the luteal phase as compared to the early follicular phase. In addition, tesosterone shows circadian variations, with a peak in the early morning hours. Testosterone is converted to DHT in target tissues; DHT is the principal ligand to androgen receptors but it can also be aromatized to estradiol [148].

Plasma testosterone levels fall slowly with age [309] and both free testosterone and androstenedione are produced in lesser quantity at midcycle in older women [310], without significant changes of testosterone during the menopausal transition [311]. At physiological menopause, the cessation of follicular activity is characterized by a significant decline of ovarian production of androstenedione, more than testosterone. The progressive fall of plasma testosterone concentrations is the consequence of the reduced peripheral conversion from its major precursor [312] and from DHEA and DHEAS, which decline with age [313]. Indeed, plasma testosterone and androstenedione levels of women in their 60's are about half those in women aged 40 years. As far as surgical menopause is concerned, bilateral oophorectomy both pre-menopausally and post-menopausally leads to a sudden 50% fall in circulating testosterone levels [314]. Recent data suggest that during postmenopause, approximately 100% of active sex steroids derives from peripheral conversion of precursors, mainly DHEA and DHEA-S, to estrogens and androgens [315]. This data support the concept that target tissues may represent a local source of testosterone and estradiol, starting from circulating ovarian and adrenal precursors. The key tissue-specific enzyme, responsible for peripheral conversion, is represented by the various forms of 17-b-HSD. Therefore, circulating levels may not even reflect the action of sex steroids in different target tissues [316]. Finally, it is important to note that SHBG, the protein binding circulating testosterone, plays an important role in influencing the free androgen index (FAI) during oral contraception and under oral, but not transdermal, administration of estrogens, at menopause [317, 318]. The increase of SHBG may be, indeed, responsible for FSD by lowering unbound steroid fractions which are the biologically active components.

c) Androgens and women's sexual function

While the androgen influence over women's sexual function has been hypothesized for a long time, it is only in recent years that basic research in laboratory animals and clinical trials with androgenic compounds are contributing to the understanding of the role of androgens on libido and sexual arousal [287].

Studies conducted in women of fertile age found an increase in the establishment of interpersonal relationships and exchange of sexual pleasure during the periovulatory period, corresponding to the plasma androgenic peak, even though no clear correlation has been reported between plasma androgen levels and sexual response [319, 320]. The strong motivation for sexual activity at the time of ovulation may be due to the peak of estradiol.

Some authors have reported that serum testosterone levels are related to genital response and to subjective physical sensation (lubrication and breast sensitivity) in response to visual erotic stimulation both in pre-menopause and post-menopause [321]. Moreover, anti-androgen administration has been associated with low libido in females [322]. Further evidence suggests that circulating free testosterone relates to sexual desire and masturbation in young women [323], while decreased free testosterone and DHEA-S were found in the majority of pre- and post-menopausal women complaining of decreased sexual desire [324]. While oral contraception seems to interfere with the spontaneous expression of sexual desire, the effects of the pill on mental well-being may play a role in sexual motivation [325, 326]. The relationship between sexual function and sex steroid changes from the use of oral contraceptives remains to be established, since women on the pill with lower androgen levels are those who declare a higher degree of sexual satisfaction [327]. No correlation has been established between the average levels of testosterone and sexual desire, sexual interactions, or autosexuality among contraceptive users, with only non-users reporting a decrease in levels of sexual

desire during the peri-menstrual period associated with the changes in free testosterone over the menstrual cycle [328]. By contrast, during the pill-free week, when testosterone levels were found more elevated in contraceptive users, many women reported an increase in sexual motivation [329]. Finally, 5a-reductase activity is significantly impaired in target tissues in those women reporting low libido following menopause [330], while a significant correlation has been found between high levels of circulating testosterone and androstenedine and a lower index of vaginal atrophy [331].

d) Androgen insufficiency syndrome

Surgical menopause is associated with the androgen insufficiency syndrome, an increasingly accepted clinical entity comprising specific symptoms [332]. The fact that androgens serve as precursors for synthesis of estrogens in women, and therefore serum levels of androgen are expected to be greater than estrogen plasma levels, suggest that androgen insufficiency may exist in pre-menopausal as well as post-menopausal women. Androgen insufficiency in both pre-menopausal and post-menopausal women is a valid clinical diagnosis, under specific conditions.

Clinical symptoms of androgen insufficiency include diminished well-being, lethargy, loss of sex drive and interest, unexplainable fatigue and blunted motivation. Other signs of androgen insufficiency include reduced pubic hair, bone mass, muscle mass, poor quality of life, and more frequent vasomotor symptoms, insomnia, depression and headache [333]. Androgen insufficiency occurs in a number of circumstances, including normal aging (physiological menopause without estrogen therapy and pre-menopausal women reporting low libido and with circulating free T levels at lower limits of detection), ovarian insufficiency (unilateral oophorectomy, hysterectomy, spontaneous premature ovarian failure, after chemotherapy, after radiotherapy, hypothalamic amenorrhea), adrenal insufficiency (adrenal failure or surgery), in combination (hypopituitarism, autoimmune adrenal and ovarian failure), iatrogenic (treatment with exogenous oral estrogens, anti-androgen therapy, oral contraceptives, GnRH agonist therapy or chronic exogenous corticosteroid administration) [334].

Despite the growing interest in treatment of sexual dysfunction with androgens in the clinical practice, no normal range of testosterone has been agreed upon. This lack of consensus of definition is due in part to the difficulties with the sensitivity of assays for total and free testosterone in women and the fluctuations during the menstrual cycle and menopausal status [333]. At present it is considered reasonable to use values at or below the lowest quartile of the normal range for women in their reproductive years to support the diagnosis of androgen insufficiency syndrome. The biologically active androgen is testosterone, which circulates bound tightly to sex-hormone-binding globulin (SHBG) and loosely to albumin and transcortin. The fraction of testosterone which remains unbound to SHBG is deemed bioavailable. Thus plasma levels of total testosterone and free testosterone as well as SHBG need to be determined clinically. Treatments include estrogen therapy to restore adequate plasma estradiol levels in order to secure the vaginal environment, and after excluding other organic issues, androgen therapy to normalise androgen levels. Despite the lack of sensitivity of the assays and limited controlled clinical studies, an increasing body of evidence is emerging suggesting that women with signs and symptoms of androgen insufficiency respond well to androgen therapy without significant side-effects.

e) Estrogen and estrogen/progestin therapy

A recent systematic review including all randomized and placebo-controlled trials of treatment for FSD in postmenopausal women concluded that many treatments that are used in practice are not supported by adequate evidence [334]. Dyspareunia due to vaginal dryness appears to be most responsive to estrogen therapy (ET) via restoration of vaginal cells, pH, and blood flow [301]. Progestins can oppose these changes and lead to a recurrence of dryness and dyspareunia depending on their biochemical properties [336, 168]. However, even though estrogen therapy and estrogen/progestin therapy may be effective treatments for vaginal atrophy, increasing vaginal lubrication, they have not been shown to consistently increase sexual desire or activity and many women with FSD remain unresponsive [337]. There is a significant subgroup of women whose sexual difficulties respond initially to estrogen therapy but who subsequently revert to their initial problems, especially when that problem was loss of libido [338]. Studies conducted in the 1970's reported that vaginal dryness was significantly decreased with estrogen therapy but women did not find any changes in masturbation, orgasm, frequency of intercourse or coital satisfaction [339]. Other reports in surgically and naturally menopausal women treated with oral conjugated estrogens failed to demonstrate positive effects on libido [340, 341], while a signifi-

cant benefit of estrogen therapy on libido, sexual activity, satisfaction, sexual function and capacity for orgasm was found in Swedish post-menopausal women [342]. A randomized, double-blind, placebo-controlled, crossover trial of estrogen and progestin, alone and in combination, found beneficial effect of estrogen and estrogen/progestin therapy on sexual desire, enjoyment, orgasmic frequency and vaginal lubrication, with no difference in coital frequency on a short-term basis [343]. A recent study with transdermal estrogen therapy in postmenopausal women showed an improvement in satisfaction with frequency of sexual activity, sexual fantasies, vaginal lubrication and lack of pain during intercourse, without any effect on sexual arousal and frequency of orgasm [344].

Collectively, these data underline the evidence that estrogen and estrogen/progestin therapies are not univocally efficacious in treating female sexual dysfunction and the addition of androgen has proved helpful. However, it is necessary to investigate the differences, mainly on plasma sex steroid and SHBG levels, among various schemes of conventional hormone therapies in terms of type of molecule, route of administration, mechanism of action and metabolism.

f) Estrogen/androgen therapy

The most interesting findings on positive sexual effects of sex steroids at menopause come from studies with oral and transdermal combination of estrogens and exogenous testosterone. In the past, testosterone propionate administered twice weekly at a dose of 25 mg, starting on the 12th day of the menstrual cycle, and at a maintenance dose of 10 mg monthly thereafter, was effective in relieving menopausal symptoms in those women who did not have complete benefit with estrogen therapy [345]. While relieving hot flushes, estrogen/androgen therapy improved well-being and libido and produced a "smoother transition" [346]. In a series of surgically menopausal women treated with estrogen/androgen therapy, sexual arousal, desire and fantasies increased in comparison with estrogen therapy alone, and a positive effect on frequency of coitus and orgasm was particularly evident during the first 2 post-injection weeks [167]. In a pilot case series of non-responders to oral estrogen therapy, androgen therapy by implants was added with a significant improvement in libido, enjoyment of sex, ability to reach orgasm and initiation of sex [347]. Similarly, women on estrogen therapy complaining of loss of desire and reduced enjoyment of sex who were treated with estrogen/androgen therapy implants showed significant improvement with a marked change in orgasmic capacbility and initiation of sex when androgen therapy was added [169]. When post-menopausal women unhappy with their estrogen therapy regimen were randomized to receive either esterified estrogens or esterified estrogens with methyltestosterone for 8 weeks, a significant improvement of sexual sensation and desire was evident with a clear increase in vaginal blood flow measured by laser Doppler velocimetry [348]. Sexual function improved with estrogen/androgen therapy, even though circulating estradiol levels were lower than those measured during previous estrogen therapy, leading to the conclusion that androgens play a pivotal role in sexual function while estrogens do not have a significant impact on sexual drive and enjoyment [337]. The addition of testosterone undecanoate improved specific aspects of sexual function such as enjoyment of sex, satisfaction with frequency of sexual activity and interest in sex more than estrogen alone in ovariectomized women [349]. A reproducible result was obtained treating women with surgical menopause on estrogen therapy with two doses of transdermal testosterone (150 ug/ and 300 ug/d) versus placebo. A significant improvement in sexual function with a further increase in scores for frequency of sexual activity and orgasm when women were taking the higher dose was reported [350]. In this study, however, there was an extremely strong response in sexual function in women on placebo and 24% of study participants withdrew from the trial because of androgen-related adverse effects [350]. Therefore, the use of androgens in the clinical management of menopause needs a certain degree of caution, in particular because the long-term effects of such medications on women's general health are still unknown. The type and route of androgen therapy seem crucial given the evidence that oral methyltestosterone, and not transdermal testosterone, decreases SHBG production and affects bioavailable plasma sex steroid levels differently when combined with different types of estrogen therapy [348,350]. There is, however, no doubt that estrogen/androgen therapy is efficacious in treating FSD at menopause and should be use in clinical practice to improve sexual symptoms at menopause.

g) Other hormonal agents

Estrogen/androgen therapies are still unavailable in several countries. In Europe long-term experience with treating climacteric symptoms, depressed mood and libido is available with tibolone, a synthetic ste-

roid with tissue-specific estrogenic, progestagenic and androgenic properties [351, 352]. Apart from the direct effects of its metabolites in the vagina and brain areas relevant to well-being [353, 354], tibolone lowers SHBG, thus increasing free estradiol, testosterone and DHEA-S levels [355]. In randomized studies against placebo or estradiol/NETA, tibolone treatment alleviates vaginal dryness and dyspareunia, ameliorating issues with libido, arousal and sexual satisfaction in post-menopausal women to a greater extent [356, 357]. Moreover, tibolone shows a positive effect on sexuality which is reproducible with that observed with estro-androgenic preparations [358]. This data, together with the recent observation that tibolone significantly increases vaginal pulse amplitude at baseline and following erotic stimulation against placebo [359], further supports the notion that such a tissue-specific compound is a good therapeutic option to relieve decreased libido, arousal and lubrication at menopause because of its estrogenic and androgenic properties.

Concomitant administration of raloxifene, a selective estrogen receptor modulator (SERM), used in the prevention of menopausal osteoporosis, did not alter the effects of the 17β-estradiol ring on symptoms of genitourinary atrophy [360] and did not counteract the improvement of vaginal atrophy observed by use of either low-dose conjugated estrogen cream or non-hormonal moisturizer in post-menopausal women [361]. DHEA, as a precursor of estradiol and testosterone, has been proposed as the treatment for decreased libido in both pre- and post-menopausal women, with encouraging results [362, 363]. Studies conducted in elderly women have shown a positive effect of DHEA on mental well-being and on motivational aspects of sexuality with a mild relief of climacteric symptoms [364].

h) Conclusion

Better understanding of the role of sex steroid hormones in modulating female sexual function requires investigation of the biochemical, cellular and physiological mechanisms by which sex steroid hormones modulate sexual function in general and genital sexual arousal in particular in experimental models. With the emerging consensus on female sexual dysfunction and sex steroid insufficiency together with establishment of a host of experimental models and the advancement in biochemical and molecular biology approaches for pre-clinical research, it is anticipated that the coming years will bring advancement in knowledge resulting in better management of female sexual dysfunction by sex steroid hormones

Further studies are needed to clarify the relevance of sex steroids to women's sexual function and the impact of hormonal treatments on the clinical expression of sexual symptoms. Well-defined endpoints and outcomes and a general consensus on the diagnostic framework for assessment and treatment of FSD are important goals for the future of sexual health and well-being. Even from a hormonal perspective, FSD must involve a multidisciplinary approach to avoid dangerous body-mind separations.

Short-summary: Sex steroids are essential in women's sexual function, but their direct involvement in sexual dysfunction is controversial, due to the multidimensionality of women's sexual health. Both estrogens and androgens contribute to preserve libido, arousal and orgasm. Menopause, particularly when it occurs following surgery, is a good clinical paradigm for studying the effects of sex steroid deprivation on women's sexual function. Several estrogen therapy and androgen therapy protocols have been proposed to treat female sexual dysfunction (FSD); the combination of the two seemed the most effective in restoring sexual function. Other hormonal agents, such as tibolone and DHEA have been proposed with promising effects, however, a better understanding of the role of endogenous and exogenous hormones on women's sexual function is mandatory.

2. Sexual arousal in women

a) Vaginal lubrication, basal and during sexual arousal

During sexual quiescence the human vagina is a potential space with an H-shaped transverse cross-section and an elongated S-shaped longitudinal section. The anterior and posterior walls of the vagina are collapsed and touching each other. Nevertheless they do not adhere as they are covered with a thin layer of fluid allowing them to separate easily. No glandular elements have ever been identified in the normal human vagina. The fluid is mainly a vaginal plasma transudate mixed with desquamated cervical and vaginal cells and cervical secretion [365, 366] for review. The vaginal fluid is transudate from the circulating blood through the vessels underlying the vaginal epithelium. A plasma-filtrate from the blood leaks out of the capillaries into the interstitial tissue space. In the vagina the fluid then passes through the epithelium. In the sexually unstimulated state, the vaginal fluid has a higher K+ and lower NA+ concentration compared to plasma throughout the phases of the menstrual cycle [367, 368]. The basal transudate that percolates through the epithelium is

modified by the cells' capacity to reabsorb Na+ ions. During non-sexual stimulation the slow passage through the epithelium results in sufficient contact time, making the cells capable of reabsorbing Na+ by the vaginal epithelium and acting as the main determinant of reabsorption of vaginal fluid through the mechanism of ionic driving force. This leads to a basal condition where the vagina is moist, but not lubricated enough to have penetration without pain.

During sexual arousal the blood supply to the vaginal epithelium is rapidly increased as a consequence of neural innervation via the sacral anterior nerves (S2-S4) [369, 370]. The increased blood flow results in increased ultrafiltrate through the vaginal epithelium cells and thus a saturation of the limited reabsorptive Na+ transfer capacity of the cells. As a consequence of this, the liquid accumulates at the vaginal surface as clear, slippery and smooth lubricant, moistening the vagina so painless penile penetration and thrusting is possible. In addition to the increased blood flow, the venous drainage is most probably reduced, resulting in vasocongestion and genital engorgement, clitoral erection and increased genital sensitivity [366].

b) DSM-IV

In the current DSM-IV classification system, female sexual arousal is described entirely in terms of genital indices of a sexual response as the " lubrication-swelling response"[371]. The definition of female sexual arousal disorder (FSAD) is consistent with this definition. This is in sharp contrast with clinical practice where it is often the lack of subjective arousal that leads women to seek treatment. Women are, in contrast to men, relatively unaware of whether they are lubricating adequately or not and tend to define sexual arousal in terms of their subjective feeling state [372]. Lack of a physical sexual response usually leads to complaints of discomfort and pain and it is rarely presented in terms of a perceived incomplete or absent lubrication and/or swelling. Moreover, the problem in diagnosing female arousal disorder is related to the lack of specificity as to what exactly constitutes a 'normal sexual arousal phase'. Women vary greatly in the ease and latency of sexual arousal, and in what kind of sexual stimulation is adequate for sexual arousal to occur [373].

Although the DSM-IV classification system is widely accepted, it lacks objective, empirically grounded criteria. Actual clinical practice confronts us with a large comorbidity of sexual dysfunctions in women. Difficulties in differential discriminating between disorders may have to do with the lack of adequate physical markers for most of the disorders, inadequate theory, and the lack of normative data as to what is 'functional' and what is 'dysfunctional'. Lack of sexual arousal may well be the underlying mechanism for many different sexual complaints. Lack of sexual arousal is often related to inadequate sexual stimulation due to contextual and relational variables rather than to somatic causes.

c) Objective Measures of genital sexual responses

Physiological measures for the assessment of sexual arousal in women have a relatively short history in sexology [23, 374]. Prior to the development of genital measures, research on the psychophysiology of sexual response was only possible by the use of extragenital measures such as heart rate, respiration, blood pressure, sweat production, and body temperature to index sexual arousal. With the work of Masters and Johnson, genital changes during sexual arousal started to be observed. For instance, they described the engorgement of the labia minora with a two to three fold increase in diameter [375]. As a result of this engorgement the labia become everted, exposing their non-squamous epithelium [300]. Labial temperature has been used to measure these changes [376, 377], whereas vaginal temperature measured by means of a thermistor probe was shown by Fisher to reflect core temperature and was relatively insensitive to changes in arousal [378]. Recently Sommer et all introduced a method to measure significant intra-subject changes in partial oxygen pressure in the vaginal wall and the minor labia during sexual arousal by means of a modified Clark oxygen electrode [379].

The erectile tissue of the clitoris, composed of the clitoral shaft with two corpora cavernosa and the corpus spongiosum, the crura and the clitoral glans, shows vasocongestion during sexual arousal in much the same way as does the penis. Only recently methods such as color Doppler ultrasonography measurements of clitoral blood flow have become available to visualize these clitoral changes [380]. Data to discriminate between normal and abnormal patterns in clitoral blood flow during sexual arousal start to appear in the literature [381] but the clinical relevance of these data is still under discussion. Duplex ultrasonography is used for measuring vaginal blood flow as well. The probe is usually tampon-shaped or fitted into a vaginal speculum [380, 382]. The challenge is to develop experimental conditions where the transducer can be comfortably attached to the measurement site, allowing for continuous mea-

surement, without requiring the presence of another person in the same room. A recent study on the effects of training with the EROS device showed not only significant increases in clitoral and corpus spongiosum peak systolic and end-diastolic velocity values but in clitoral and corpus spongiosum diameter as well [383]. Magnetic Resonance Imaging (MRI) is another promising method to monitor sexual response [384]. Using rapid dynamic serial high-resolution MRI Maravilla et al described the genital changes during sexual arousal in a small group of healthy women [384]. Non-invasive BOLD-fMRI was used by Park et al for the first time to visualize those parts of the brain that are activated during cognitive sexual arousal [385].

Most of the advances of the past two decades are in the methods used to monitor changes in vaginal vasocongestion. These methods vary in terms of validity, specificity, and practical applicability. The two most widely used techniques to measure vaginal vasocongestion are vaginal photoplethysmography, first introduced in 1975 by Sinchak and Geer [386], and the oxygenation-temperature method developed by Levin and Wagner in 1977 [387]. Levin and Wagner's device consists of a heated oxygen electrode fitted into a suction cup that is attached to the vaginal wall. The electrode is heated by an electric current to a set temperature. The amount of electrical power needed to keep the disc at this temperature can be monitored. Heat is lost from the disc mainly by conduction through the tissue and tissue fluid to the blood. Increased blood perfusion under the electrode will increase heat loss and increased power will therefore be needed to maintain the electrode at the set temperature. The change in power in milliwatts is an indirect measure of the change in blood flow under the electrode, reflecting the pooling of blood in the vascular bed. The electrode also records the amount of oxygen that diffuses across the skin, reflecting transient changes in blood flow.

The vaginal photoplethysmograph is a menstrual tampon-sized device, easy to insert and sterilize, containing incandescent light, or an infrared or visible red light-emitting diode as a light source, and a light sensor. The light source illuminates the blood vessel plexus under the epithelium of the vaginal wall, and the light sensor picks up the light that is backscattered from the illuminated area [388]. Two signals are usually obtained from the light sensor. When the signal is coupled to a DC amplifier, slowly developing changes in vaginal blood volume (VBV) are observed, which are thought to reflect pooling of blood in the vaginal tissue. With AC coupling, a measure of vaginal pulse amplitude (VPA) is obtained, reflecting phasic changes in vaginal engorgement with each heart beat. The greater the blood content of the vaginal tissue, the greater the signal's amplitude. VPA has been shown to have excellent divergent and convergent validity and is a more sensitive and reliable measure than VBV [371].

Each technique has its advantages and limitations [389]. For instance, the oxygenation-temperature measure can be calibrated in terms of absolute blood flow and is relatively free of movement artifacts. The reliability of the signal does not seem to be compromised by masturbation, clitoral vibration, or orgasm. Disadvantages are its expense, the fact that the electrode should not be applied for long periods of recording to protect the vagina from heat damage, and the device needs to be attached by the researcher. The vaginal photoplethysmograph does not determine absolute levels of blood flow and is not reliable during and after orgasm [388], but surpasses the other measure with respect to practical applicability. It can be inserted by the subject herself and is well tolerated, thus diminishing the intrusiveness of the measure and allowing for long recording periods. With the right statistical design, that is a one-session within-subjects design or a placebo-controlled crossover design in the case of pharmacological studies, and the data obtained from vaginal photoplethysmography can be readily interpreted.

Practical applicability is not a trivial issue. Studies measuring sexual responses in the vagina are limited as it is, with the restriction to solo sexual activities and their contrived context [374, 390]. It therefore seems crucial to use a measure and a procedure that most women would be willing to undergo, respecting a woman's privacy, and allowing her to become sexually aroused in the laboratory. Balancing validity and applicability concerns, at present, vaginal photoplethysmography seems to be the method of choice.

3. Evidence of organic and stimulus related factors contributing to FSAD

Recently, investigators interested in the pathophysiology of female sexual dysfunction have proposed that in some women, female sexual arousal problems are associated with vascular and clitoral erectile insufficiency [31]. These authors suggest that future management strategies for women with sexual arou-

sal problems should be aimed at assessing vasculogenic sexual dysfunction, especially if these women are post-menopausal. It is highly unlikely that organic factors in female sexual dysfunction are absent. Nevertheless, the finding of a vascular irregularity does not necessarily mean that it is the organic factor causing the sexual difficulties. Psychophysiological assessment therefore should be more routinely implemented as a diagnostic tool to answer the question whether or not an adequate genital sexual response is possible in the presence of possible organic abnormalities.

Another important question is how well the available vaginal vasocongestion measures differentiate between women with and without sexual problems. Only a small number of studies exist to date that assessed differences in vaginal response between women with and without sexual problems, all using vaginal photoplethysmography. Some of these studied sexual responses to erotic stimulus materials in low arousal or non-orgasmic women [391-393], other studies combined women with different sexual dysfunctions into one group [22, 394], one studied low desire and anorgasmic women [395], one study examined sexual responses of women with dyspareunia to oral sex and intercourse scenes [396] and one study compared sexual responses of women with and without FSAD [397]. It is difficult to compare these studies and interpret the different findings, because the nature of the sexual problems varied between and even within studies, different erotic stimuli were used, and studies differed with respect to the way vaginal responses were measured (using either VPA or VBV or both) and analysed.

The Meston and Gorzalka [395] study was the first to compare different diagnostic categories, thus making the important step toward differentiating patterns according to the presenting sexual problem. Wouda et al [396] were the first to study vaginal responses of women with sexual problems to sexual stimuli differing in content. Eighteen women with dyspareunia participated. In this study an erotic scene depicting fellatio and cunnilingus followed a neutral baseline period. Then the women were subjected to a return-to-baseline period followed by a cunnilingus scene and an intercourse scene. There were no differences in VPA between the women with dyspareunia and a control group of women without sexual problems in the first four phases of the experiment. But during the intercourse scene, responses of the control group further increased while in the dyspareunia group responses declined. There were no differences in subjectively reported sexual arousal to the last scene. These results suggest a number of things. First, differences in vaginal vasocongestion response may be highly situation- or stimulus specific. Only during the intercourse scene VPA was significantly lower in the clinical group. Second, genital measures and subjective feelings did not correspond.

A large number of studies have addressed this issue of correlation between psychophysiological measurements and subjective feelings of arousal. In a few studies positive correlation between VPA or VBV and subjective feelings of sexual arousal were reported, but the majority failed to find a relationship between genital and subjective sexual arousal [23, 398]. This finding, confirmed in an MRI study [384], seems to be unique for women. In men without sexual problems, correlation between penile circumference change and subjective report are usually fairly high [23].

Laan et al consistently found VPA to occur automatically in response to an explicit erotic stimulus such as erotic film [398]. That is, vaginal vasocongestion increases within seconds after the onset of the stimulus, without most women being aware of this happening, even when the stimulus is negatively evaluated or induces little or no feelings of sexual arousal. Women simply do not attend to genital changes when assessing their subjective feeling state. Their subjective experience of sexual arousal is determined less by feedback from their genitals (which becomes more important as genital arousal increases) than by the intensity and appraisal of the sexual stimulus. Therefore, genital measures should always be used concurrently with subjective measures of sexual arousal.

These findings suggest an important role for the sexual stimulus in psychophysiological studies. In order to meaningfully compare clinical groups within and between labs, some level of standardization with respect to the type of erotic stimulus seems essential [305]. Finally, measuring vaginal vasocongestion in the absence of a sexual stimulus may lead to false conclusions. For instance, a recent study demonstrated an estrogen related difference in VPA between pre-menopausal and untreated post-menopausal women during initial baseline, before any erotic stimulation had taken place [305]. During subsequent erotic stimulation, however, this difference in VPA between groups disappeared, suggesting that inadequate erotic stimulation may be more important in sexual arousal disorders than a vasculogenic dysfunction related to menopause [397]. This study thus

demonstrates that when measuring VPA without adequate sexual stimulation, one could wrongfully determine organic factors contribute to arousal problems, while in fact with adequate stimulation there is an adequate lubrication-swelling response.

The findings of this study were replicated in a recent study where genital responses of four groups of women were compared: medically healthy pre- and post-menopausal women with and without FSAD [397]. In selecting the groups with FSAD the criteria of DSM-IV were striclty adhered to, meaning that the main complaint had to be a diminished or absent lubrication-swelling response, that there was marked distress as a result of the sexual dysfunction and no comorbidity of medication, medical condition and/or psychopathology. The only significant difference that was found was a difference in VPA between pre- and post-menopausal women in a non-sexually stimulated baseline condition. During visual sexual stimulation no differences in VPA between the four groups could be observed. The sexual problems of the pre- and post-menopausal women with FSAD are therefore not related to their potential to become genitally aroused. During the visual sexual stimulation the women with FSAD, however, reported weaker sexual arousal and genital sensations, less positive affect, and more negative feelings. Contextual and relational variables resulting in a lack of adequate sexual stimulation are therefore most likely the underlying cause for their sexual arousal problems. In a recent MRI study no differences were found between pre-and post-menopausal women in changes during sexual arousal of the vaginal wall, vaginal mucosa, clitoris, femoral vein signal intensity, relative regional blood volume, and clitoral volume [384].

In medically healthy women, impaired genital responsiveness is not a valid diagnostic criterion. The current DSM-IV FSAD definition therefore is in need of revision. The only studies showing significant impairment of psychophysiological genital responses are studies of women with FSAD who have a medical condition that is known to have a potential negative impact on genital neuro-vascular and/or neuro-endocrine functions [399-401].

In assessing sexual arousal in women there is a need for simultaneous measurements of both the cognitive and physical aspects of arousal. Subjective arousal estimates are necessary to answer the question whether or not the women is able to experience feelings of sexual arousal under different stimulus conditions. In assessment of the physical aspects of arousal the main question to be answered is whether or not with adequate stimulation by means of audiovisual, cognitive (fantasy) and/or vibrotactile stimuli a sufficient lubrication-swelling response is possible. If such a response is possible, even when other investigations indicate the existence of a variable that might compromise physical responses, an organic contribution to the arousal problem of the individual women is clinically irrelevant.

Although psychophysiological testing has not been a routine assessment [402], it can be useful both in the diagnostic phase and in assessment of the effects of medical and/or pharmacological interventions [403].

II. ORGASM: PHYSIOLOGY OF ORGASM IN FEMALES

Mah and Binik have recently written about human orgasm: “Despite numerous efforts, orgasm remains the most poorly understood of the sexual responses, and attempts to propose a universally accepted definition of orgasm have met with little success”.[23, 300, 404,]. The most accurate definitions of human orgasm are probably those integrating bio-psychological perspectives which thus describe both the complex of genital and systemic changes and modifications and the emotional and mental components of the acme of sexual pleasure [300, 404-406]. A so-called “orgasmic platform”, potentially responsible of either the genital pleasure at the acme and one possible biological basis for the greater capacity for multiple orgasm, has been suggested in women as the result of genital sexual arousal [375, 389, 404]. Sensory trigger points have been advocated at the orgasmic platform level, including the clitoris and vagina, clitoral and periurethral glans, cervix, uterus, anal mucosa, and proprioceptive stimuli from the levator ani and perivaginal muscles [407]. Non genital trigger points are, for instance, the breast and nipples, skin and sensory organs [366, 404]. At least two major situations have been described anatomically: clitoral versus vaginal orgasm [375, 404, 407]. Clitoral stimulation is the main source of sensory input for eliciting orgasm. A large majority of women report that clitoral stimulation is important for achieving orgasm; furthermore, several authors suggest that clitoral stimulation, either during coitus or during non-coital sexual activities (i.e. self-masturbation or hetero-masturbation and petting), is fundamental for obtaining the orgasmic phase in most women [375, 389, 404, 407-410]. Orgasm attained with clitoral stimulation tends to be more localized and intense, sharper and physically more satisfying.

On the other hand, coital orgasm is generally described as more diffuse throughout the whole-body, with throbbing feelings and stronger, longer lasting and more psychologically satisfying [404, 408, 411-414]. Singer previously suggested also other types of women's orgasm, including the vulva's orgasm identified by orgasmic platform contractions and induced by both coital or non coital sexual activity as well as the uterus' orgasm as produced by cervical jostling from deep coital thrusting, with the potentiality to obtain a so-called blended orgasm with elements of both [415]. Both anatomic and functional biologic modifications of these triggers points and areas can significantly affect the women's orgasmic phase.

Orgasmic responses cannot be totally separated from arousal responses since there is an overlap and a continuum in the physiological and psychological changes that occur during sexual activity. In addition, certain changes that occur during arousal are necessary to achieve orgasm. However, there are a number of physiological changes that accompany orgasm.

1. Physiological changes that accompany orgasm

The physiological changes that occur with orgasm in women include changes in the balance of autonomic function, and muscular contractions. In addition, circulating levels of several hormones increase in concentration. Specifically, rhythmic contractions of the vagina, uterus, and anal sphincter and changes in vaginal and clitoral blood flow, [71, 203, 204, 375, 388, 416-421] have been reported. Increases in heart rate, blood pressure and respiration also occur during orgasm [375, 421, 423-425]. Circulating levels of prolactin, vasopressin, oxytocin, adrenaline and vasointestinal polypeptide have been reported to increase with orgasm [416, 426-429]. Prolactin in particular increased with orgasm and was maintained for approximately 60 minutes after orgasm [428-430], and thus may be a useful measurement of orgasm in future studies.

Similar physiological changes occur during orgasm in men and women. In men orgasm is generally associated with ejaculation. In some women reports of secretions from the periurethral glands have been reported during orgasm, although it is unclear whether ejaculation in women consistently occurs and if these secretions differ from urine, or whether it is always associated with orgasm [425, 431-435].

Cardiovascular changes and increase in heart rate, respiration and blood pressure that occur with orgasm are common responses seen during various types of exercise, therefore monitoring cardiovascular changes independently of specific genital changes is not a good marker for orgasm. Changes in circulating hormonal levels, such as prolactin, may be reliable indices of orgasm; however these values cannot be measured in real time and may vary between assays and individual. The most reliable index of orgasm appears to be monitoring genital changes.

2. Orgasm is a spinal reflex

Evidence based on human and animal studies indicate that sexual climax (orgasm) is a reflex mediated by the spinal cord which may involve a spinal pattern generator [436-439]. Studies in men and women have reported that orgasmic reflexes are still present after spinal cord injury [200, 201, 440]. By classifying women based on sensory preservation of their dermatomes, Sipski and colleagues showed that differences in genital responses to audio-visual erotic stimulation were based on the degree of sensory damage in the T12-L3 dermatomes. In contrast, women with injury of the lower motor neurons and S2-S5 dermatomes are less likely to reach orgasm through direct genital stimulation compared to women with injury at or above T11 [200, 440]. These data suggest that orgasmic responses require intact reflexes that relay in the sacral spinal cord.

a) Neurobiology- CNS pathways

Female genital structures need to be altered from their basal, unexcited state into active, sensitized areas for pleasure. The major genital sites where sexual arousal/pleasure is generated include labia minora/introitus, the clitoral shaft, glans, and bulbs; periurethral glans; the urethra; Halban's fascia; the G-spot and the anterior fornix erogenous zone. Breasts, nipples, and inside of thighs are the other female erogenous sites (xxx). Spinal cord reflexes are mainly responsible for the sexual arousal responses of these multiple genital and non-genital peripheral anatomic structures. The afferent reflex arm is primarily through the pudendal nerve. The efferent arm consists of coordinated somatic and autonomic activity. The bulbocavernous reflex involving sacral cord segments S2, S4 and S4 is the one spinal reflex in which pudendal nerve stimulation results in pelvic floor muscle contraction. Vaginal and clitoral cavernosal autonomic nerve stimulation is another spinal sexual reflex resulting in clitoral, labial and vaginal engorgement [147]. Masters and Johnson noted that the anterior third of the vagina becomes vasoconges-

ted during arousal to form the orgasmic platform [375]. After adequate sensory stimulation, central neurotransmitter discharge during orgasm results in repeated 1-second motor contractions of the pelvic floor (three to eight per orgasm) followed in 2 to 4 seconds by repeated uterine and vaginal smooth muscle contraction [147].

A number of spinal sites control descending these spinal reflex circuits by inhibitory and excitatory means. The lumbosacral spinal cord receives sensory input from pelvic, hypogastric and pudendal nerves, which relay information to the dorsal horn, the medial, central and lateral gray matter of the lumbosacral spinal cord [143, 224, 225]. (**Figure 8**) This sensory information is relayed to supraspinal sites via the spinothalamic and spinoreticular pathways [407]. The fast myelinated fibers of the spinothalamic pathway terminate in the posterolateral nucleus of the thalamus and are then relayed to the medial thalamus. The spinoreticular fibers are slower and terminate in brain stem reticular formation.

b) Modulatory input

Modulatory input regarding female sexual function is carried out by higher centers of the central nervous system. In the brainstem, several nuclei, including the nucleus paragigantocellularis, the raphe nuclei pallidus, and locus ceruleus project to pelvic efferent neurons and interneurons in the lumbosacral spinal cord, most likely role to modulate lumbosacral spinal cord reflexes [142, 442-444]. The periaquaductal gray matter of the midbrain is heavily interconnected with the brainstem and hypothalamic sites related to sexual behavior, seemingly serving as a relay center [445]. Within the hypothalamus***, the medial preoptic area, nucleus paraventricularis, and ventromedial nucleus***, are believed to have major roles in female sexual function [416]. Serotonin, dopamine, epinephrine, histamine, opioids and gamma-aminobutyric acid are neurotransmitters and neuropeptides modulating female sexual function.

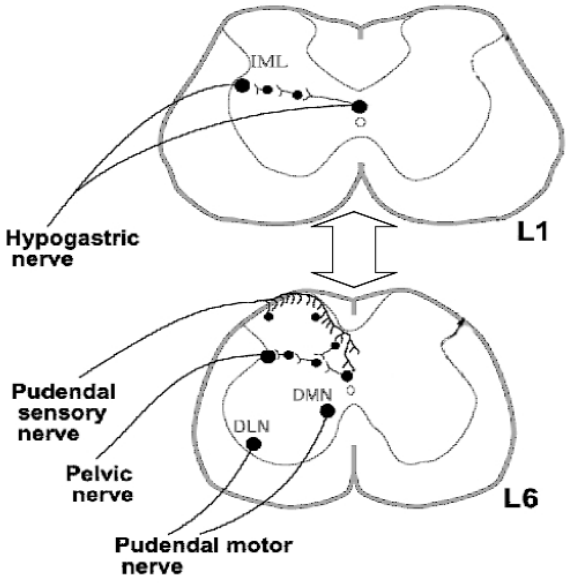

Figure 8 : The lumbosacral spinal cord receives sensory input from pelvic, hypogastric and pudendal nerves, which relay information to the dorsal horn, the medial, central and lateral gray matter of the lumbosacral spinal cord

Serotonin applied to the spinal cord inhibits spinal sexual reflexes. Orgasmic dysfunction has been reported by the use of selective serotonin reuptake inhibitor anti-depressants, which elevate the level of serotonin in the brain [446, 447]. Cyproheptadine, a serotonin2 antagonist, has been effective in alleviating anti-depressant induced anorgasmia [448].

Oxcytocin may work synergistically with sex hormones to facilitate muscle contractions during orgasm. Oxcytocin from the paraventricular nucleus of the hypothalamus is secreted into the blood stream during arousal and orgasm. Using a continuous blood sampling technique and anal electromyography, Carmichael et al reported a positive correlation between oxcytocin levels and the intensity, but not duration, of orgasmic contractions in females and males. For multi-orgasmic women, the amount of oxcytocin increase also correlated positively with subjective ratings of orgasmic intensity [416].

Although 30% to 40% of women cannot achieve orgasm without concurrent clitoral stimulation or through coitus alone, only 5% to 8% of women are totally unable to achieve orgasm with any type of stimulation [449, 450].

D. CLINICAL PATHOPHYSIOLOGIES OF SEXUAL DESIRE, AROUSAL AND ORGASMIC DYSFUNCTION IN WOMEN

Sexual dysfunction in women is defined as disorders of sexual desire, arousal, orgasm and/or sexual pain, which result in significant personal distress and may have a negative effect on a woman's health and an impact on the quality of life. The aim of this section is to try and distinguish among several of the most

frequent clinical pathophysiological mechanisms of women's desire, arousal and orgasmic dysfunctions, aiming to correlate with several modifiable and unmodifiable risk factors. As most of the research on female sexuality has focused on psychological and relationship aspects of this issue, there are a limited number of evidence based studies about female sexual function and very few for orgasmic disorders.

I. NEUROLOGIC PATHOPHYSIOLOGY

Female sexual dysfunction due to neurologic causes is currently unexplored and probably under-diagnosed. The same neurogenic disorders that cause erectile dysfunction in men can cause sexual dysfunction in women. Many neurological disorders such as multiple sclerosis, peripheral neuropathy and lumbar radiculopathy can cause abnormal innervation to the female genital organs.

It is assumed that any neural lesion, central or peripheral, which causes sexual dysfunction, should have sensory deficit as its mainstay. Therefore, the need to quantitatively measure the sensory function of the vagina and clitoris is becoming obvious.

1. Measurement of sensory function of the genitalia

Quantitative sensory testing is used in assessment of sensory function for diagnosis of neural disorders. It is most commonly used for assessment of neuropathies and other peripheral disorders. [451]. These tests are based on administration of quantified stimuli, usually of pressure, vibration or temperature, in a controlled way. Most commonly, the subject defines the sensory threshold by indicating the onset of perceived sensation either verbally or by button-press.

a) Nerve Fibers

Nerves consist of fibers of variable diameter with the thicker fibers having a faster conduction velocity. Three types of fibers are generally recognized in the sensory subclass of nerve fibers: A-beta fibers, the largest fibers, mediate touch, mild pressure, sensation of joint position and vibration. A-delta fibers, smaller than A-beta fibers, mediate sensation of cold and early components of pain sensation. C fibers, the slowest and smallest, mediate sensation of warmth, the main component of pain sensation and subserve most autonomic peripheral functions. The thermal senses, warm and cold, are served by small nerve fibers, and are probably less relevant for sexual function. Nevertheless, a complete assessment of sensory function should include modalities of all types. At the peripheral level, the same class of fibers that subserve autonomic function subserve thermal senses. Disorders that affect these fibers, such as diabetic neuropathy, affect both sensory and autonomic fibers [451]. Measurement of small fiber sensory function can therefore give indirect insight regarding the function of the as yet unexplored autonomic system in these organs.

b) Methodology

A system and methodology for quantitative assessment of genital sensory functions with age-corrected normograms for thresholds of vibratory and thermal sensations for the clitoris and vagina is available [452]. Age dependency of the genital vibratory threshold is impressively similar to its age dependency for the skin of limbs [453], supporting the validity of this test in the genital area. Clitoral measurement was found to have a smaller age effect, perhaps due to the richer innervation of the clitoris, rendering the age effect less significant. Quantitative sensory testing is often criticized or even dismissed because of its subjective nature [454]. However, some authors have shown that results are repeatable and, therefore, can be used as a valid descriptor of the sensory state [455, 456].

2. Specific disorders affecting sexual dysfunction

Central and peripheral neurologic disorders may cause sexual dysfunction and could induce both autonomic motor and sensory disorders. It is expected that patients with multiple sclerosis, spinal cord injuries, herniated disc disorders, lumbosacral plexus disorders, and peripheral neuropathies will have impaired sensory function, which will be expressed as sensory threshold increases.

a) Neuropathy

It has been shown that sensory testing of the genitalia in 36 neurogenic females with sexual dysfunction (15 with diabetes, 14 with Multiple Sclerosis and 7 with lumbar discopathy) can be a useful tool in diagnosing female sexual dysfunction of neurogenic origin, (most strongly the assessment of clitoral vibratory stimuli) [457]. Although perineal trauma occurs in both genders, data supporting the association between sexual dysfunction and blunt perineal trauma in women is lacking. A study that looked at the patient characteristics of women with sexual dysfunction that had undergone blunt perineal trauma

implicated a neurogenic form of sexual dysfunction, with primary complaints of orgasmic disorders and abnormalities on genital sensory testing [458]. In another publication the same authors reported three cases of post-traumatic clitoral neuropathy and neuralgia resulting from trauma to the genitalia. The consequent numbness, pain and dysautonomia have led to sexual dysfunction in all three women [459].

b) Conclusion

Although there are significant anatomic and embryologic parallels between men and women, the multifactorial nature of female sexual dysfunction is clearly distinct from that of the male. There is considerably more research on these issues in males. From a clinical point of view, deficits in genital sensation are probably responsible for many cases of female sexual dysfunction. To date, there are only sparse data on the effect of neurological diseases affecting the peripheral nervous system or various surgical techniques (in particular hysterectomy) on sexual arousal and orgasm. Development of new diagnostic tests and surgical techniques, which spare the genital nerve, will be mandatory. There is a tremendous need for more research in this area.

3. NEUROLOGICAL DISORDERS

The knowledge obtained from the studies about the effect of neurological disorders on female orgasm leads to better understanding of the neurological pathways that control sexual response in normal women. There are limited number of well designed, controlled studies dealing with neurological orgasmic dysfunction. The majority of these studies examined the effect of spinal cord injuries on female sexual responses.

a) Spinal cord injury

There is little available literature about sexual dysfunction in women with spinal cord injury (SCI) [200, 201, 220, 460-467]. Women's desire for sexuality and sexual activities seems to decrease after injury [465]. Charlifue et al [468] reported that sex was less important after injury in their series of 231 SCI women; other authors found a significantly higher level of hypoactive sexual desire after injury as compared with their sexual drive prior to injury itself [469]. A decrease in frequency of self-masturbation in these women has been reported [470] with preferred sexual activities after SCI reported to be kissing, hugging and touching [468].

The influence of SCI on sexual response depends on the degree and location of injury in the spinal cord. Among women with spinal cord injury, 7% to 23% are unable to achieve orgasm [471]. Most of the data available about women's sexual dysfunction after SCI comes from laboratory-based research [200, 201. 220, , 464-466]. Pathophysiology of orgasmic phase in women with SCI's has been studied in laboratory settings [200, 201]. In a study of 25 women with SCI at and above the level of T6 and 10 able-bodied control subjects, the ability to achieve orgasm were documented [200]. Subjects underwent a 75 minute protocol in the laboratory, designed to obtain information on the physiological events accompanying orgasm. Data were analyzed both within and across neurological groups: complete SCI, incomplete SCI, and able-bodied controls. Fifty two percent of subjects with SCI achieved orgasm. The capacity to achieve orgasm was shown to be unrelated to level or completeness of injury in women at levels of injury T6 and above.

Sipski et al reported the results of a study enrolling 12 women with a lower motor neuron (LMN) injury affecting the S2-S5 spinal reflex arc and 50 SCI women with UMN injuries [201]. Ability to achieve orgasm was assessed historically and in the laboratory. Historically, only 55% of SCI women were able to reach the orgasm post-SCI, whereas 44% were orgasmic in the laboratory [200, 201]. These authors demonstrated that in each condition, SCI subjects were significantly less likely to achieve orgasm than controls, and orgasm was less likely if a woman had a complete LMN injury affecting the sacral segments than any other level and degree of injury [200]. Latency to orgasm was greater in women with SCI's compared to normal subjects. Sipski showed a significant difference in average latency to orgasm when able-bodied subjects were compared to SCI subjects [201]. On the other hand, the so-called systemic modifications that usually accompany the orgasmic phase, such as blood pressure, heart rate and respiratory rate fluctuations, were generally similar between women with and without SCI.

In women with complete upper motor neuron (UMN) injuries affecting the sacral segments, the ability for reflex without psychogenic lubrication of the vagina should be maintained [462, 466, 468]. The presence of psychogenic arousal in the absence of arousal induced by genital stimulation was documented in women with complete SCIs at and above the level of T6 [466]. In contrast, in women with incomplete UMN injuries affecting the sacral segments data seem to demonstrate an ability to main-

tain both the capacity for reflex and psychogenic lubrication. Sipski et al also reported that those women with higher ability to perceive a combination of light touch and pinprick sensation in the T11-L2 dermatomes have a greater likelihood of achieving psychogenic lubrication [201]. With all levels and degrees of SCIs, the ability to achieve psychogenic arousal depends on the degree of sensory preservation in the T11-L2 dermatomes but not on the degree of sensory preservation at T6-9 or S2-5 levels [201]. Moreover, psychogenic control of female genital vasocongestion is dependent on sympathetic stimulation [468, 469]. Therefore, preservation of sensory function in T11-L2 is a precondition for the ability of SCI women to have psychogenic arousal.

Orgasm has also been studied in SCI women showing that approximately 50% have the ability to achieve orgasm [470]. In women with T6 injury and above the capacity to achieve orgasm is unrelated to the level of the injury [200]. A significant difference was noted in the ability of women with complete lower motor neuron injuries, affecting S2-5, to achieve orgasm as compared to other types of injuries[466]. The authors concluded that an intact sacral reflex arc is needed to achieve orgasm and that orgasm may be a reflex response of the autonomic nervous system [200, 472, 473]. Furthermore, Sipski et al [200] also proposed that the orgasmic sensory experience may be partially derived from afferent autonomic innervation, which remains after complete SCI. Whipple et al, however, suggested that the vagus nerve can provide innervation to the cervix and is the source of cerebral transmission of orgasmic sensation in women [220].

b) Multiple sclerosis

Current prevalence rates for multiple sclerosis (MS) are 1/1000 Americans and 2/1000 Northern Europeans [473]. A disorder affecting both the brain and the spinal cord, multiple sclerosis can cause difficulties in achieving orgasm. Sexual dysfunction is common among multiple sclerosis (MS) patients and has a reported prevalence of 46%-80% [472, 474-478]. Sexual activity ceases or is significantly unsatisfactory in 39% of MS women [472]. Symptoms reported included fatigue in 68%, reduced sensation in 48%, reduced vaginal lubrication and difficulty with arousal in 35%, difficulty reaching orgasm or anorgasmia in 72%, and dyspareunia and other sexual pain disorders Villeroy [472, 474-477, 479].

In a case-control study, Zorzon et al [480] reported data concerning sexuality in a series of 70 consecutive women suffering from MS as compared to a control group of age-matched women with chronic disease (rheumatoid arthritis, systemic lupus erythematosus, psoriatic arthritis and ankylosing spondylitis) and another of healthy subjects. The number of MS patients who reported a reduction in sexual desire was higher than in both patients suffering from a chronic disease and normal subjects. The same authors found a significant difference in sexual desire between patients and healthy controls. In this series MS women had decreased vaginal lubrication compared to healthy controls while the difference from chronic disease controls was not statistically significant. Changes in vaginal sensation, while very common, were more common in MS cases than in both chronic disease controls and healthy subjects. Overall, more than one-third of women experienced a decrease in vaginal lubrication and libido.

Similar frequencies in modifications of vaginal lubrication and vaginal sensation, orgasmic capacity and diminished sexual desire have also been previously reported by other researchers [477,481-484]. Problems with sexual function were reported significantly more often by women with physical disability due to the disease, (expressed by lower Expanded Disability Status Scale (EDSS scores) [485]. In 47 women with advanced multiple sclerosis, 38.3% reported diminished orgasmic capacity and 12.8% anorgasmia. The changes in sexual function correlated with neurological symptoms from the sacral segments, such as weakness of the pelvic floor and bladder and bowel dysfunction [486]. Zorzon et al also reported data concerning a correlation analysis in the same cohort of women with MS [486]. Spearman correlation analyses between symptoms of sexual dysfunction and characteristics of both patients and clinical type of MS was performed. Sexual dysfunction significantly correlated with relapsing-remitting MS but not with either the primary-progressive or the secondary progressive type. A close correlation was also found between sexual dysfunction and age at onset of symptoms and the current age of the woman but not with the duration of the neurological disease itself. Similarly, a significant correlation was found between sexual and physical disorders, sphincteric and bladder dysfunction, fatigue score and both cognitive deterioration, as assessed by the Mini Mental State Examination [487] and the neurological impairment, as assessed by the EDSS [488]. Other studies have shown a correlation between sexual and bladder dysfunction in MS patients [489, 490]. Nortvedt et al also reported a significant reduc-

tion in the quality of life in MS patients with both sexual disorders and bladder dysfunction [490].

A similar correlation was demonstrated between sexual dysfunction and low educational level and a high value for either depression, as assessed by the Hamilton Depression Rating Scale (HDRS) [491], or anxiety [492], as assessed by the Hamilton Anxiety Rating Scale (HARS) [491]. After a 2-year follow-up, the percentage of patients with at least one sexual disorder remained stable at more than 70% [493]. Although men reported at least one sexual dysfunction more frequently than women, when both men and women were considered altogether, in a univariate analysis, changes in sexual function throughout time correlated with modifications in bladder function and EDSS score. After removing the effect of psychological aspects, only changes in bladder function maintained a significant correlation with fluctuations in sexual function. When comparing women suffering from chronic diseases and healthy subjects, Zorzon et al reported that anorgasmia and hyporgasmia were the more commonly reported sexual dysfunction in MS patients, followed by decreased vaginal lubrication and reduced libido [480]. Fewer women with MS were able to achieve orgasm than their peers (chronic disease controls and healthy controls) [480]. More than one-third of women reported greater difficulty or inability to achieve orgasm than before the disease, with a statistically significant difference as compared with chronic disease controls. Anorgasmia or hyporgasmia was reported more frequently with a statistically significant difference in comparison with healthy controls.

Interestingly, Hennessey et al reported the results of a survey on urinary, fecal and sexual dysfunction in 68 men and 106 MS women [494] and found that although sexual problems occurred in 52% of MS women enrolled, 61% were satisfied with their sexual activity.

Yang et al performed pudendal somatosensory evoked potential testing on 14 women with MS. The most common complaint among these patients was difficulty with orgasm. An abnormal or absent pudendal somatosensory evoked potential was highly associated with lack of or difficulty achieving orgasm [495].

It is probable that primary sexual disorders in some neurogenic MS patient result from the demyelination process that interrupts the continuity of the neural pathways, altering the neural function that is essential for normal sexual performance. Clearly, the neuropathy caused by autoimmune-induced damage to the myelin sheath is the main reason for the classic neural symptoms of the disease. Moreover, electrodiagnostic data imply that pudendal somatosensory innervation is necessary for normal female orgasmic function [495]. Clinical use of sensory testing in MS patients was reported in a group of 24 females, showing that sensory testing of the genitalia in MS patients, most strongly the assessment of clitoral vibratory stimuli, can be a useful tool in diagnosing female sexual dysfunction of neurogenic origin [496].

4. Depression and antidepressants

The incidence of depression in women varies during the life span. The peak incidence during childbearing years appears to be associated with cyclic hormonal changes. Women also present with reproductive-specific mood disorders: pre-menstrual dysphoric disorder (PMDD), depression in pregnancy, post-partum mood disorder (PDD) and peri-menopausal depressive disorder [497-500]. The fluctuation of ovarian steroids during specific phases of the reproductive cycle may bear some relationship to the particular vulnerability of women for mood disorders. The ovarian hormones could exert their effects on mood directly or indirectly by their effects on neurotransmitter, neuroendocrine, or circadian systems. Hormonal changes associated with the reproductive cycle may provoke affective changes in predisposed individuals. Moreover, there are a variety of disturbances in biological rhythms observed in mood disorders. An example is depression associated with the luteal phase of the menstrual cycle [501-503].

Major depression is frequently related to women's sexual dysfunction (over 70% of patients) [503-505]. Changes in sexual interest/satisfaction and loss of libido are frequently and consistently related to major depression [506-508]. Nevertheless, a good quality sex life is regarded by 70% of the general population and by as many as 75% of depressed patients as a fundamental part of quality of life [509-510].

Antidepressant medications can exacerbate pre-existing sexual dysfunction or induce new sexual disorders [500, 506-526]. Sexual dysfunction has been reported to be associated with all classes of antidepressants (MAOIs, TCAs, SSRIs, SNRIs and new generation antidepressants) in patients with depression and various anxiety disorders [520]. The clinical assessment of depressed women requires a comprehensive evaluation of sexual function prior to the

affective disorder, disturbances associated with the onset of depression and changes or dysfunctions associated with antidepressant treatment. Other factors to be included in evaluating sexual dysfunction include inquiry about concurrent medical conditions, somatic treatments, lifestyle risk factors, and response to antidepressants [516].

Absent or delayed orgasms are the sexual side effects most commonly associated with selective serotonin reuptake inhibitors (SSRI's) [519], with desire and arousal disorders also frequently reported [516, 517]. The negative effects of SSRIs on sexual function appear strongly dose-related and can vary among group according to serotonin and dopamine reuptake mechanisms, induction of prolactin release, anticholinergic effects, inhibition of nitric oxide synthase and pharmacokinetics [516]. While men taking SSRIs report higher rates of sexual side effects, women seem to experience more severe sexual dysfunction [521]. Sexual dysfunctions which last during long-term administration of antidepressants may result in treatment discontinuation [515, 516, 522]. This places patients at increased risk for recurrence, relapse, chronic illness, and mortality (e.g., suicide). Recently; Zajecka et al reported that in a series of 681 outpatients with chronic forms of DSM-IV [371] major depressive disorders, sexual dysfunction was reported by 48% of women before any antidepressant treatment [511]. After a 12 week treatment course with nefazodone or Cognitive Behavioral Analysis System (CBASP) or a combination of both nefazodone and CBASP, a statistically significant linear improvement in sexual function was noted in all 3 treatment groups. Improvement in depressive symptoms was associated with improved sexual interest and satisfaction.

Similar results have also been reported by Bobes et al [523]. Using the Changes in Sexual Functioning Questionnaire (CSFQ) [524], sexual desire/interest showed a substantial baseline effect (30% of patients indicated a maximum score) for depressed women treated with nefazodone at baseline and treated with paroxetine at final visit. As compared to the baseline, nefazodone treatment was able to promote significant improvement in depressed women in terms of sexual desire/frequency, pleasure, sexual arousal and orgasm [523]. Michelson et al underlined similar results, even accounting for the decreased sexual function (most pronounced with orgasm) that occurred during continued treatment for increased depressive symptoms [525]. Sexual function was assessed in depressed patients participating in a multi-center trial of acute and chronic fluoxetine therapy. Patients were evaluated at study entry (baseline), after 13 weeks of fluoxetine 20 mg daily, and during 25 weeks of chronic therapy with fluoxetine 20 mg daily, fluoxetine 90 mg weekly, or placebo. In a 13-week open-label trial among 501 patients who met DSM-IV criteria for depression, 51.6% of women reported improvement, 35.0% reported no change, and 13.4% of women and 17.4% reported worsening of overall sexual function. During double-blind chronic therapy there were no statistically significant differences in change in sexual function between treatments [525].

Nappi et al demonstrated that depression may be bimodally related to women's sexual dysfunction [526]. In a cross-sectional study, frequency of self-reported sexual symptoms in 355 women attending menopause clinics was investigated and related to other vasomotor, psychological, physical, and genital complaints. As expected, pain during sexual intercourse and low libido/lack of arousal were significantly more frequent with age and years since menopause. Reduction of sexual pleasure/satisfaction (45.9%) was common with age, but was more frequent the longer the time since the menopause. However, examining the intensity of sexual symptoms in relation to the presence of other complaints, Nappi and co-workers found that physical, psychological and genital well-being significantly affects the components of sexual response after the menopause and depressive symptoms were more common in women with sexual complaints [526].

Thus, depression is an important co-factor in many diseases that are potentially associated with sexual dysfunction in women. Some authors underlined the role of depression in worsening the quality of life and sexual function in MS patients [527-528]. Janardhan et al demonstrated that depression and fatigue were independently associated with impaired quality of life in MS, after accounting for physical disability, suggesting that their recognition and treatment can potentially improve quality of life [527].

Zorzon et al examined 62 men and women with MS using MRI of the brain [528]. When comparing patients with and without sexual dysfunction, the only significant difference was in the pontine brain parenchymal fraction (BPF). When a linear multiple regression analysis was performed, sexual disorders were associated with depression and, after adjusting for depression and anxiety, with bladder dysfunction and pontine BPF. This relationship between sexual dysfunction and pontine atrophy confirmed the correlation of sexual dysfunction with bladder dysfunc-

tion and highlighted the role of depression in determining sexual dysfunction even in this particular subgroup of women. To confirm the significant role of depression as a co-factor of sexual dysfunction, Salonia et al recently reported data about sexual dysfunction in 30 women suffering from coronary artery occlusive disease (CAD) [529]. Sexual dysfunction was reported by 9 of 30 women, 7 of whom had this complaint prior to symptoms of ischemic heart disease. According to the results of the Female Sexual Function Index (FSFI) [530], 77.8% of these women reported hypoactive sexual desire disorder (HSDD), 77.8% sexual arousal dysfunction, 100% orgasmic disorder, and 67% a combination of hypoactive sexual desire, arousal, orgasmic and sexual pain disorders. Fifty-seven percent of the enrolled women showed depressive symptoms, as determined by the BDI [531], which significantly correlated with the Female Sexual Distress Scale (FSDS) [532] and with each one of the FSFI domains.

5. Endocrine alterations

a) Thyroid disease

While peer review literature reports some contributions of thyroid disease to men's sexual dysfunction [533-538], there were no papers found evaluating sexual function and dysfunction in women complaining of either hypothyroidism or hyperthyroidism. Preliminary data has recently been reported regarding sexual function and dysfunction in 48 women with thyroid disease (30 hypothyroidal women, and 18 hyperthyroidal subjects) [533]. All patients underwent a detailed evaluation and the results of their FSFI scores were compared with those of a control group of healthy age-matched women. Women complaining of thyroid problems had lower scores for both the lubrication and the orgasm domain of the FSFI as compared with the control group, and dysthyroidal women reported significantly higher genital pain during both coital and non-coital sexual activity than controls. When co-morbidities were evaluated, a high rate of depression was found in the women with thyroid disease; the BDI score correlated significantly with the desire, arousal and satisfaction domains of the FSFI. A higher rate of depression also correlated with a higher rate of sexual distress, as determined by the Spearman correlation analysis between the BDI and the FSDS. When the FSDS was correlated with the different FSFI domains, a significant correlation was found between women's sexual distress and overall sexual satisfaction.

b) Hyperprolactinemia

Hyperprolactinemia is the most common endocrine disorder of the hypothalamic-pituitary axis [539], occuring more commonly in women. It is associated with pronounced reductions of both sexual motivation and function. Elevated levels of prolactin (PRL) inhibit GnRH pulsatility [540, 541]. Although some experimental evidence suggests that hyperprolactinemia suppresses physiologic reproductive functions while maintaining sexual drive, other studies clearly indicate that chronic PRL elevation negatively impacts sexual libido [542, 543]. Hulter et al assessed sexual function and sexual appreciation in a comprehensive interview of 48 women with well-defined hypothalamo-pituitary disorders [544]. A total of 79.2% of the women had developed a lack of or a considerable decrease in sexual desire, while problems with lubrication and orgasm were reported in 64.6% and 68.7% of the women, respectively. In this series, normal menstrual pattern, young age and intra-sellar tumor growth correlated better with normal sexual desire and sexual function than did normal prolactin levels and normal testosterone levels. In a previous study [545], the same authors investigated sexuality in 109 women with morphologically verified hypothalamo-pituitary disorders, finding that 62.4% had noticed a decrease in sexual desire. This problem was shown for 84.1% of the women in this group with hyperprolactinemia, but only in 32.6% of the women with normal serum prolactin.

A correlation between hyperprolactinemia and sexual disturbances among uremic women on hemodialysis have been reported [546, 547]. Mastrogiacomo et al reported that among 99 women on maintenance hemodialysis, the rate of sexual intercourse and the ability to reach orgasm were significantly lower than in age-matched controls [546]. Eighty percent declared a reduction in their sexual desire, and the frequency of intercourse decreased after dialysis. Aging, an unmodifiable risk factor, decreased the sexual activity in both the sick and healthy populations, but in uremic patients sexual activity ended at an earlier age. Patients with hyperprolactinemia reported lower frequency of intercourse as well as lower percentage of orgasm than women with normal prolactin levels.

Recently a correlation has been made between hyperprolactinemia and antidepressive, antipsychotic and neuroleptic drugs. Several drugs are known to affect sexual function negatively, including psychoactive drugs (opiates), hypotensive drugs and antihistamines [406, 540]. Antipsychotic and neuro-

leptic drugs reduce sexual drive, in part related to drug-induced of hyperprolactinemia. Neuroleptics typically elevate plasma prolactin, associated with both loss of libido and anorgasmia [406, 540, 548-555]. Antidepressant agents such as SSRI's may induce hyperprolactinemia [556-559], although no research has been found which accurately reports prevalence and characteristics of this phenomenon. In women this secondary hyperprolactinemia induces symptoms from decreased sexual drive to orgasmic disturbances such as anorgasmia and delayed orgasm [512, 556-559].

c) Diabetes mellitus

Few studies have investigated the significance of diabetes in causing women's sexual dysfunction [401, 570-579]. Neuropathy, vascular impairment and psychological problems have been correlated with decreased libido, spontaneity of arousal, vaginal lubrication and orgasmic function and dyspareunia in women complaining of diabetes mellitus. The most common sexual dysfunction in women with diabetes is decreased sexual arousal with slow and/or inadequate lubrication. Women with diabetes may also experience a decrease in sexual desire and increase in dyspareunia, whereas problems with orgasm are not more frequent.

Jensen et al reported that diabetic spouses of diabetic men had more problems with arousal than healthy spouses [567]. Although the mechanism is unclear, the rate of sexual dysfunction among women with type-II diabetes was significant, while type-I did not demonstrate any significant change [575, 578]. In 1998 Enzlin et al wrote a review of the literature on this topic [582]. Enzlin showed that diabetes slightly increased the risk of women's sexual disorders. Schiel et al [583] studied 127 type-I diabetics, 36% of whom were women and 117 type-II diabetics, 54% of whom were women. He showed that overall prevalence of sexual dysfunction in women was 18% among type-I diabetic patients and 42% among type-II diabetic subjects.

Enzlin et al reported on prevalence and characteristics of sexual dysfunction in 120 women with type-I diabetes mellitus as compared with 180 age-matched healthy controls [584]. With a response rate of 80.8%, Enzlin showed that significantly more women with diabetes (27%) than age-matched controls (15%) reported sexual dysfunction. Diabetic women presented a higher prevalence of arousal dysfunction than healthy women, however there was no significant difference in decrease of desire. There was no significant difference in orgasmic disorders or sexual pain disorders between the women with and without diabetic complications. A significant difference was found for decreased lubrication, although often 2 and 3 sexual problems were reported.

Patients complaining of sexual disorders were not significantly different in age, BMI, length of disease or HbA_{1c} values as compared with those without sexual complaints. A significant association was found between the number of complications and the number of sexual complaints, although this analysis did not show any statistically significant correlation between sexual complaints and peripheral neuropathy, autonomic neuropathy, nephropathy and retinopathy, menopausal status, use of hormone therapy or use of oral the contraceptive pill. Based on BDI score, twice as many diabetic women were depressed than controls.

Erol et al published data on the prevalence of sexual dysfunction in 72 women with type-II diabetes mellitus without other systemic co-morbidities and 60 age-matched healthy subjects [585]. Mean FSFI scores of patients was 29.3 compared to 37.7 for controls, with the main complaints of the diabetic women being reduced libido (77%), diminished clitoral sensation (62.5%), complained of vaginal dryness (37.5%) vaginal discomfort (41.6%) and orgasmic dysfunctions (49%). The authors concluded that the higher rate of sexual disorders among diabetic patients was responsible for lowering their quality of life.

In order to evaluate the prevalence and predictors of sexual dysfunction in women with both type-I and type-II diabetes mellitus, 72 diabetic women, 42 type-I and 30 type-II were compared with healthy age-matched controls [586]. Women complaining of diabetes mellitus had worse FSFI scores for the desire, lubrication and orgasm domains as compared with the control group, and significantly higher sexual pain at the genitalia level (both coital and non-coital sexual activity) than controls. The BDI score, 48% in diabetic women, was significantly correlated with the arousal, orgasm and satisfaction domains of the FSFI. The Spearman correlation analysis was also statistically significant between BDI and FSDS score. A significant correlation was also found between aging and reduced desire and between aging and lubrication.

Sexual dysfunction is highly prevalent in diabetic women and these patients are clearly at higher risk of developing sexual desire, arousal and orgasm disorders than age-matched controls. More investigation is needed to better understand the contributions of

the psychological and diabetes-related somatic factors to sexual dysfunction in women with diabetes mellitus.

6. Pelvic surgery

a) Pelvic surgery for rectal cancer

When a conventional low anterior and abdomino-perineal resection with extended lymphadenectomy is performed for advanced lower rectal cancer, sexual and bladder function are often sacrificed [587-589], reported to be between 10% and 60% [589]. Extended circumferential margins are required for a complete resection, or multimodality treatment is utilized, including preoperative external beam radiation therapy, radical surgery and intra-operative radiotherapy, to improve the cure rate of both the presentations of rectal cancer [589-594]. Sexual and bladder dysfunctions are usually caused by a non-nerve-sparing surgical approach during the procedure, with the surgical damage of one or more of the autonomic nerves consisting of the paired sympathetic hypogastric nerve, sacral splanchnic nerves and the pelvic autonomic nerve plexus. Several kinds of nerve-sparing surgery (NSS) for organ-confined or advanced rectal cancer have been developed aiming at both preserving sexual and genitourinary function and extending the surgical margins [587, 594-606]. Enker et al reported that in patients undergoing abdomino-perineal resection for primary cancer of the rectum, performed in accordance with the principles of total mesorectal excision (TME) and autonomic nerve preservation (ANP), sexual function was preserved in approximately 57% of patients undergoing APR versus 85% of patients undergoing sphincter preservation [607].

Data on this topic in women are very rare and conflicting. A few papers reported the results of both prospective and retrospective studies aiming at evaluating urinary, bowel and sexual function in both men and women, but without any standardized method from the woman's point of view. In addition, most of the outcome studies enrolling both men and women paid attention only to the male hemisphere.

Recently, Pocard et al studied prospectively the pre- and post-operative urinary and sexual function in 7 women who underwent a sphincter-preserving operation for rectal carcinoma by means of a curative TME with ANP, without preoperative irradiation, with complete surgical identification and subsequent preservation of both hypogastric and sacral splanchnic nerves [608]. Four out of the 7 women were sexually active before undergoing the surgical procedure. Sexual activity and ability to achieve orgasm was unchanged in these women and no incidence of dyspareunia was reported. Chorost et al reported similar results in a retrospective review on the medical records of 52 consecutive patients who underwent potentially curative procedures for rectal cancer [609]. Pre-surgical discussion about the potential risk of sexual dysfunction was not documented in the pre-operative consent in 37 of 52 patients, however, only 1 out of the 16 women reported post-therapy sexual dysfunction.

Multimodality treatment can increase the chances of damaging the urogenital nerves and organs which could result in voiding and sexual disorders [587, 593, 602]. There is a paucity of literature devoted to the impact of surgery alone or multimodality treatment on women's sexual function. Mannaerts et al reported the sexual outcome results of a population of both men and women suffering from locally advanced primary and locally recurrent rectal cancer [594]. Using questionnaires, sexual function was evaluated during the 6 months prior to aggressive multi-modality therapy as well as during follow-up (median 14-months, range 4-60 months) to assess clinical outcome. Interest in sexual activity and ability to achieve orgasm decreased in women after the treatments. Among the study population, the mean quality of orgasm was reduced from in both the primary rectal cancer group and the locally recurrent rectal cancer group. Age greater than 60 years significantly reduced the ability to have post-operative orgasm as well as the ability to have sexual intercourse [594]. The same authors, reporting the long-term functional outcome after a multi-modality treatment for locally advanced primary and locally recurrent rectal cancer, found that 56% of respondants complained of sexual inactivity [610]. In a retrospective small survey of 43 patients with low rectal cancer who underwent low anterior resection with or without neoadjuvant or adjuvant radiotherapy, Chatwin found that sexual dysfunction was reported 2 of the 11 sexually active women [611]. Despite their reported fecal, urinary and sexual dysfunction, most patients were satisfied with their quality of life.

Recently Quah et al reported the results of a retrospective analysis of pre-operative and post-operative bladder and sexual function in patients who underwent laparoscopically-assisted and conventional open mesorectal resection for cancer [612]. No significant difference in sexual function was found in women.

b) Radical cystectomy for urologic malignancies

No paper was identified dedicated to the evaluation of sexual function in women after surgery for bladder cancer [613-619]. Genitourinary (GU) cancers are commonly associated with treatment-related sexual dysfunction varying from mild to severe. Sexual dysfunction may occur as a result of cancer and its treatment. Sexual function is sensitive to the effects of both physical and emotional trauma, particularly when the cancer affects the genital organs.

Marshall et al described anterior exenteration in women performed accurately with a disciplined anatomic approach [615]. Women undergoing cystectomy with the simultaneous removal of uterus, ovaries, and parts of the vaginal wall face had issues regarding their femininity as well as concerns regarding future sexual function. Excision of the uterus, a portion of the vagina and the urethra seems to reduce the potential for pelvic recurrence but a vaginal reconstruction and continent urinary diversion provide a better quality of life with maintenance of sexual function and urinary continence.

Bjerre et al conducted a study aimed at evaluating the sexual profile in women after urinary diversion by either radical cystectomy with continent Kock reservoir or ileal conduit diversion [616]. No significant differences were found among the 37 patients who completed the questionnaire. Among whose sexual activity decreased, almost one-third gave physical problems or decreased desire as the reason and 30% felt less sexually attractive, with cystectomized patients reporting a higher percentage than the others. A higher frequency of dyspareunia among patients with a continent reservoir was an unexpected finding.

Nordstrom et al described the sexual function outcome of 66 men and women who underwent an ileal conduit urinary diversion because of bladder cancer or incontinence/bladder dysfunction [617]. Five of the 6 women treated by cystectomy, who had been sexually active pre-operatively, reported either a decrease or cessation of coital activity post-operatively, due mainly to a decrease in sexual desire, dyspareunia and vaginal dryness. One woman reported the inability to experience orgasm after surgery. Compared with women with bladder cancer, those with incontinence/bladder dysfunction were more likely to have an active sexual life after urostomic surgery. A post-operative increase in activity was shown by 7 women in this group, 4 of whom had been sexually inactive before surgery, because the surgery eliminated the need for incontinence pads or indwelling catheters. Hautmann et al presented data about a nerve sparing cystectomy with orthotopic bladder replacement in women [618], but neglected to make observations regarding sexual function.

Horenblas et al have reported preliminary results of a modified cystectomy, called sexuality preserving cystectomy and neobladder, the intent of the surgical technique being to achieve maximal tissue conservation, potentially preserving normal sexual function and satisfactory urinary tract reconstruction [619]. The surgery consists of pelvic lymph node dissection followed by cystectomy with preservation of all internal genitalia. An ileal neobladder was then anastomosed to the urethra. This type of surgical approach was suggested for women suffering from bladder cancer stages T1-T3 with absent tumor growth in the bladder neck and absent invasive tumor in the bladder trigone. Three women aged 38 to 71 years old were enrolled in this protocol and all reported normal vaginal lubrication during sexual activity.

c) Hysterectomy and sexual function

Reports of deterioration of sexual function after hysterectomy is estimated to be between 13% and 37%, which may be through one or more mechanisms [620-625]. Quality of sexual life after hysterectomy may be influenced by several situations resulting in conflicting suggestions [626-632]. Many of the studies exploring sexuality after hysterectomy have methodological flaws, including vague measures of sexual satisfaction and potential for recall bias [633]. In a comprehensive review article, Carlson reported that in women undergoing hysterectomy for non-malignant conditions there is a marked improvement in symptoms and quality of life during the early years after surgery [626]. Hysterectomy did not seem to cause long-term psychiatric morbidity and psychological status generally improved after surgery itself. Rhodes et al [625] recently published the results of a 2-year prospective study which examined measures of sexual function prior to hysterectomy and at 6, 12, 18 and 24-month follow-up after surgery. A total amount of 1101 women completed the study. These authors showed that both sexual desire and frequency of sexual relations significantly increased after hysterectomy and throughout the follow-up period. Frequency and strength of orgasm also increased significantly after surgery. Lack of orgasm pre-operatively was most significantly associated with absence of orgasm after surgery; possibly influenced by aging. Women also reported vaginal dryness improved after hysterectomy.

In contrast, several papers reported a decrease in quality and frequency of sexual activity after hysterectomy. Rako [627, 628] emphasized the importance of the ovaries as a critical source testosterone as well as estrogen; thus removal of the uterus, even after ovary-sparing procedures, can jeopardize their function. Loss of a physiologic level of testosterone in women after hysterectomy can decrease quality of life in terms of libido, sexual pleasure, and sense of well-being. An analysis by Cutler et al correlated the impact of hormonal deficit on sexuality and overall quality of life in hysterectomized women [629]. In the US more than half a million women per year undergo hysterectomy as treatment for chronic benign gynecologic conditions [634], a rate 5 times higher than that of the European countries. Estrogen, progesterone and androgen levels all tend to be altered by hysterectomy. Furthermore, all these sex hormones affect physiologic systems including the cardiovascular system, bone metabolism, cognitive function, sexual response and sexual attractiveness [629].

These conditions are made worse when hysterectomy is accompanied by bilateral oophorectomy. Since the ovaries provide approximately half of the circulating testosterone in pre-menopausal subjects, after surgery many women report impaired sexual function despite estrogen replacement. Shifren et al [350, 635] reported that in women with impaired sexual function after surgically induced menopause high dose transdermal testosterone may be useful, increasing the Brief Index of Sexual Functioning for Women (BISFW) [636] scores for frequency of sexual activity and pleasure-orgasm. In the same group of surgically menopausal women, the percentages of those who had sexual fantasies, masturbated or engaged in sexual intercourse at least once a week increased two to three times from baseline. This issue is actually strongly debated [350, 637, 638].

The estrogen deficiency which results from pre-menopausal hysterectomy with bilateral oophorectomy is associated with vaginal dryness [625, 639], although several reports also demonstrate vaginal dryness after pre-menopausal simple hysterectomy due to potential ovarian damage and failure subsequent to the surgery itself [640-642]. The vaginal orgasm, consequent to the stimulation of nerve endings in the uterovaginal plexus, should be hindered by hysterectomy with cervix removal, but theoretically clitoral orgasm should not be damaged [643]. However, surgical damage to the pelvic autonomic nerves during radical hysterectomy is thought to be responsible for considerable morbidity, including sexual dysfunction.

Surgical preservation of the pelvic autonomic nerves in both laparoscopic and traditional radical hysterectomy deserves consideration in an attempt to improve both cure and quality of life in cervical cancer patients as well as chronic benign conditions [632, 644-665]. Well-designed prospective studies are needed to evaluate the impact of this common surgery on overall sexual function in both pre- and post-menopausal women.

7. Cerebrovascular accidents-orgasmic dysfunction

The most common sexual problems in women that have been identified after stroke include decline in libido, coital frequency, vaginal lubrication and orgasm. A number of studies have examined the impact of stroke on female sexual dysfunction but there are few prospective studies. In a prospective 6-month follow-up study, Korpelainen et al assessed the impact of stroke on libido, sexual arousal, coital frequency and satisfaction with sexual life in 38 men and 12 women, 32 to 65 years old [666]. Only married patients with an active sexual life before the stroke and without other peripheral or central nervous system conditions known to affect the autonomic nervous system, severe aphasia or psychiatric illnesses or diseases affecting daily activity were included in the study. The women, all of whom were able to attain orgasm prior to their strokes, reported decreased vaginal lubrication and ability to reach orgasm, with 30% and 20% anorgasmic at 2 and 6 months respectively.

E. SUMMARY

Animal models will continue to be indispensable for studies of the neurobiology of sexual behavior. This includes understanding the neuroanatomical and neurochemical mechanisms that underlie sexual desire, viewed by many clinicians and motivational theorists as distinct from arousal in both animals and humans. Lesion and drug studies, neurochemical and neuroanatomical analyses and molecular approaches provided by animal studies guide our emerging work in the neuroanatomy of sexual response in humans, using functional magnetic resonance imaging or positron emission tomography. Animal models are needed to further understand the hormonal processes

that lead to changes in sexual arousal, as invasive and direct studies of brain or organ function possible in animals cannot be conducted in human subjects.

The understanding of peripheral mechanisms and neurotransmitters regulating the female genital sexual arousal response is limited. Modulation of vaginal and clitoral engorgement, vasocongestion and vaginal lubrication may be antagonistic, regulated by parasympathetic and sympathetic components of the autonomic nervous system of the female genitalia. VIP and NO may be the primary facilitators with ***noradrenaline*** and NPY the primary inhibitors of the genital arousal response. There is a need to expand current understanding of the physiological mechanisms responsible for the arousal response in order to improve clinical management of arousal disorders in women.

In assessing sexual arousal in women there is a need for simultaneous measurements of both the cognitive and physical aspects of arousal. Subjective arousal estimates are necessary to answer the question whether or not the woman is able to experience feelings of sexual arousal under different stimulus conditions. In assessment of the physical aspects of arousal the main question to be answered is whether or not, with adequate stimulation by means of audiovisual, cognitive (fantasy) and/or vibrotactile stimuli, a sufficient lubrication-swelling response is possible. If such a response is possible, an organic contribution to the arousal problem of the individual women is clinically irrelevant.

Sex steroids are essential in women's sexual function, but their direct involvement in sexual dysfunction is controversial, due to the multidimensionality of women's sexual health. Both estrogens and androgens contribute to preserve libido, arousal and orgasm, and menopause in particular, when it occurs following surgery, is a good clinical paradigm for studying the effects of sex steroid deprivation on women's sexual function. The fact that androgens serve as precursors for synthesis of estrogens in women and therefore serum levels of androgen are expected to be greater than estrogen plasma levels in women suggests that androgen insufficiency may exist in pre-menopausal as well as post-menopausal women. Although androgen insufficiency may result from a number of circumstances, the diagnosis is difficult because of the lack of precise definitions as well as sensitive assays for free testosterone. Plasma levels of total T, free T and SHBG need to be determined clinically. An increasing body of evidence suggests that women with signs and symptoms of androgen insufficiency respond well to androgen therapy without significant side-effects. Several estrogen therapy and androgen therapy protocols have been proposed to treat female sexual dysfunction, however, a better understanding of the role of endogenous and exogenous hormones on women's sexual function is mandatory. This requires investigation of the biochemical, cellular and physiological mechanisms by which sex steroid hormones modulate sexual function in general, and genital sexual arousal in particular, in experimental models.

The control of sexual function is based upon spinal mechanisms. The spinal cord provides the autonomic and somatic innervation of the sexual organs. Sensory information from the sexual organs project to interneurons in the lower spinal cord. These interneurons likely generate the coordinated activity of sexual responses. Evidence based on human and animal studies indicate that sexual climax (orgasm) is a reflex mediated by the spinal cord, which may involve a spinal pattern generator. Human studies have reported that orgasmic reflexes are still present after spinal cord injury. By classifying women based on sensory preservation of their dermatomes, orgasmic responses have been shown to require intact reflexes that relay in the sacral spinal cord. From a clinical point of view, deficits in genital sensation such as from spinal cord injury and multiple sclerosis are probably responsible for many cases of female sexual dysfunction. Data on the effect of neurologic diseases affecting the peripheral nervous system or various surgical techniques (in particular hysterectomy) on sexual arousal and orgasm are limited. Development of new diagnostic tests, and surgical techniques which spare the genital nerve, are mandatory. There is a tremendous need for more research in this area.

CONCLUSION

Sexual problems in women are highly prevalent, frequently distressing, and poorly understood at present. There has been a long history of neglect of sexual problems generally in medicine, but especially in women. The causes and treatments of sexual dysfunction in women have been of academic concern for more than half a century, but there are limited integrative (psychologic and biologic) research efforts at understanding physiology and pathophysiology of women's sexual health issues.

Current understanding of the psychologic and biologic mechanisms responsible for sexual function must be expanded in order to improve clinical management of sexual dysfunction in women. Clinical pathophysiologies of sexual desire, arousal and orgasmic dysfunction in women include neurologic disorders; depression and anti-depressants; endocrine disorders such as hyper- and hypothyroidism, hyperprolactinemia, diabetes mellitus; pelvic surgery including surgery for rectal cancer, radical cystectomy for urologic malignancies and hysterectomy; and stroke.

There is emerging knowledge on women's sexual dysfunction from the establishment of a host of experimental models, from advances in psychological, biochemical and molecular biologic approaches and the development of new diagnostic tests. Well-defined end-points and outcomes and a general consensus on the diagnostic framework for assessment and treatment of FSD are important goals for the future of sexual health and well-being involving both mind and body. It is anticipated that the coming years will bring new knowledge and improved clinical care in the management of women's sexual dysfunction.

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