

The Endocrinology of the Reproductive Years

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ABSTRACT

Introduction. The relationship between reproductive physiology and reproductive behavior, a central theme in Professor Lorraine Dennerstein's career, is complex but presumably serves to optimize human reproduction.

Aim. To review the endocrinology of the reproductive years and significant work by Professor Dennerstein relating that endocrinology with reproductive behavior.

Methods/Main Outcome Measures. Published works of reproductive endocrinology by Professor Dennerstein.

Results. An exquisitely controlled signaling loop between the ovaries and the hypothalamus and pituitary in the brain represents the overlay of a dynamic neuroendocrine system on a responsive but ultimately decaying gonadal system. The most visible hallmark of this elegant interplay is the menstrual cycle, with coordinated hormone patterns directing the maturation and release of oocytes, and either supporting an early pregnancy or resetting the system for the next cycle. The recognition that these hormone patterns, or their perturbation, are related to psychosocial behaviors is reflected in Professor Dennerstein's earliest writings relating sex steroids to sexual behavior and menstrual cycles to affect, leading to studies describing psychological symptoms in the premenstrual syndrome (PMS). These were followed by clinical trials of progestins for PMS with conflicting results, and an emerging interest in measuring endogenous hormones in that disorder. Her study of reproductive hormones across the menstrual cycle in women with PMS definitively refuted the theory that deficient progesterone secretion was the etiology of cyclic symptoms. Extension of that work demonstrated the cyclic pattern of sexual behavior, but the absence of a defined relationship with measured sex steroid patterns. Her interest in the effect of age on menstrual cyclicity evolved into her landmark work on the menopausal transition, the ultimate result of ovarian gamete depletion and absolute loss of spontaneous reproductive capacity.

Conclusion. Professor Dennerstein clearly demonstrated that reproductive behavior is related to reproductive physiology, and can be measured and quantified. **Randolph JF Jr. The endocrinology of the reproductive years. J Sex Med 2008;5:2274–2281.**

Key Words. Menstrual Cycle; Premenstrual Syndrome; Reproductive Hormones

When I saw the topic on which I was asked to speak, "The endocrinology of the reproductive years," I was a bit intimidated because it is such a broad subject. Moreover, I knew Henry Berger would be sitting right in front of me, and that he is renowned throughout the world for his knowledge on that exact topic. Then I thought about it more and asked myself, "What aspect of this topic would be most helpful to set the stage for the rest of today's discussions?" so that is what I will try to accomplish this morning. My goal is to put the underpinnings in place so that all of today's references to reproductive hormones make some sense.

In thinking about what would be an appropriate message from the many possibilities on which I could speak, a central theme of Dr. Dennerstein's august career emerged in the concept that reproductive physiology is related to behavior. Specifically, "How does one put psychiatry and hormones together and have them make sense?" I will begin by very briefly touching on the female reproductive system, not to dwell on detailed anatomic illustrations, but to emphasize the foundation of all the research that you will hear about today so that it fits together and makes some sense. More specifically, I will talk about the menstrual cycle and attempt to put it into a framework that also makes

Table 1 The human reproductive system

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1. Induces sexual development, maturation, and maintenance.
 2. Facilitates oocyte proliferation, storage, maturation, and release.
 - a. Does so in a decaying function over the reproductive life span.
 3. Promotes gamete interaction.
 4. Optimizes embryonic/fetal transport, implantation, development, and delivery.
 5. Recovers.
 6. Influences behavior?
-

sense. In particular, I will ask the question “How do we connect the menstrual cycle, that outward sign of a healthy reproductive potential, with brain function and behavior?” In doing so, I will present some highlights of Professor Dennerstein’s work, especially with respect to the menstrual cycle, as she was so instrumental in establishing that connection.

In speaking about the female reproductive system, it is important to remember its primary objective, that of reproduction, as seen in Table 1. We have a tendency to split things into compartments when we think about the reproductive system, but it is not a system in isolation. The reproductive system has to induce sexual development, maturation, and maintenance of function, with maintenance being a critically important concept in that the process of reproduction must cycle repeatedly to allow many opportunities to reproduce because the whole goal is to perpetuate our species. The reproductive system facilitates oocyte growth early on until 20 weeks gestation when the total number of oocytes for the entire life span is produced and then stored, matured, and released in a decaying function that I will not address this morning. This afternoon you will hear more about the decaying part of that function, especially with respect to the relationship with behavior. The reproductive system promotes gamete interaction to get sperm and eggs together so that reproduction can occur, and then optimizes transport through the fallopian tubes and implantation in the uterus with subsequent development through gestation and a safe delivery. Very importantly, the woman must recover from that delivery and resume normal menstrual cyclicity to allow the process to occur again.

The question that this raises for social creatures, such as humans, is “How does this complex biological process influence behavior to allow reproduction to take place?” Particularly, I want to address the issue of “getting gametes together.” The interaction of the egg and sperm in the distal

fallopian tube cannot take place unless a male has interacted with a female at the right time and in the right manner to place the sperm at the optimal location. The question of how this process influences behavior then becomes central to these discussions. Because female reproductive receptivity is dependent upon the menstrual cycle, if one can understand the menstrual cycle in terms of hormones and related events, it puts reproduction into perspective and makes sense.

I will go through the menstrual cycle in the way that I teach medical students and residents in training, which is relevant to observable physical events by asking the question “If you have a healthy sperm and a healthy egg, how can you get them together?” Moreover, “if the system is not successful in that particular cycle in allowing pregnancy to occur, how is the stage reset to facilitate a conception in the next cycle?” That concept of cyclicity is very important, as emphasized in Table 2. The human body demonstrates many rhythms, and the menstrual cycle is a great example of a long-term rhythm that roughly matches the lunar cycle in terms of length, at least through the early and middle portions of the reproductive life span. The logical demonstration of this cyclicity will set the stage for much of Professor Dennerstein’s research, and is schematically depicted in Figure 1.

Let me start with the anatomic structures involved, particularly structures in the brain. We will be talking about the brain a great deal today as we explore the relationship of physiology and behavior. The hypothalamus is in the central part of the base of the brain, receiving communication from all other parts of the brain and spinal cord. The pituitary gland is located immediately underneath the hypothalamus, hanging down from it in what appears to be an upside-down mushroom. The ovaries are located in the pelvis on either side of the uterus where the outward sign of menstrual bleeding originates. With respect to the hypothalamus, pituitary, and ovaries, let us explore the communication between these structures and describe how they talk to each other because that is central to any discussion of reproductive physiology. Let us talk about hormones, because

Table 2 The human menstrual cycle

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1. Optimizes the circumstances for successful reproduction.
 - a. “Gets good gametes together.”
 2. If unsuccessful, sets the stage for optimal circumstances in the next cycle.
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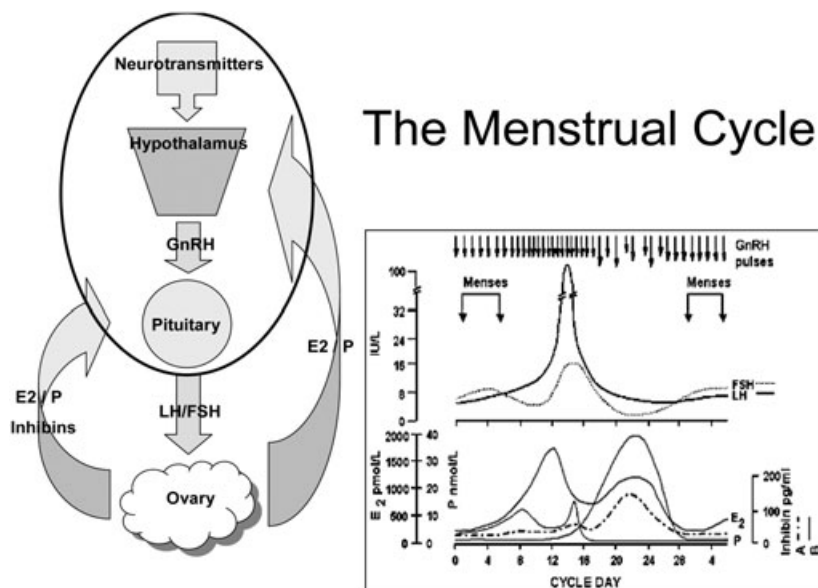


Figure 1 An integrated representation of the endocrine structures and secretory patterns essential to the human menstrual cycle. The left panel depicts regions and transmitters in the brain and hormone feedback loops with the ovary. The right panel depicts the hormone secretion pattern from each corresponding structure over the course of a normal menstrual cycle.

hormones are simply a way for those essential structures to communicate [1].

How does one structure tell another structure what to do? The hypothalamus works through gonadotropin-releasing hormone (GnRH), the releasing protein that it secretes from nerve processes on blood capillaries. It is a marvelous system where nerve cells receiving and transmitting nerve signals within the brain release a peptide hormone into a tiny portal system of blood vessels that take these hormone signals directly to the pituitary. The gonadotrophs, the cells in the pituitary that respond to GnRH, then talk to the ovary by releasing luteinizing hormone (LH) and follicle stimulating hormone (FSH) into the general circulation to talk to specific cells in the ovaries with instructions for specific activities. The ovaries then talk back to the brain with constant feedback communication to both the pituitary and the hypothalamus with both steroid and protein hormones. The most important of the steroid hormone signals are estradiol, the most potent of the estrogens produced by ovarian follicles and the corpus luteum, and progesterone, produced primarily by the corpus luteum after an ovulation has occurred. In addition to these steroid hormones, the peptide inhibins are secreted and are primarily involved in controlling the release of FSH by the pituitary. The ovaries use the same steroid hormones to talk back to the hypothalamus and close the loop by regulating the secretion of GnRH. Finally, neurotransmitters from other parts of the brain modulate the secretion of GnRH in the hypothalamus,

and influence the feedback loop from the ovaries and pituitary.

Now, how does all this fit together to explain cyclicity? This is particularly important because a striking feature of this unique system is that a single hormone, GnRH, controls the release of two hormones, LH and FSH. The key to understanding this is, once again, the concept of biologic rhythms, the very basic theme of all endocrinology. There are long-term rhythms, such as the menstrual cycles, and short-term rhythms such as the secretion of most hormones. Hormone secretion tends to occur in bursts or pulses, with ever-changing concentrations of each hormone facilitating normal function. One of the earliest examples of this aspect of hormone secretion was the demonstration that GnRH must be secreted in a pulsatile fashion to maintain the secretion of LH and FSH from the pituitary gland. It was then demonstrated that the variation in the two components of hormone pulses, the frequency that they occurred and the size of each pulse, was instrumental in determining whether LH or FSH was secreted and in what amount.

If we consider the standard 28-day menstrual cycle well studied in 20-year-old university students, ovulation occurs on day 14 in the middle of the cycle, with the first 14 days involving follicular growth, and the second 14 days involving hormone secretion by the corpus luteum. It has been demonstrated that GnRH pulses change over the course of these different phases. Pulse frequency increases over the course of the follicular

phase to a midcycle surge initiating ovulation, and then slows down again over the course of the second half of the cycle under the influence of feedback. It is this rise and fall of GnRH pulses that is one of the basic underpinnings of menstrual cyclicity, with the requirement for a fall in pulse frequency after the rise in order to set the stage for the next cycle. The differential secretion of the gonadotropins LH and FSH then makes sense because different patterns of GnRH secretion favor secretion of one over the other. Specifically, the somewhat slower GnRH pulses at the beginning of the cycle favor the release of FSH to initiate follicular growth in the cohort of follicles that have become activated to respond to FSH. With follicular growth, hormone secretion from the growing follicles in the ovary feed back to both the pituitary and the hypothalamus. Specifically, inhibins reduce the secretion of FSH while estradiol increases GnRH pulsatility, which favors the increasing secretion of LH. When a mature follicle secretes enough estradiol just prior to the midpoint of the cycle, this positive feedback induces a sudden burst of GnRH that initiates the surge of both LH and FSH, and results in the maturation and release of an oocyte, and the transformation of this follicle into the corpus luteum.

In the ovaries, the first half of the cycle is dominated by the growth of a pool of follicles that are able to respond early in the cycle to the rising levels of FSH. Later in the first half of the cycle, as FSH starts to fall because of negative feedback by inhibin B, the largest follicle is selected to grow and become dominant, and make increasing amounts of estrogen and inhibin. With the LH surge and release of the oocyte, the dominant follicle becomes the corpus luteum, a lipid-laden structure that secretes increasing amounts of the hormones progesterone, estradiol, and the second type of inhibin, inhibin A, which feeds back to the pituitary and further decreases FSH secretion. Progesterone, which plays a very central role in many of today's discussions, is important as a negative feedback regulator in that it is critical for slowing down the pulses of GnRH from the hypothalamus. One could characterize steroid hormone secretion from the ovary across the cycle as a gradual increase in the secretion of estradiol in the first half of the cycle, and then a rise and fall of both progesterone and estradiol across the second half of the cycle.

An absolutely beautiful aspect about this system is that it is carefully coordinated to promote its primary purpose—reproduction. Fertilization

takes place within a few hours after ovulation if the appropriate social actions have occurred and competent gametes are present. The resultant fertilized egg actually does not implant in the uterus until a week later, just at the time when the secretion from the corpus luteum is at its peak. This peak in the middle of the second half of the cycle coincides with the need to help a conceptus implant and grow. If pregnancy should occur, the system maintains that state: progesterone and estradiol stay high and keep the gonadotropins low so that the ovary will be quiescent during the subsequent gestation. However, in most cycles in our society, conception does not occur despite everything being in place for a pregnancy. It is then that the system must ready itself for the next cycle and the next opportunity to conceive. This occurs because the high progesterone and estradiol secretion has caused the GnRH pulses to slow down in frequency such that the corpus luteum is no longer stimulated to secrete. Progesterone and estradiol levels fall, ultimately initiating the onset of menstrual bleeding and release of the negative feedback to the hypothalamus with the resultant increase in pulse frequency with the initiation of the next cycle. So, the concept of growth with estrogen and recovery with progesterone secretion is very central to all the concepts that we will talk about throughout the rest of this morning. This cycle must be normal with normal cyclic hormone secretion for reproduction to occur.

An important part of this construct of reproductive function is that the majority of the structures I mentioned are located within the brain. In discussing a psychiatrist who is interested in hormones, the brain is central to understanding the potential relationship. Again, this makes sense when one considers the multiple integrative activities centered in the hypothalamus. It functions as a gatekeeper for many basic human functions such as thirst, hunger, temperature control, and sexual behavior. Because sexual behavior is the activity that leads to getting gametes together, and is controlled by the hypothalamus as evidenced by a number of animal models, it is logical to conclude that the known effects of the reproductive system on the hypothalamus would also play a role in sexual behavior to optimize the ultimate goal of reproduction.

My hope is that this background has set the stage for the rest of this morning's discussions by simply describing the cyclic hormone changes in the active reproductive years. It provides the framework for the central theme, which allows us

again to ask the central question, “Is reproductive physiology related to reproductive behavior?” As Dr. O’Connell mentioned in her introduction, there was very little evidence to support this in the 1970s when Professor Dennerstein began her career. Her early work and the questions that she asked helped frame that entire debate. More specifically, she asked about the relationship of the menstrual cycle and its underlying hormonal parameters to human behavior. In particular, I will address the relationship of menstrual cycles to sexuality, affect, and psychological disorders with just a bit at the end about the transition to reproductive aging.

To review Professor Dennerstein’s work in this area, I looked at her distinguished career and divided her work into three overlapping stages, her early, mid-, and later work when she was transitioning to reproductive aging and behavior. Her earliest writings included reviews of the available literature, which set the stage for her more active investigations thereafter. The earliest of her articles that I could find explored the known relationship of oral contraceptives and sexuality, with suggestions for a relationship but conflicting evidence from limited data [2]. A subsequent review explored the relationship of affect across the menstrual cycle, with some published evidence for cyclic variation but little evidence for a direct hormonal link [3]. Such a hormonal connection is critical in that hormones drive the menstrual cycle and that hormones can be modulated, thereby providing an opportunity to modify affect. She also described an interesting case of cyclic psychosis treated by ablating the menstrual cycle with marked improvement in the psychotic symptoms, suggesting that the cyclicality was the underlying problem rather than the absolute levels of hormones [4].

Subsequently, Professor Dennerstein applied the knowledge that she had gained from her review work, and conducted a number of clinical trials to see if the modulation of hormones could modify behavior. Specifically, she conducted two clinical trials in women with premenstrual syndrome (PMS). Prior to that time, uncontrolled trials had suggested that progesterone therapy was effective for treating the symptoms of PMS. In a well-designed, randomized, blinded crossover clinical trial of oral micronized progesterone, she was able to demonstrate an improvement in the symptoms [5]. A subsequent trial of dydrogesterone did not demonstrate any clinical benefit [6], and a later trial of transdermal estradiol gel for menstrual migraines demonstrated some benefit

[7]. Collectively, at a time when there was a dearth of rigorous science in this area, Professor Dennerstein provided scientific rigor to questions important to human reproductive behavior.

Simultaneously with her early reviews and clinical trials, Professor Dennerstein utilized her psychiatrist’s expertise in assessing behavior to recognize that it must be quantitatively measured to be associated with objective hormone data. So, early in her career, she developed the Scale of Sexual Response [8], a subsequently validated instrument for measuring human sexuality that has paved the way for some of the instruments that are in even wider use today. She used this questionnaire and other validated instruments to carefully assess women with documented PMS [9]. She demonstrated with rigorous studies, in women with well-documented PMS, that depression, stress, and self-esteem had demonstrable cyclic variation consistent with less objective reports [10]. She pioneered the addition of the rigorous collection of biological samples over the course of the menstrual cycle simultaneously with the acquisition of validated questionnaire data, recognizing the cyclic variation in hormones and the need to characterize this variation to detect differences. These studies set the stage for the landmark study that I will showcase this morning.

The article I wish to highlight, “Menstrual cycle hormonal profiles of women with and without premenstrual syndrome” [11], is illustrative of the way that Professor Dennerstein’s work changed the landscape in the field of women’s health, and was a landmark when it appeared in the *Journal of Psychosomatic Obstetrics and Gynecology* in 1993. To set the stage for this work, at that time, progesterone was theorized to be central to the etiology of PMS with the specific theory that a deficiency in progesterone secretion from the corpus luteum was the primary physiologic cause, prompting the use of supplemental progesterone as a primary treatment for the disorder. A number of observational studies had supported this theory, but a rigorous scientific exploration had not been reported. The goal of Professor Dennerstein’s study was to describe daily urinary hormone levels through an entire cycle in women with well-documented PMS vs. controls. It used scientific rigor combining good physiologic measures with validated measures of PMS to describe the hormone patterns and relate them to the symptoms. A previous pilot study of 19 women with PMS had suggested some validity to the theory that progesterone deficiency was present in PMS.

Table 3 Mean \pm SD 24-hour urinary concentrations of estrogen ($\mu\text{g}/24$ hours) and pregnanediol ($\text{mg}/24$ hours) for 65 women with premenstrual syndrome (PMS) and 18 women with no cyclical symptoms (volunteers) at five different cycle phases

	Menstrual cycle phase				
	Menses	Follicular	Ovulatory	Luteal	Premenstrual
Estrogen					
PMS	9.1 \pm 6.2	18.9 \pm 5.9	49.0 \pm 9.6	29.6 \pm 6.3	26.7 \pm 6.3
Volunteers	13.4 \pm 8.4	22.1 \pm 7.4	44.8 \pm 7.8	28.4 \pm 8.4	25.9 \pm 10.4
Pregnanediol					
PMS	0.5 \pm 0.5	0.4 \pm 0.5	0.5 \pm 0.5	2.5 \pm 0.5	2.7 \pm 0.6
Volunteers	0.6 \pm 0.6	0.5 \pm 0.3	1.2 \pm 1.7	2.5 \pm 0.8	2.4 \pm 0.6

Adapted from Dennerstein et al. [11].

The bulk of the previous work in this area had not documented the presence of PMS well, and had not used validated instruments so that the diagnosis was retrospective and unconfirmed. In general, sample sizes in previous studies were small, a common theme in much of Professor Dennerstein's work over her entire career. Of the few studies that had measured hormones, most had used either a single serum sample or pooled urine samples, making interpretation difficult with the cyclic changes in hormones that we explored earlier. So, this well-designed prospective study recruited 65 women with PMS confirmed by validated instruments, and 18 women with no reported cyclic symptoms as an essential control group of the appropriate age with regular cycles and no hormone use. The study measured symptoms for two consecutive cycles and collected daily 24-hour urine samples throughout the second of these cycles. Simply the collection of the urine was an impressive achievement as anyone who has tried to collect all urine for one 24-hour period can attest. The urine samples were assayed for total estrogens and pregnanediol, the metabolites of estradiol and progesterone measurable in urine. The women filled out daily symptom diaries and validated menstrual distress questionnaires to concurrently document a range of symptoms. Of note, this design then became the model for a number of different studies investigating biologic changes over the menstrual cycle.

The results were quite different than what was predicted or what was seen in the pilot study. The women with PMS had longer cycles with a mean increase in cycle length of about 2 days. Remarkably, the second half of the cycle did not differ in length between the two groups as would have been predicted if there was a decrease in progesterone secretion in the women with PMS. The cycle length difference was due to a shorter first half of the cycle in the control women, with ovu-

lation occurring 2 days later in the PMS subjects. Not only was the second half of the cycle not different in length between the two groups, but also the integrated pregnanediol secretion over the entire cycle was a little higher in the women with PMS, contradicting the prevailing theory at the time. As seen in the original table taken from that article, Table 3, with the cycles normalized and divided into five different segments, there are no differences in either total estrogen or pregnanediol concentrations. The cyclic patterns of both hormones were exactly consistent with previously described hormone patterns over cycles in normal women. Thus, this study could not find any evidence that progesterone deficiency was present in women with documented PMS, a critical finding that completely changed the thinking about the cause and treatment of the disorder. It became clear that the problem was more complex, and that a simply identifiable hormone problem was not present. A subsequent theory following this work suggested that women with PMS responded differently to normal levels of progesterone, although no subsequent studies have supported this. It also argued against the rationale that progesterone supplementation was an appropriate primary treatment modality for PMS because the deficiency it was purported to correct could not be documented.

This study also led to a number of other investigations central to the question of hormones and behavior including a companion extension that related sexual interest to the measured hormones over the course of the cycle [12]. Using the sexual interest question on the daily symptom diary, Professor Dennerstein demonstrated that sexual interest was higher in the follicular and ovulatory phases of the cycle, and was correlated with feelings of well-being. Not only was this good science but also made intuitive sense in that feeling good about oneself would be associated with increased

interest in sex. Sexual interest did not correlate with any hormone values in this study.

Finally, I want to briefly explore the next phase in Professor Dennerstein's career when she began the "transition" to look into the effects of aging on the relationship of hormones and behavior. Initially, she conducted a study looking at the effects of age and nonhormonal contraception, specifically tubal ligation and intrauterine device use, on menstrual cycle characteristics and hormone levels over the course of the cycle [13]. Of note, age was correlated with the day of the preovulatory estrogen peak, as well as cycle length, noting that the first part of the cycle begins to shorten with increasing age. The second part of the cycle did not appear to change in length, reminiscent of the cycle similarities between the control and the PMS group in Professor Dennerstein's previous landmark article. Age did not correlate with the length of menstrual bleeding, but a previous tubal ligation also shortened the first part of the cycle in a similar manner to women who were older. This is consistent with the theory that tubal ligation decreases ovarian blood flow and may accelerate ovarian aging.

Professor Dennerstein then made the critical and essential step in studying a time-related phenomenon by moving from cross-sectional to longitudinal studies, initially reporting on the relationship between earlier premenstrual complaints with subsequent perimenopausal experiences [14]. As I mentioned earlier, reproductive cyclicality includes a decaying function in terms of the number of oocytes available for ovulation with the inevitable depletion of a fixed initial pool. Looking over time in individual women to add that information was a critical step in understanding reproductive physiology with respect to changes unique to women at midlife. This early foray into longitudinal studies noted that women with a history of premenstrual complaints were more likely to develop dysphoria, skeletal complaints, digestive complaints, respiratory symptoms, interpersonal stress and significant hassles—risks that were also associated with smoking and low exercise.

In conclusion, and in preparation for this afternoon's theme of studies of reproductive aging, I hope that I have convinced you that, in exploring the central theme of the relationship of reproductive physiology with reproductive behavior, Professor Dennerstein convincingly demonstrated not only that such a relationship exists, but also that it was measurable in women having normal men-

strual cycles. This early body of work is illustrative of Professor Dennerstein's enormous contributions specifically in three critical areas. She is to be applauded for bringing a multidisciplinary approach, melding psychosocial and biological sciences together to study a particularly complex problem. As an integrator, she thought outside the box and merged the silos of thinking that tend to restrict innovation. She brought scientific rigor to a field plagued with simplistic study design and analytic methods by instituting excellent study design, rigorous methods, and the advanced analytic approaches necessary to explore complex problems both cross-sectionally and longitudinally. Finally, she brought multidimensionality to her studies by looking at multiple parameters simultaneously to explore complex relationships. Everything is related to everything in human beings, necessitating a broad approach to answer complex questions.

On a global note, I think it is safe to say that she is one of the early driving forces in transforming an ill-defined domain of human health into a recognized field of study—the area of women's health. In my training as an obstetrician gynecologist in the early 1980s, I never heard that term despite spending most of my waking hours working in the field. The field of women's health research is now firmly established with much of the credit resting on Professor Dennerstein's shoulders. She has become a model and a mentor to an entire generation of both international and Australian investigators and clinicians in this field. Today is a testimonial to these accomplishments, Lorraine. We might not be here if you had not done all this work, and certainly not with the breadth and depth with which we all have become accustomed. For that, we all thank you tremendously.

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Statement of Authorship

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Appendix**Additional Relevant References of Potential Interest**

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