ROGERS

Endocrine and Metabolic Aspects of Gynecology

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TO

DOROTHEA

MICHAEL, PRISCILLA, and PETER

Preface

The preface to a book usually attempts to defend the need or purpose of the book and to suggest which segment of the medical population should read it. This is sometimes hard to do. In the field of endocrine gynecology there are excellent books and the sections on endocrinology in several of the more recent general texts of gynecology are critical and thoughtful. It was felt, however, that a short but reasonably comprehensive review of the various endocrine aspects of gynecology could find a place and be helpful to students and practitioners alike. Insofar as possible, an effort has been made to discuss physiologic mechanisms. In many areas of this subject, these are not clearly defined and are subject to controversy. Where disagreement exists it has been presented because the author believes students should be aware of such differences of opinion.

Over the past years the specialty of gynecology has changed markedly. It is fascinating to read the older gynecologic literature which dealt largely with surgically remediable lesions or surgical techniques. The modern gynecologist must be versed in other disciplines and be as well an endocrinologist, psychiatrist, physician and counselor. That the author, an internist, should have the temerity to offer a book on gynecologic matters reflects the healthy growth of the specialty.

I would like to take this opportunity to express my deep appreciation to my colleagues in obstetrics and gynecology who have so warmly received me into their circles and from whom I have learned much.

I am indebted to Dr. Janet W. McArthur, Dr. William B. Schwartz, Dr. Bernard J. Clark and Dr. Sophia B. Bamford, each of whom reviewed chapters, and to Dr. Douglas J. Marchant for helpful suggestions. I am particularly grateful to Dr. Edwin B. Astwood for reviewing several chapters and Dr. George W. Mitchell, not only for reviewing much of the manuscript, but for providing the opportunity to work in his department.

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Chapter One

Physiology of Menstruation

Many of the disorders to be discussed under the broad heading, endocrine gynecology, are reflected in aberrations of the menstrual cycle. It is therefore pertinent to review briefly present-day concepts of the physiology of normal menstruation. There are numerous gaps in our understanding of this complex process and. additionally, many of our concepts of menstruation are based on observations in lower animals that are assumed to apply to women.

HYPOTHALAMUS

In the last two decades the function of the hypothalamus in effecting the production and release of gonadotropins from the adenohypophysis has been more clearly defined. Stimulation of certain areas of the hypothalamus results in ovulation. It is now generally agreed that this influence of the hypothalamus upon the adenohypophysis is mediated by humoral agents reaching the pituitary by way of the hypophysial portal circulation. This is discussed in more detail in Chapter Ten.

GONADOTROPINS

The pituitary gonadotropins are the follicle-stimulating hormone (FSH), the luteinizing hormone (LH), which is also called interstitial cell-stimulating hormone (ICSH), and luteotropic hormone (LTH). The gonadotropins are glycoproteins of large molecular weight. FSH and LH are probably secreted by certain types of basophilic cells and LTH by acidophilic cells.[1] Although there has been controversy as to whether the pituitary gonadotropins represent one moiety acting on different end organ systems, it is now generally regarded that FSH and LH are separate entities. FSH and LH have been isolated separately

from pituitary extracts in animals[2,3] and in humans.[4,5,6] Furthermore, two distinct qualitatively different gonadotropic activities have been demonstrated in urine by chromatographic methods.[7] FSH is secreted in barely detectable amounts in prepubertal girls, but at the menarche is found in measurable quantity.

Both FSH and LH are secreted throughout the menstrual cycle. FSH is responsible for the growth and development of the ovarian follicle. Early in the cycle, as the primordial ovarian follicle migrates from beneath the tunica albuginea, the granulosa cells surrounding the ovum proliferate and a crescentic cavity is formed by liquefaction of a portion of the granulosa cells. Fluid accumulating in this cavity slowly distends the follicle. The connective tissue surrounding the follicle becomes differentiated into the theca interna and becomes rich in epithelioid cells that are thought to be the main source of estrogens. The development of the follicle up to the state of antrum formation is independent of the follicle-stimulating hormone, but its further growth is dependent upon FSH. The factors responsible for the selection of one follicle for growth and development while other follicles undergo an atretic process are unknown. The cells of the theca interna produce increasing amounts of estrogen, which is generally regarded to diminish production of FSH. The basis for this assumption is the observation that long-term treatment of intact animals with estrogen reduces pituitary gonadotropin content. Estrogens in small amounts, however, appear to effect release of FSH from the pituitary.[8]

The luteinizing hormone is generally regarded as the hormone responsible for ovulation. Without LH, the follicle-stimulating hormone can produce follicular growth but estrogen production by the follicle is limited. Just prior to midcycle there is an increased secretion of LH, and rupture of the ovarian follicle and ovulation occur. Following the discharge of the ovum the collapsed follicle undergoes transformation into the corpus luteum. The theca interna proliferates and the granulosa cells are transformed into granulosa lutein cells which elaborate progesterone. Estrogens are also produced by the corpus luteum. Estrogens are necessary for the luteinizing hormone to function properly, and the luteinizing hormone is also necessary for the production of estrogen. Progesterone in lower animals has, in large doses over a long period of time, a suppressive action on the production of LH.[9] Such a relationship in the human has not been clearly demonstrated.

The relationships of FSH and LH to estrogen and progesterone, diagrammatically shown in Figure 1, are reviewed in Hisaw's classic paper.[10] Recently the careful studies of urinary gonadotropin excretion by McArthur,[11] Taymor[12] and others[13] have defined the cyclic variations during the human menstrual cycle. At midcycle there is an increase in the excretion of both gonadotropins, during the early phase of which there is a change in the ratio of FSH to LH with a transient preponderance of LH. During the luteal phase there is a decline in the excretion of both gonadotropins, followed by a rise in excretion toward the end of the luteal phase that continues into menstruation (Fig. 2).

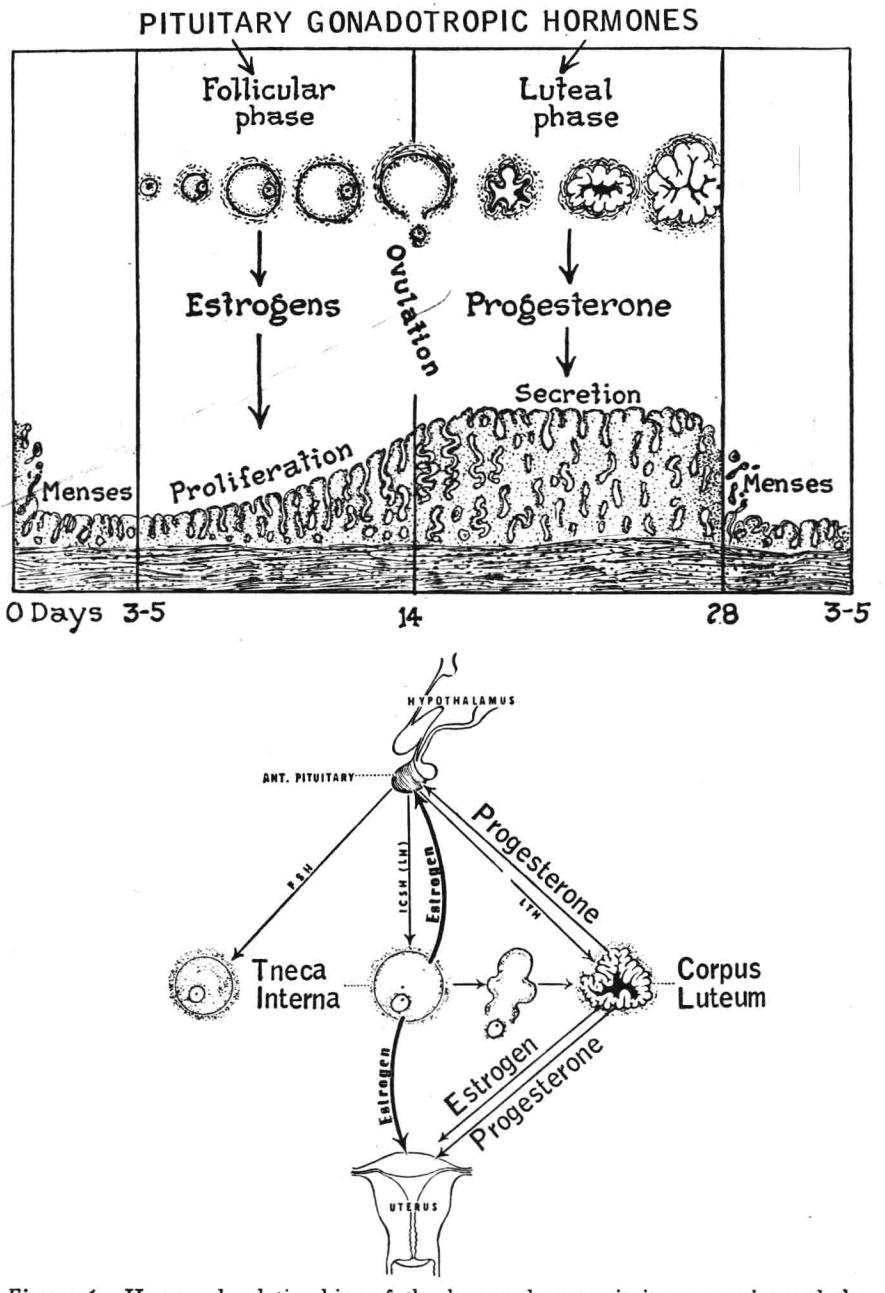

Figure 1. Hormonal relationships of the hypothalamus, pituitary, ovaries and the endometrium in the menstrual cycle. (From Williams Obstetrics by N. J. Eastman and L. M. Hellman, 12th Ed., 1961. By permission of Appleton-Century-Crofts.)

The third gonadotropic hormone, luteotropin, has been shown in the rat to be necessary for the maintenance of a functioning corpus luteum[14] and it is assumed that it has a similar function in the human female. The action of this gonadotropin is not well understood and varies in different species. It has been suggested that there is a discharge of luteotropic hormone over a relatively short period of time after ovulation, this single release of LTH being sufficient to maintain the corpus luteum for its normal life span.[15] If pregnancy occurs, a

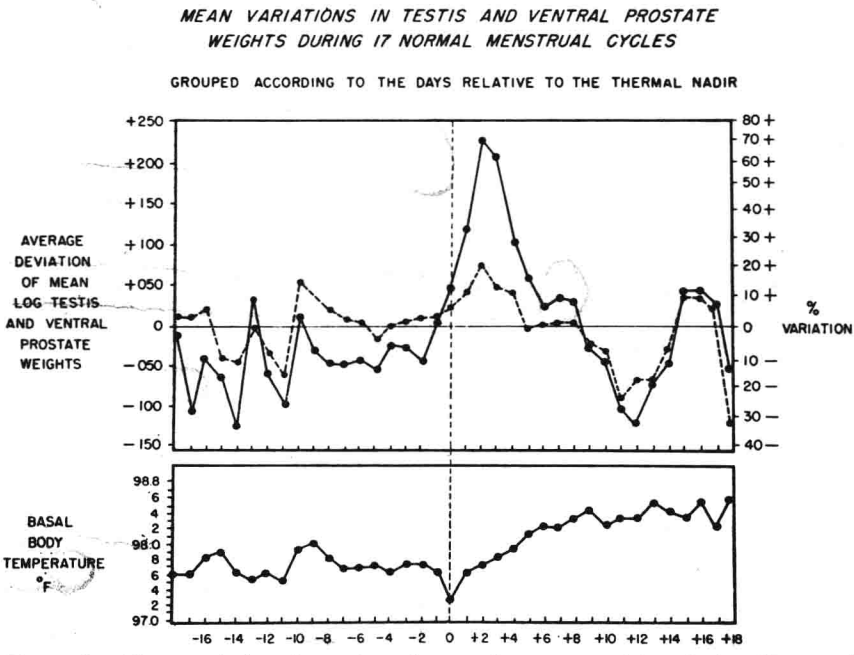

Figure 2. Mean variations in testis and ventral prostate weights during 17 normal menstrual cycles. The broken lines represent rat testis weights, an index of FSH activity. The unbroken lines represent ventral prostate weights, an index of LH activity. (Modified from McArthur, J. W., Worcester, J. and Ingersoll, F. M,: The urinary excretion of interstitial cell and follicle stimulating hormone activity during the normal menstrual cycle. J. Clin. Endocrinol. *18:* 1186–1201, 1958. Reproduced with the permission of the publishers, J. B. Lippincott Co., Philadelphia.)

secondary release of LTH is thought to occur which may be continuous throughout gestation. The relationship between progesterone and LTH is not clearly defined but some evidence indicates that progesterone can suppress LTH production.[16] Small amounts of estrogen appear to effect the release of luteotropin. There is also some evidence to suggest that oxytocin is involved in the regulation of the release of LTH. The daily administration of oxytocin to cows during the early follicular phase and continued into the luteal phase results in shortened cycles and cystic and small corpora lutea.[17] In some way the uterus is involved in this mechanism because oxytocin injected into hysterectomized cows has no effect on shortening the cycle. The insertion of foreign bodies, such as beads or balloons, into the uteri of cows or sheep during the early luteal phase leads to a significant shortening of subsequent

cycles. It may be that the presence of these foreign bodies leads to the release of oxytocin which results in interference with the initial LTH release, and this in turn leads to incomplete luteinization and nonfunctioning corpora lutea. If the foreign bodies are inserted in the late luteal phase of the cycle, the life of the corpora lutea is prolonged. These observations suggest some sort of stimulus from uterus to hypophysis.[15] Another curious observation is that hysterectomy in rats, mice and guinea pigs leads to a prolonged maintenance of the corpora lutea, apparently the result of sustained secretion of LTH.[18] It has also been shown by Rowlands and Short[19] that the corpora lutea of hysterectomized guinea pigs have a higher concentration of progesterone than the corpora lutea of pregnant guinea pigs, suggesting again some sort of uterine control of luteal function.

ESTROGEN

The major estrogenic steroids are estradiol-17β, estrone and estriol and 16-epiestriol (Fig. 3). The ovary elaborates estradiol-17β and

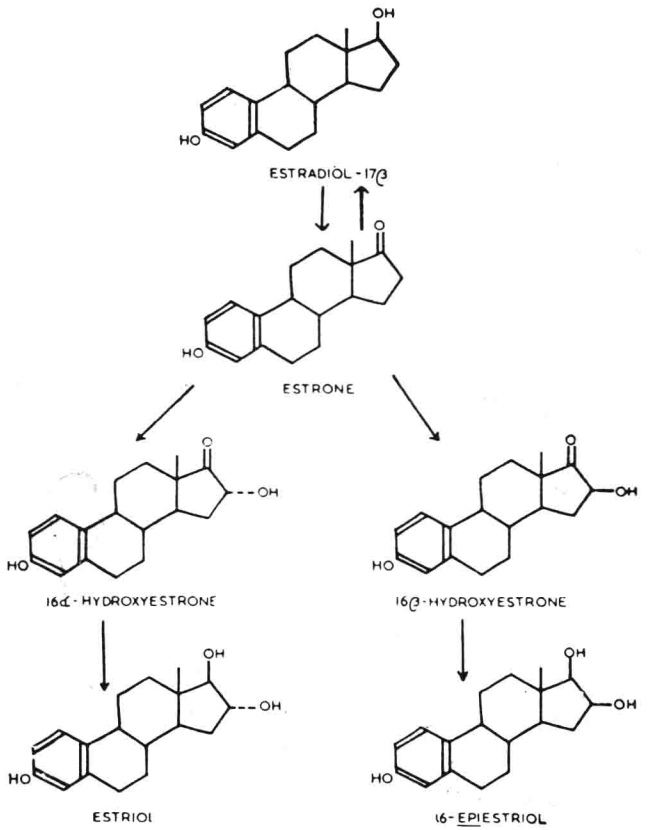

Figure 3. Structural relationships of the major estrogenic steroids. (From Marrian. G. F.: The urinary estrogens and their quantitative determination. Cancer *10:* 704-706, 1957. Reproduced with permission of the publishers.)

estrone, estriol being a degradation product of estradiol and estrone. Both acetate and cholesterol are probably precursors of the estrogens[20] and there is considerable evidence that progesterone can be converted to estradiol-17β with androstenedione as an intermediate. The metabolic conversion of progesterone to 17α-hydroxyprogesterone and Δ^4-androstene-3,17-dione has been demonstrated in bovine ovarian tissue,[21] and Zander[22] demonstrated both 17α-hydroxyprogesterone and Δ^4-androstene-3,17-dione in extracts of human follicles. Ryan and Smith[23] demonstrated conversion of progesterone-4-C^{14} to estrone and estradiol in the human ovary. The probable metabolic pathway is shown in Figure 4. The conversion of testosterone to estradiol has also been

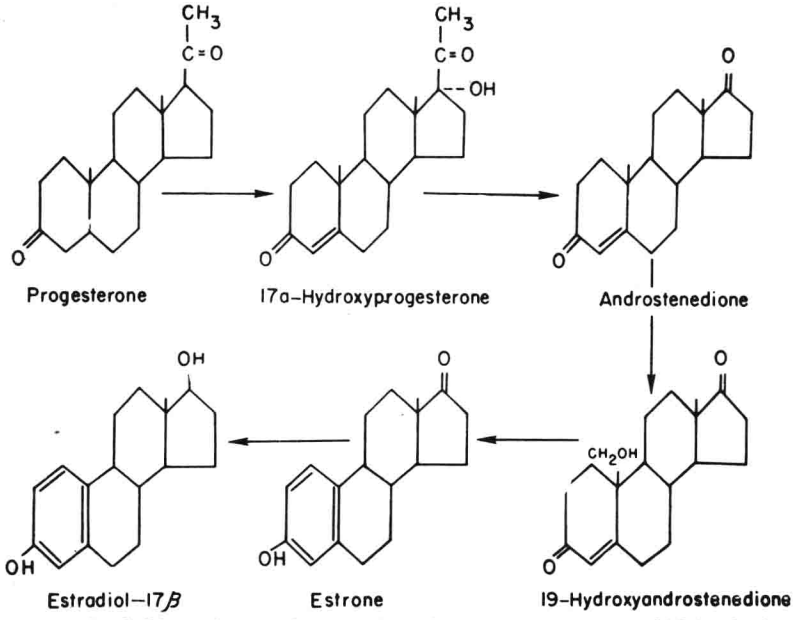

Figure 4. Probable pathway of conversion of progesterone to estradiol in the human ovary. (From Short, R. V. and London, D. R.: Brit. M. J.: 1724–1727, 1961. With the permission of the publishers.)

shown[24,25] in human ovarian tissue slices and androstenedione can be converted to testosterone. As yet, testosterone has not been demonstrated in normal ovarian tissue so that its role in the biogenesis of the ovarian steroids remains to be clarified.

The main sources of estrogen are the ovary, the adrenal cortex, the Leydig cells of the testes, and the placenta. Estriol, the metabolic product of estradiol and estrone, is found in greatest concentration in the urine of women during the luteal phase of the menstrual cycle and during pregnancy. Histochemical studies[26,27] have clearly indicated the ovarian theca cells are responsible for the production of estradiol. The classic bioassay methods of estrogen assay, such as that of Allen and Doisy, have gradually been replaced by chemical assays. In common use is the method described by Brown,[28,29]

The estrogens are rapidly inactivated chiefly in the liver, are excreted in the bile, and in some animals, and probably the human, undergo an enterohepatic circulation. Estrogens are excreted in the feces and urine and are recovered as sulfates or glucuronates.[30,31] Roberts and Szego[32] have shown that the major portion of the estrogens in the peripheral blood is in the form of a conjugate of estriol which is protein bound and appears in the beta-globulin fraction. Chemical assays of excretion of estrogens in the urine show a clearly defined

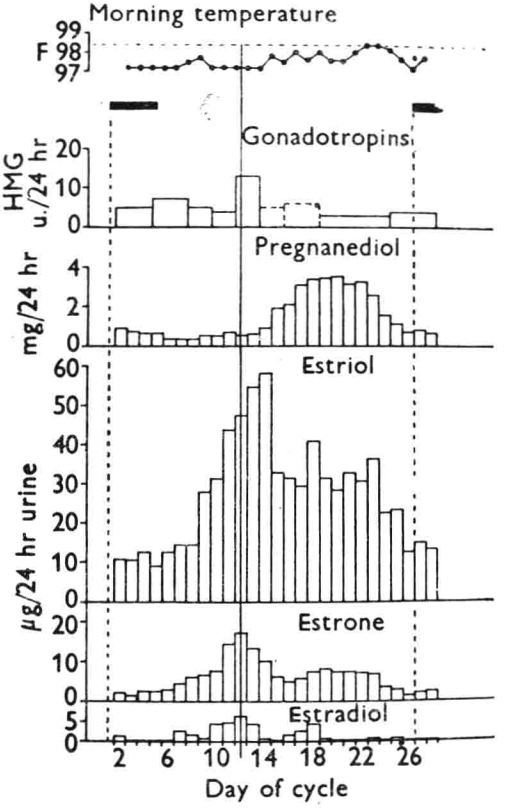

Figure 5. Urinary excretion of sex hormones during the menstrual cycle. (From Brown, J. B., Klopper, A. and Loraine, J. A: The urinary excretion of estrogens, pregnanediol and gonadotrophins during the menstrual cycle. J. Endocrinol. *17:* 401–410, 1958. Reproduced with permission of Cambridge University Press, New York.)

peak at about the thirteenth day of the cycle. Following this elevation there is a short period of decrease of excretion followed by another rise in the midluteal phase[33,34] (Fig. 5).

Under the stimulus of estrogen the uterine endometrium undergoes a period of growth divided into two subphases, the preovulatory or proliferative phase and the postovulatory or secretory phase. The latter phase is largely under the influence of progesterone but previous stimulation of the endometrium by estrogen is necessary for its proper development. The shedding of the endometrium is dependent upon withdrawal of hormonal support. The ribonucleoprotein and alkaline phosphatase content of the endometrium increases under the influence of estrogens.[35] The vaginal epithelium proliferates, glycogen deposits in