INADEQUATE CORPUS LUTEUM FUNCTION: A PATHOPHYSIOLOGICAL INTERPRETATION OF HUMAN BREAST CANCER EPIDEMIOLOGY

BARRY M. SHERMAN, MD, AND STANLEY G. KORENMAN, MD

Detailed hormonal studies of normal and abnormal human reproductive cycles have led to the conclusion that inadequate corpus luteum secretory function was one of the characteristic features of infertile and/or irregular menstrual cycles. When the epidemiology of breast cancer was reviewed in that light, the hypothesis was strongly suggested that estrogenic stimulation in the absence of sufficient cyclic progesterone secretion may provide a setting favorable to the development of mammary carcinoma.

Cancer 33:1306–1312, 1974.

NUMEROUS EPIDEMIOLOGIC STUDIES HAVE DEMonstrated breast cancer risk factors related to reproductive experience (Table 1).[30] These may be explained on the basis of inadequate function of the corpus luteum, a common manifestation of disorders of follicular maturation. The altered hormonal environment of the mammary gland consequent to persistent estrogenic stimulation, in the absence of an adequate progestational phase, may provide a hormonal setting in the mammary gland favorable to the development of carcinoma.

NORMAL PHYSIOLOGY

Recent technological advances in the area of hormone measurement have permitted the sequential analysis of gonadotropins, estrogens, and progesterone during the normal human menstrual cycle.[2,3,6,49] The hormonal changes during the cycle reflect two dynamic events illustrated in Fig. 1. Progressive follicular maturation culminates in ovulation. It is followed by corpus luteum formation, maturation, and decay. During each menstrual cycle, estradiol secreted by the maturing follicle reaches a peak serum level of 300–500 pg/ml at mid-cycle, in many cases 24–48 hours prior to the LH surge.[2,39] There is a second rise in estradiol levels during the luteal phase, presumably reflecting synthesis by the corpus luteum. Estrone levels follow the same general pattern as estradiol although a substantial portion results from peripheral conversion of adrenal androstenedione.[46]

Serum progesterone levels which are in the 100 pg/ml range during the preovulatory half of the cycle undergo a 100-fold rise to levels of 10–15 ng/ml as the principal secretion of the mature corpus luteum. Progesterone is responsible for the rise in basal body temperature, the change to the secretory state of the endometrium, and transient changes in the breast, manifested clinically as fullness and tenderness.

The patterns of hormonal change recently observed by measurements in serum were reflected in the measurement of urinary gonadotropins and steroid excretion products. Thus, a mid-cycle gonadotropin peak and a mid-cycle estrogen peak have long been observed, while more recent studies have shown luteal phase increases in pregnanediol, estradiol, estrone, and the metabolite estriol.[5,17,22,46] Of particular note is that excretion of androgens is increased during the luteal phase, including androsterone and etiocholanolone as well as individual and total 17-ketosteroids.[3,20]

During the menopausal years, excretion of estrogens is low and attributed to conversion of adrenal androstenedione to estrone.[12] The pattern of hormonal secretion during the premenopausal years and progressively following cessation of vaginal bleeding is not known.

From the Division of Endocrinology, Department of Internal Medicine, University of Iowa and Veterans' Administration Hospitals, Iowa City, Iowa.

Supported by NIH Grant 1-R01HD06104, RR 59 from the General Clinical Research Centers Program, and P-593 from the American Cancer Society.

Address for reprints: Barry M. Sherman, MD, Department of Internal Medicine, University Hospitals, Iowa City, Iowa 52242.

Received for publication August 21, 1973.

HORMONAL INFLUENCES ON THE BREAST

In man, as well as other animals, estrogens and progesterone each have a distinct role in glandular development, estrogens acting to cause duct elongation, and progesterone to bring about alveolar proliferation. Progesterone has its most profound effect during pregnancy, but may exert similar influences albeit to a lesser extent during each luteal phase.[28] The presence of receptors indicates that the organ is a target of the hormone involved. Estrogen receptors have been found in neoplastic human breast and are presumed to be present in the normal epithelium as well, though not readily demonstrable.[21,24] Receptors for other hormones, particularly progesterone, have not been demonstrated in human breast tissue.

In vitro studies on mouse mammary explants demonstrated that the hormonal requirements of the breast go far beyond estrogen and progesterone. Insulin, hydrocortisone, and prolactin were required for growth of mammary tissue in vitro and for synthesis of the milk protein casein, and the components of lactose synthetase.[47,48] Human chorionic somatomammotropin (HCS) has been found to satisfactorially substitute for prolactin in the stimulation of casein synthesis, indicating that the high levels of both hormones during pregnancy regulate the preparation of the breast for lactation. Mammary gland prolactin and HCS receptors have been demonstrated in experimentally induced mammary tumors.[9]

At yet a higher level of integration, steroid hormones, particularly estrogens, modify the secretion of pituitary hormones. Estradiol appears to trigger the mid-cycle LH/FSH surge and enhances the secretion of both growth hormone and prolactin.[16,39] It is therefore reasonable to assume that in states of altered ovarian function the breast is subject to the consequenes of disordered secretion of both ovarian and pituitary hormones.

PATHOPHYSIOLOGY OF THE ABNORMAL MENSTRUAL CYCLE

Abnormalities of the menstrual cycle have defied rigorous classification in spite of their frequency and clinical concern. Broadly considered, such disorders can be divided into three categories: 1) primary amenorrhea, and secondary amenorrhea or oligomenorrhea; 2) with; and 3) without evidence of androgen excess.

Primary amenorrhea is often the result of a chromosomal defect. Circulating estrogen levels are low, while gonadotropins are increased.

Secondary amenorrhea may result from premature ovarian failure, a rare occurrence, or a disturbance of the pituitary gland or hypothalamus. Recent studies employing the hypothalamic gonadotropin-releasing hormone indicate that in patients with otherwise normal pituitary function, secondary amenorrhea may result from a defect at or above the level of the hypothalamus.[51] In our laboratory, daily measurement of serum estradiol and progesterone in six subjects with secondary amenorrhea showed concentrations equal to those found during the normal follicular phase.[40]

Menstrual cycles which occur at irregular intervals are common during the years directly following menarche and directly preceding menopause.[44] Irregular cycles persist throughout reproductive life in some individuals, while in others, cycles become progressively rarer, frequently associated with weight gain and the development of hirsutism.

Investigation of the hormonal changes which occur during irregular menstrual cycles and in infertile women is very limited. We have recently assessed daily serum concentrations of LH, FSH, estradiol, and progesterone during six cycles in four obese women, two of whom were hirsute. All had unpredictable menses. In each case, vaginal bleeding was preceded by hormone changes which reflected follicular maturation and luteinization. However, luteal phase progesterone levels were far below those observed in a group of 10 women with normal cycles (Fig. 2).

Subnormal progesterone secretion during a luteal phase of less than 10 days was observed in 10 cycles in four women, three of whom were unaware of any menstrual or

TABLE 1. Breast Cancer Risk Factors

Increased	Decreased	No effect
Late first pregnancy	Early first pregnancy (early marriage)	Oral contraceptives
Nulliparity (non-married)	Castration	Lactation
Early menarche	Oriental	
Late menopause		
Obesity		
Low androgen excretion		
Low $E_3/E_1 + E_2$ excretion		

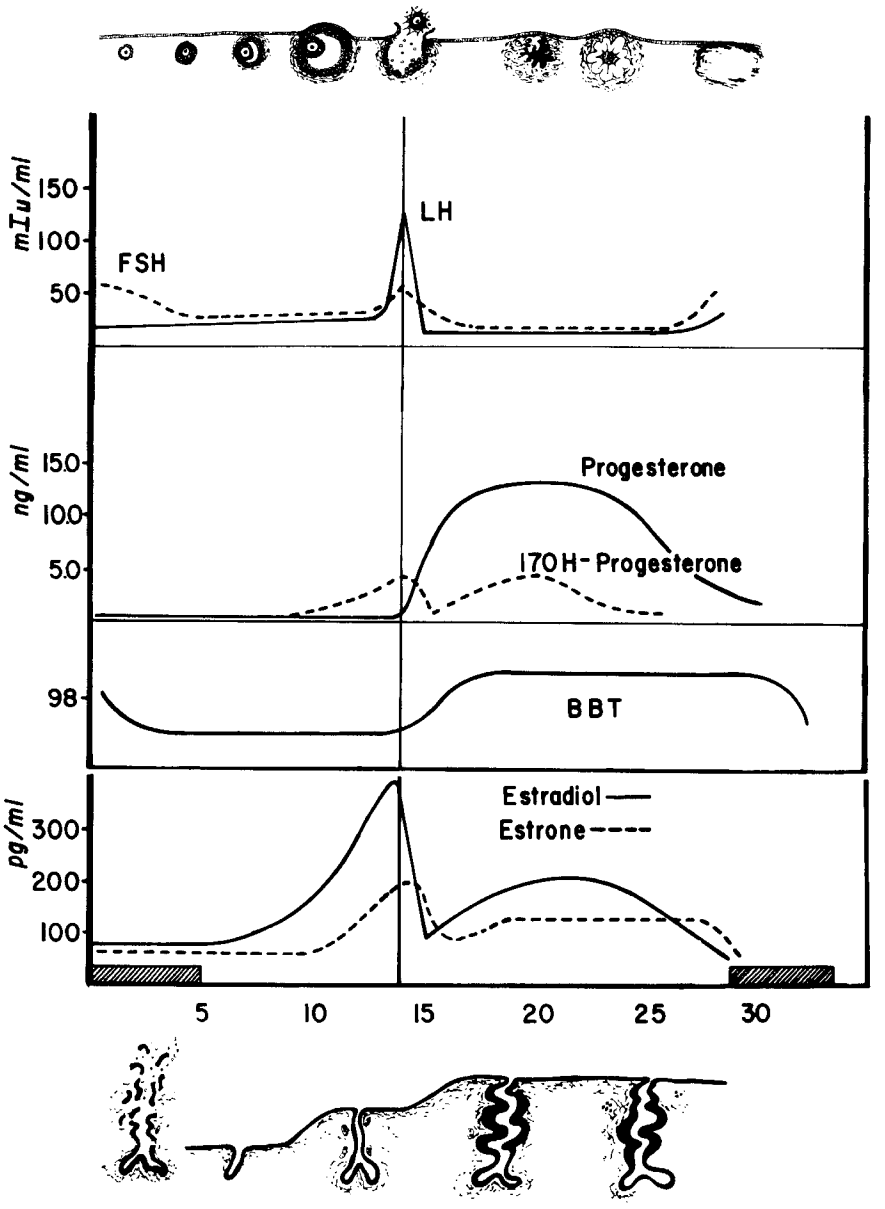

FIG. 1. The changes in concentration of relevant hormones throughout the menstrual cycle are illustrated and correlated with the sequential anatomical changes in the ovary and endometrium.

reproductive abnormality (Fig. 3). This entity has been termed the short luteal phase and is also associated with subnormal preovulatory estradiol levels and the absence of a rise in estradiol during the luteal phase.[41,43]

Low serum progesterone levels are reflected in low urinary pregnanediol excretion. Inadequate progesterone secretion results in a failure to develop a secretory endometrium. Biopsy of the endometrium has been used clinically to assess corpus luteum function.[15] Using this technique to obtain samples of endometrium 2 days prior to anticipated vaginal bleeding, limited endometrial development has been found to be associated with infertility in from 6–20% of infertile women with regularly occurring menstrual cycles.[11, 23,32] The irregular cycles which occur following menarche and prior to menopause may also have inadequate corpus liteum function. In a group of over 2000 infertile women, ages 15–50, Malkani found pre-menstrual endometrial biopsies which reflected progesterone insufficiency to be most common at the extremes of the reproductive age range and in patients with cycles of 42–60 days in length.[31]

It is therefore apparent that limited luteal phase progesterone secretion occurs in the

presence or absence of gross irregularity of the menstrual cycle.

The epidemiologic importance of these findings was strengthened by a study of premenstrual endometrial biopsies from 87 women with breast cancer and 50 normals. A normal secretory endometrium was found in 68% of controls and only 17% of breast cancer cases.[18]

BREAST CANCER EPIDEMIOLOGY

The frequent occurrence of menstrual cycles deficient in progesterone secretion may be the physiological basis for the risk factors for breast cancer indicated in Table 2.

Menarche and Menopause

Several studies have shown that women who had menarche at 16 years of age or under had almost twice the risk of developing breast cancer as those with later onset of menses.[42] It should be noted that these studies were performed in populations with a higher mean age at menarche and that the ensuing fall of the average age of menarche consequent to improved nutrition and other factors has been accompanied by increasing rates of breast cancer. Women with natural menopause at age 55 or greater have twice the risk of breast cancer as those with menopause prior to the age of 45.[45]

If a prolonged period of irregular and presumably progesterone-deficient cycles occurs following menarche and prior to menopause, estrogenic activity in the absence of normal cyclic rises in progesterone secretion may result. Prolonged menstrual irregularity and inadequate corpus luteum function would also directly affect potential fertility and the age at first pregnancy, another strong factor in breast cancer risk.

Parity

Early parity exerts a strong protective effect against breast cancer. Women who have their first child at age 35 or greater have over twice the breast cancer risk as those who have their first child under the age of 20.[29] The finding of increased breast cancer risk in nulliparious women has been repeatedly confirmed since first reported by Rigoni-Stern in 1842.[35] It is unknown whether early pregnancy reflects the protective effect of establishment of hormonally normal cycles, whether the hormonal consequences of pregnancy itself exerts a protective effect, or whether the initial pregnancy exerts an effect to normalize subsequent reproductive cycles.

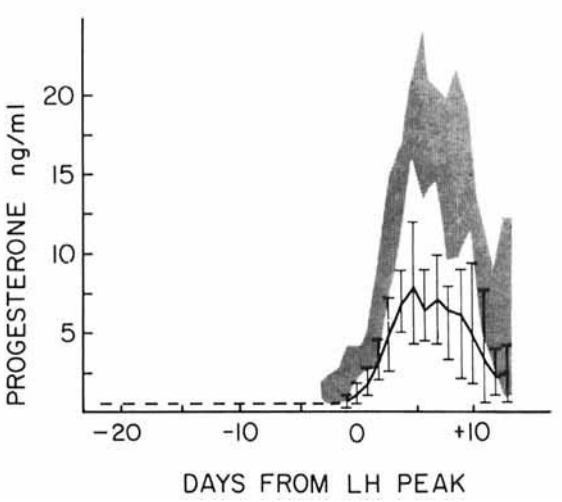

FIG. 2. The mean and range of serum progesterone during 6 cycles in four obese women with irregular menses are compared to the mean ± 2 SEM in 10 normal cycles (shaded area). Progesterone levels are synchronized around the day of LH peak.

Obesity

Obesity has been correlated with increased estrogen excretion in the urine of post-menopausal women and is related to the occurrence of endometrial carcinoma. It is known that carcinoma of the breast and endometrium frequently occur in the same individual.[37] Obesity in post-menopausal women has been

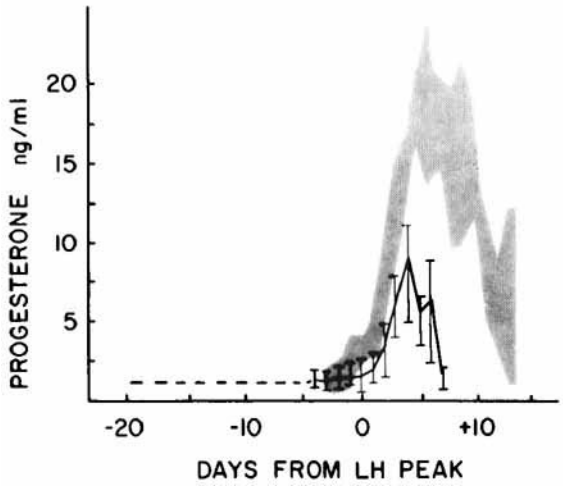

FIG. 3. The mean and range of serum progesterone during 7 cycles in four women with a short luteal phase is compared to the mean ± 2 SEM in 10 normal cycles (shaded area). Progesterone levels are synchronized around the day of LH peak.

positively correlated with breast cancer incidence.[10] In young women of childbearing age, obesity is often related to the occurrence of oligomenorrhea and infertility. The relationship of obesity during reproductive years to the eventual development of breast cancer is unclear.

Urinary Androgen Excretion

Some of the strongest data supporting a hormonal defect in women with breast cancer come from studies of urinary androgen excretion.[6,7,25] In 1960 Bulbrook observed that women with breast cancer excreted less androsterone and etiocholanolone than normal women. Those with the lowest androgen excretion had a rapidly progressive course and responded poorly to oophorectomy or adrenalectomy. Results of a recent controlled prospective study demonstrated that the decrease in urinary androgen excretion is detectable up to 9 years prior to the recognition of breast cancer.[8]

In women, androstenedione produced both by the adrenal glands and ovaries is a principal precursor of urinary androsterone and etiocholanolone. The plasma levels, metabolic clearance, and production rates of androstenedione are substantially higher during the luteal phase than during the follicular phase of the normal menstrual cycle.[1] Inadequate corpus luteum formation would therefore result in diminished urinary androgen excretion.

Urinary Estrogen Ratio

Several groups have investigated estrogen excretion products in the urine of patients with breast cancer. One group has reported a decreased excretion of estriol relative to the excretion of estrone and estradiol,[26,33,34] and suggests that estriol normally exerts a protective effect against the possible carcinogenic properties of estradiol. Others have reported that patients with breast cancer have normal or even elevated levels of estriol in the urine rather than low levels as noted above.[19]

During the menstrual cycle, the urinary estriol quotient (estriol/estrone + estradiol) is greater than 1.0 during the luteal phase and less than 1.0 during the follicular phase.[5,17] Corpus luteum inadequacy and/or widely spaced cycles would therefore result in a low estriol excretion ratio.

TABLE 2. Possible Physiological Basis of Breast Cancer Risk Factors

Risk factor	Possible Physiological basis
Early pregnancy	Early establishment of normal menstrual cycles
Late pregnancy and nulliparity	Relative infertility due to inadequate corpus luteum function
Early menarche and late menopause	Increased life time incidence of cycles with inadequate corpus luteum function
Westernization	Environmental "stress" producing "psychogenic" amenorrhea or oligomenorrhea
Low androgen excretion, low $E_3/E_1 + E_2$ excretion	Decreased luteal phase androgens and estrogens due to inadequate corpus luteum function

Nationality

One of the most striking epidemiologic correlations of breast cancer is the low incidence of breast cancer in women in Japan and China as compared to Western women.[14,27] To our knowledge the incidence of irregular cycles and infertility in women of Western cultures has not been compared to that of Oriental societies. Neither is it known whether the change to a more industrialized culture has been accompanied by a higher incidence of menstrual irregularity or infertility, or a great incidence of breast cancer.

Contraceptive Agents

Initial studies examining the incidence of breast tumors in women who have taken oral contraceptive agents have failed to demonstrate an increased incidence of breast cancer.[4,13,38] Very incomplete information suggests that oral contraceptive agents may exert a protective effect on the potential development of benign breast neoplasms.[50] It is of interest that all oral contraceptive agents contain a high concentration of a progestational agent, and it is possible that a protective effect for breast tumors in the general population may be exerted through progesterone-containing oral contraceptive agents.

CONCLUSION

Age at menarche and menopause, parity, and androgen and estrogen excretion have all been strongly related to breast cancer development. Treated independently, these risk factors have been of little assistance in identification of individuals with a predisposition to breast cancer development or to our understanding of basic mechanisms involved in the

genesis of breast cancer. In very practical terms, the hypothesis that breast cancer risk factors are the manifestation of inadequate corpus luteum function can be tested epidemiologically. If correct, a vigorous attempt can be made, early in reproductive life, to identify and treat those who manifest luteal phase inadequacy.

The hypothesis that breast cancer risk factors reflect abnormal regulation of the female reproductive cycle directs attention to the interaction of estrogen, progesterone, prolactin, and the gonadotropins at the cellular level. The carcinogenicity of estrogen in women has been inferred from extensive animal experimentation. It has been appreciated for some time that castration of pre-menopausal women harboring metastatic breast cancer results in remission in a significant number of cases, and within the past few years receptor proteins which specifically bind estradiol have been identified in some breast tumors. Surprisingly, there is little information regarding the cellular mechanisms of action of progesterone on the normal breast or its role in breast cancer. Basic investigation is therefore necessary to move us beyond the simplistic postulate that unopposed estrogen effect is carcinogenic or that adequate progesterone "protects" against breast cancer development.

REFERENCES

1. Abraham, G. E., Lobotsky, J., and Lloyd, C. W.: Metabolism of testosterone and androstenedione in normal and ovariectomized women. *J. Clin. Invest.* 48:696–703, 1969.

2. Abraham, G. E., Odell, W. D., Swerdloff, R. S., and Hopper, K.: Simultaneous radioimmunoassay of plasma FSH, LH, progesterone, 17-hydroxyprogesterone and estradiol 17-β during the menstrual cycle. *J. Clin. Endocrinol. Metab.* 34:312–318, 1972.

3. Adlercreutz, H., Luukkainen, T., and Svahborg, A.: Simultaneous determination of urinary estrogens, individual 11-deoxy-17 ketosteroids, total 17-ketosteroids, total 17-ketogenic steroids, pregnanediol and plasma cortisol during the menstrual cycle and in early pregnancy. *Ann. Med. Exp. Biol. Fenn.* 45:277–284, 1967.

4. Arthes, F. G., Sartwell, P. E., and Lewison, E. F.: The pill, estrogens and the breast. *Cancer* 21:1391–1394, 1971.

5. Brown, J. B.: Urinary excretion of estrogens during the menstrual cycle. *Lancet* i:320–523, 1955.

6. Bulbrook, R. D., Hayward, J. L., Spicer, C. C., and Thomas, B. S.: Urinary steroid excretion of normal women and women with advanced breast cancer. *Lancet* ii:1235–1240, 1962.

7. Bulbrook, R. D., Hayward, J. L., and Thomas, B. S.: The relation between urinary 17 hydroxycorticosteroids and 11-deoxy-17 oxosteroids and the fate of patients with mastectomy. *Lancet* i: 945–947, 1964.

8. Bulbrook, R. D., Hayward, J. L., and Spicer, C. C.: Relation between urinary androgen and corticoid excretion and subsequent breast cancer. *Lancet* ii: 395–398, 1971.

9. Costlow, M. E., Buschow, R., and McGuire, W. L.: Prolactin and estrogen receptors in hormone dependent mammary carcinoma. *Endocrinology* 92:55, 1973 (abstr.).

10. DeWaard, F., Halewijp, E. A., and Huizinga, J.: The biomodal age distribution of patients with mammary carcinoma. *Cancer* 17:141–151, 1964.

11. DiPaola, G. R., Ribas, J. M., and Arrigal, L. A.: Critical study of the retarded progestational phase. *Int. J. Fertil.* 16:189–194, 1971.

12. Dove, G. A., Morley, F., Batchelor, A., and Lunn, S. F.: Oestrogenic function in post-menopausal women. *J. Reprod. Fertil.* 24:1–8, 1971.

13. Fechner, R. E.: Breast cancer during oral contraceptive therapy. *Cancer* 26:1204–1211, 1970.

14. Feinleib, M., and Garrison, R. J.: Interpretation of the vital statistics of breast cancer. *Cancer* 24:1109–1116, 1969.

15. Foss, B. A., Horne, H. W., Jr., and Hertig, A. J.: The endometrium and sterility. *Fertil. Steril.* 9:193–206, 1958.

16. Frantz, A. G., Kleinberg, D. L., and Noel, G. L.: Studies on prolactin in man. *Recent Progr. Horm. Res.* 28:527–590, 1972.

17. Goebelsmann, U., Midgley, A. R., Jr., and Jaffe, R. B.: Regulation of human gonadotropins—VII. Daily individual urinary estrogens, pregnanediol and serum luteinizing and follicle stimulating hormones during the menstrual cycle. *J. Clin. Endocrinol. Metab.* 29: 1222–1230, 1969.

18. Grattarola, R.: The premenstrual endometrial pattern of women with breast cancer. *Cancer* 17:1119–1122, 1964.

19. Hellman, L., Zumoff, B., Fishman, J., and Gallagher, T. F.: Peripheral metabolism of LH, estradiol and estriol glucosiduronate in women with breast cancer. *J. Clin. Endocrinol. Metab.* 33:138–144, 1971.

20. Ismail, A. A. A., Harkness, R. A., and Loraine, J. A.: Some observations on the urinary excretion of testosterone during the normal menstrual cycle. *Acta Endocrinol.* 58:685–695, 1968.

21. Jensen, E. V., DeSombre, E. R., and Jungblut, P. W.: Estrogen receptors in hormone responsive tissues and tumors. *In* Endogenous Factors Influencing Host Tumor Balance, R. Wissler, T. Dao, and S. Wood, Eds. Chicago, Chicago University Press, 1972; pp. 15–30.

22. Johannson, E. D. B., Wide, L., and Gemzell, C.: Luteinizing hormone (LH) and progesterone in plasma and LH and estrogens in urine during 42 normal menstrual cycles. *Acta Endocrinol.* 68:502–512, 1971.

23. Jones, G. S., and Castro, V. M.: Hormonal findings in association with abnormal corpus luteum function in the human—The luteal phase defect. *Fertil. Steril.* 21:1–13, 1970.

24. Korenman, S. G., and Dukes, B. A.: Specific estrogen binding by the cytoplasm of human breast carcinoma. *J. Clin. Endocrinol. Metab.* 30:639–645, 1970.

25. Kumaoka, S., Sakauchi, N., Abe, O., Kusama, M., and Takatani, O.: Urinary 17-ketosteroid excretion in

women with advanced breast cancer. *J. Clin. Endocrinol. Metab.* 28:667–672, 1968.

26. Lemon, H. M., Wotiz, H. H., Parsons, L., and Mozden, P. J.: Reduced estriol excretion in patients with breast cancer prior to endocrine therapy. *JAMA* 196:112–120, 1966.

27. Lin, T. M., Chen, K. P., and MacMahon, B.: Epidemiologic characteristics of cancer of the breast in Taiwan. *Cancer* 27:1497–1501, 1971.

28. Lloyd, C. W.: Control of mammary growth and lactation. *In* Textbook of Endocrinology, 4th ed. R. H. Williams, Ed. Philadelphia, W. B. Saunders, 1968; pp. 480–482.

29. Lowe, C. R., and MacMahon, B.: Breast cancer and reproductive history of women in South Wales. *Lancet* i:153–157, 1970.

30. MacMahon, B., Cole, P., and Brown, J.: Etiology of human breast cancer—A review. *J. Natl. Cancer Inst.* 50:21–42, 1973.

31. Malkani, P. K.: Inadequate secretary endometrium. *Int. J. Fertil.* 7:53–60, 1962.

32. Moskowski, E., Woodruff, J. D., and Jones, G. S.: The inadequate luteal phase. *Gynecology* 83:363–372, 1962.

33. Marmorston, J., Crowley, L. G., Myers, S. M., Stern, E., and Hopkins, C. E.: Urinary excretion of estrone, estradiol and estriol by patients with breast cancer and benign breast disease. *Am. J. Obstet. Gynecol.* 92:460–467, 1965.

34. ———: Urinary excretion of neutral 17-ketosteroids and pregnanediol by patients with breast cancer and benign breast disease. *Am. J. Obstet. Gynecol.* 92: 447–459, 1965.

35. Mustacchi, P.: Ramizzini and Rigoni-Stern on parity and breast cancer. *Arch. Intern. Med.* 108:639–642, 1961.

36. Ross, G. T., Cargille, C. M., Lipsett, M. B., Rayford, P. L., Marshall, J. R., Strott, C. A., and Rodbard, D.: Pituitary and gonadal hormones in women during spontaneous and induced ovulatory cycles. *Recent Progr. Horm. Res.* 26:1–62, 1970.

37. Sall, S., and Calanog, A.: Steroid extretion patterns in post-menopausal women with benign and neoplastic endometrium. *Am. J. Obstet. Gynecol.* 114: 153–161, 1972.

38. Sartwell, P. E., Arthes, F. G., and Tonaseia, J. A.: Epidemiology of benign breast lesions—Lack of association with oral contraceptive use. *N. Engl. J. Med.* 288:551–554, 1973.

39. Sherman, B. M., and Korenman, S. G.: Further studies of gonadotropin and estradiol secretion during the preovulatory phase of the human menstrual cycle. *J. Clin. Endocrinol. Metab.* 36:1205–1209, 1973.

40. ———: Unpublished observations.

41. ———: Measurement of plasma LH, FSH, estradiol and progesterone in disorders of the human mentstrual cycle—The short luteal phase. *J. Clin. Endocrinol. Metab.* 38:89–93, 1974.

42. Staszewski, J.: Age at menarche and breast cancer. *J. Natl. Cancer Inst.* 47:935–940, 1971.

43. Strott, C. A., Cargille, C. M., Ross, G. T., and Lipsett, M. B.: The short luteal phase. *J. Clin. Endocrinol. Metab.* 30:246:231, 1970.

44. Treloar, A. E., Boynton, R. E., Behn, B. G., and Brown, B. W.: Variation of the human menstrual cycle through reproductive life. *Int. J. Fertil.* 12:77–126, 1967.

45. Trichopoulos, D., MacMahon, B., and Cole, P.: Menopause and breast cancer risk. *J. Natl. Cancer Inst.* 48:605–613, 1972.

46. Tulchinsky, D., and Korenman, S. G.: A radioligand assay for plasma estrone; normal values and variations during the menstrual cycle. *J. Clin. Endocrinol. Metab.* 31:76–80, 1970.

47. Turkington, R. W.: Induction of milk protein synthesis by placental lactogen and prolactin in vitro. *Endocrinology* 82:575–583, 1968.

48. Turkington, R. W., Juergens, W. G., Topper, Y. J.: Hormone dependent synthesis of casein in vitro. *Biochem. Biophys. Acta* 111:573–576, 1965.

49. Vande Wiele, R. L., Bogumil, J., Dyrenfurth, I., Ferin, M., Jewelewicz, R., Warren, M., Rizkallah, T., and Mikhail, G.: Mechanisms regulating the menstrual cycle in women. *Recent Progr. Horm. Res.* 26:63–95, 1970.

50. Vessey, M. P., Doll, R., and Sutton, P. M.: Investigation of the possible relationship between oral contraceptives and benign and malignant breast disease. *Cancer* 27:1395–1399, 1971.

51. Yen, S. S. C., Rebar, R., Vandenberg, G., and Judd, H.: Hypothalamic amenorrhea and hypogonadotropinism—Responses to synthetic LRF. *J. Clin. Endocrinol. Metab.* 36:811–815, 1973.