MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

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GALACTORRHEA

by Jean Wilson

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VIII. POSSIBLE ROLE OF PROLACTIN IN CARCINOMA OF THE BREAST

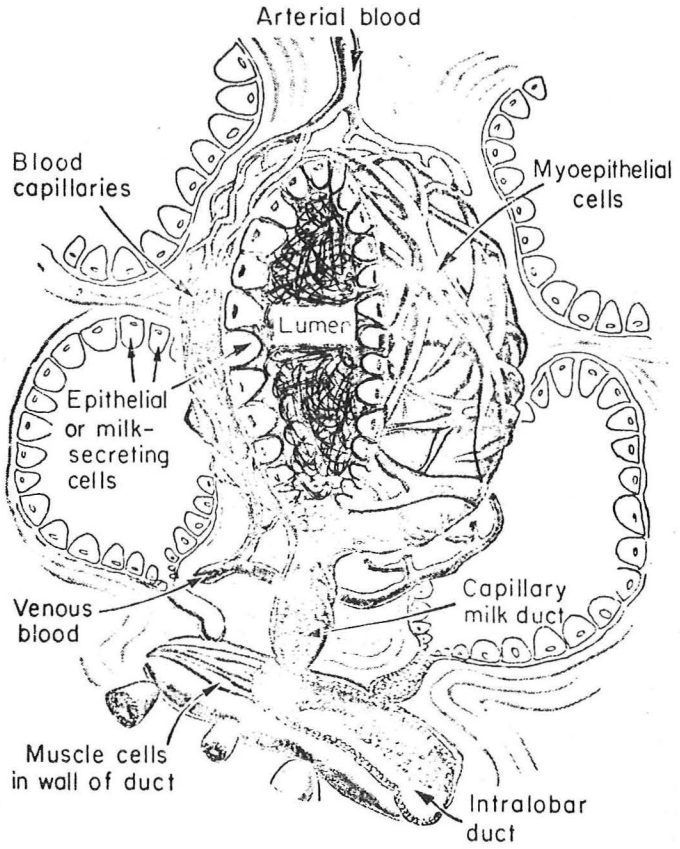

Figure 1
Diagram of an alveolus and an intralobular duct (Ref. 8)

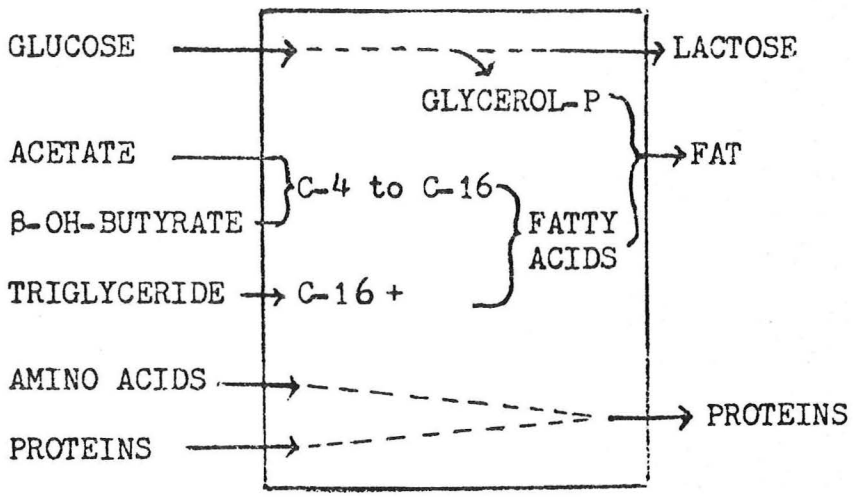

Figure 2
Outline of mammary gland metabolism (Ref. 10)

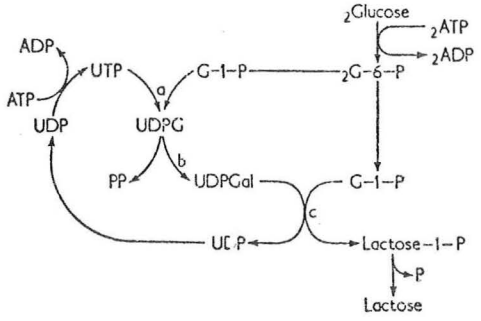

Figure 3, Mechanism of lactose synethesis in the mammary gland (Ref. 1)

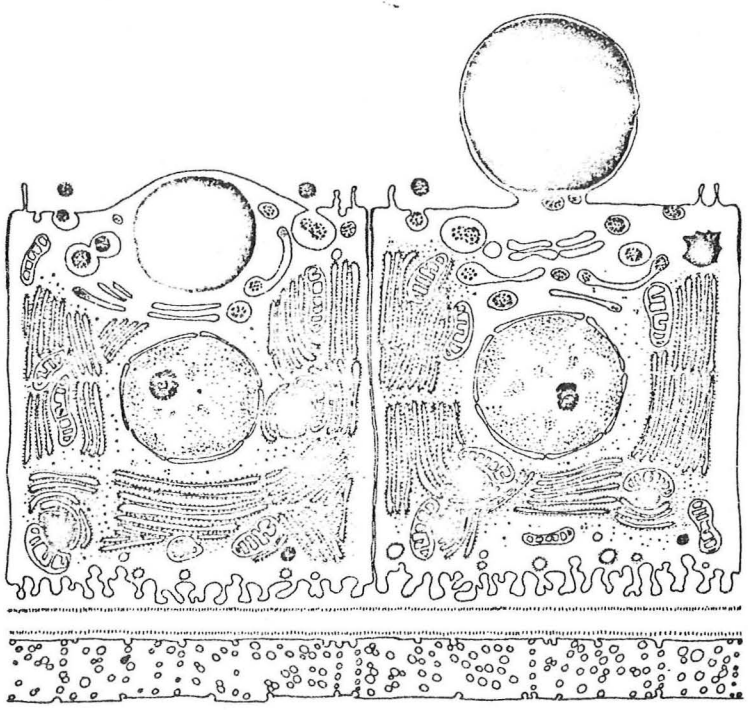

Figure 4. Schematic representation of alveolar cells in the mammary gland. Fat droplets (black) in the ergastoplasm and partly in close association with mitochondria. Right: a milk fat globule is being pinched off. Protein granules, ("micelles") in the Golgi cisterns and in the alveolar lumen. B 1 = Basement membrane of the epithelium. Notice the cytoplasmic "feet" and coated vesicles. B 2 = Basement membrane of the adjacent capillary. E = capillary endothelium.

Ref. 9

Figure 5. Daily milk yields of a goat before and after complete hypophysectomy and during replacement therapy (Ref 15)

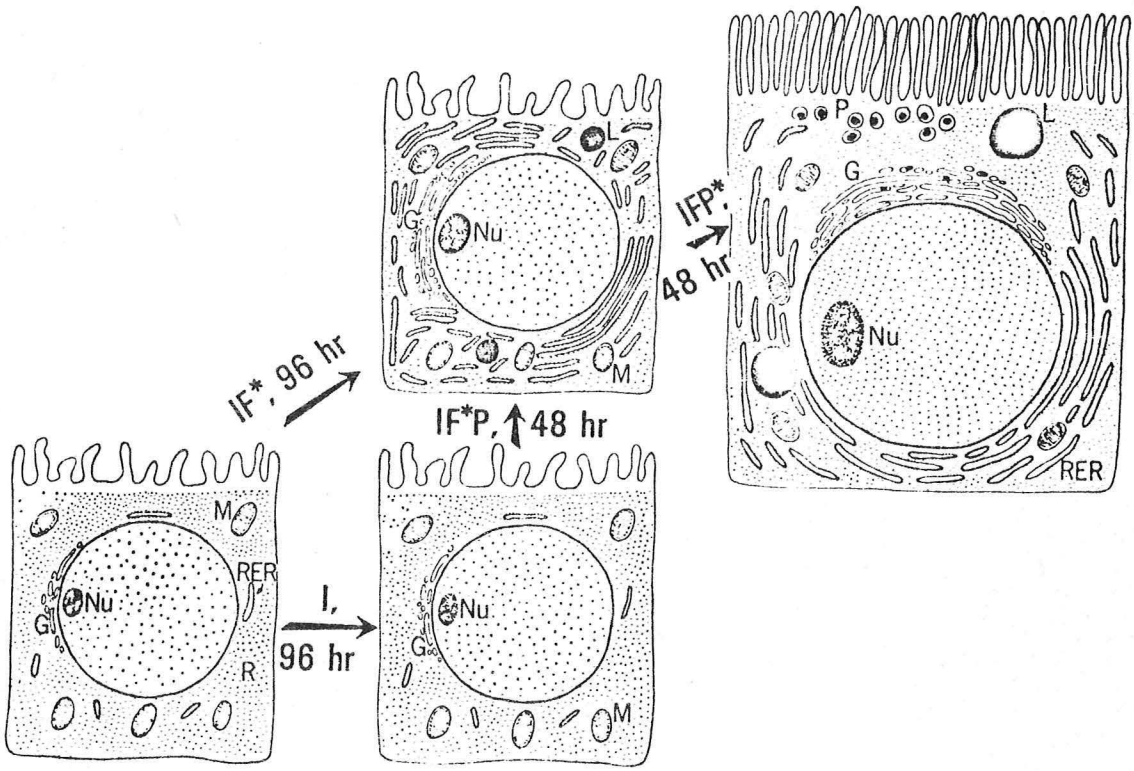

Figure 6. Schematic representation of the ultrastructural changes within alveolor cells of explants of mouse mammary gland cultured in vitro with added hormones (I, Insulin; F, hydrocortisone; P prolactin) (Ref. 3)

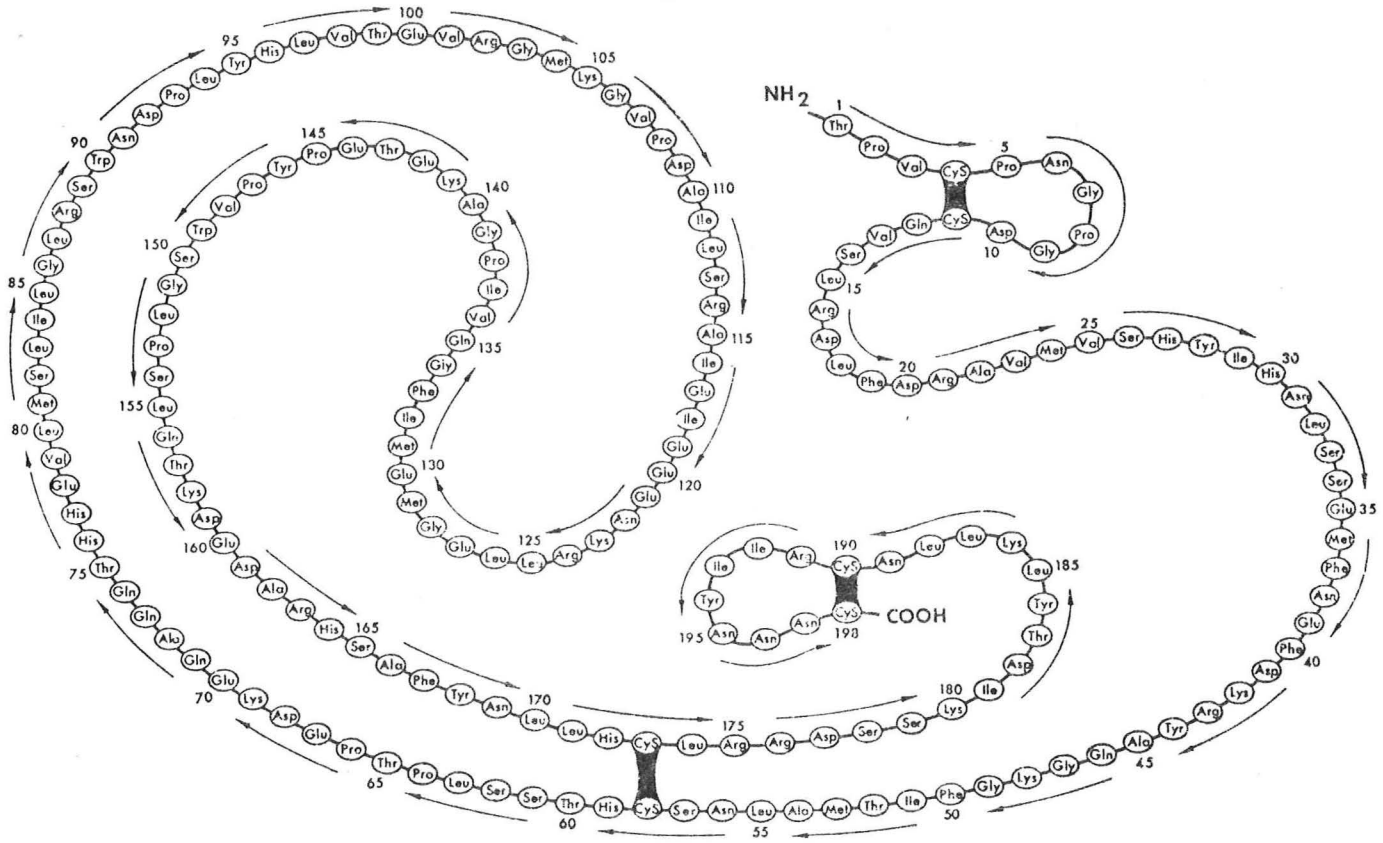

Figure 7. The amino acid sequence of ovine prolactin (Ref. 21)

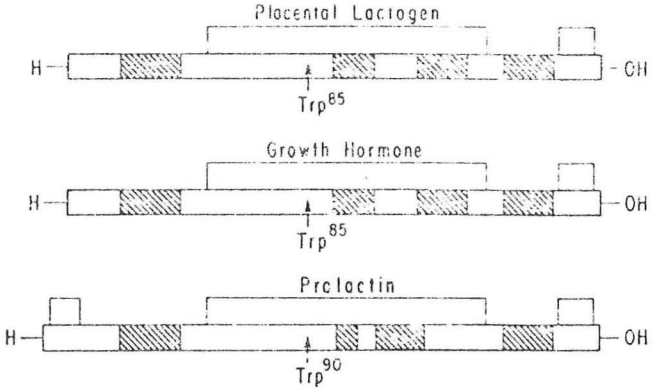

Figure 8. Diagramatic representation of the lactogen growth hormone, and prolactin molecules (Ref. 20)

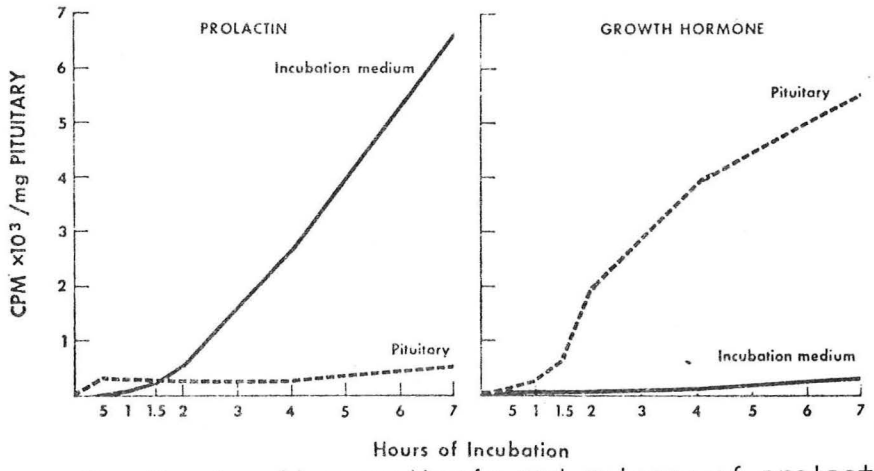

Figure 9. The <u>in vitro</u> synthesis and release of prolactin from rat pituitary explants in organ culture (Ref. 34)

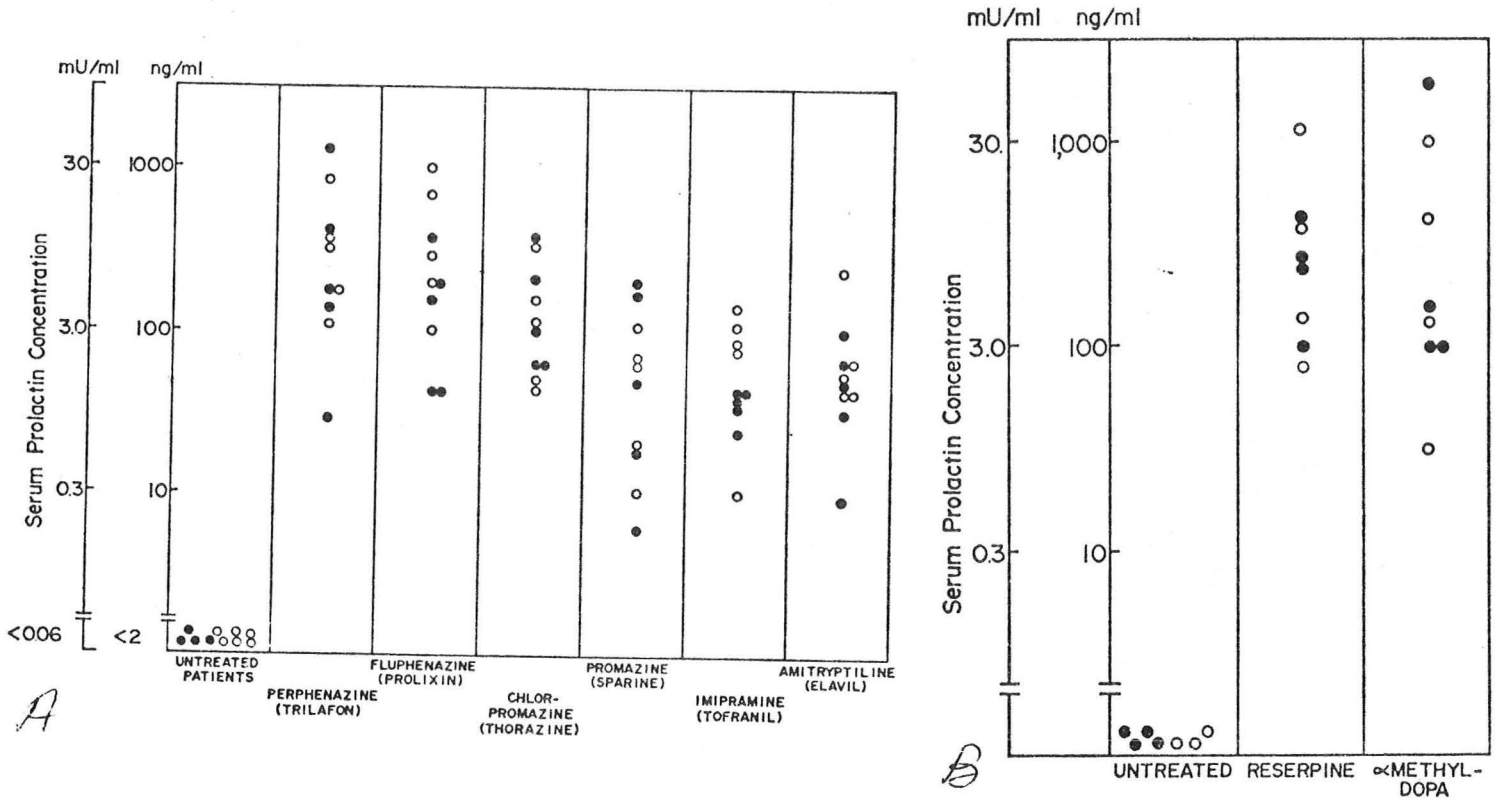

Figure 10. Serum prolactin levels in psychiatric patients (A) and hypertensive patients (B) treated chronically with various drugs. (Ref. 67)

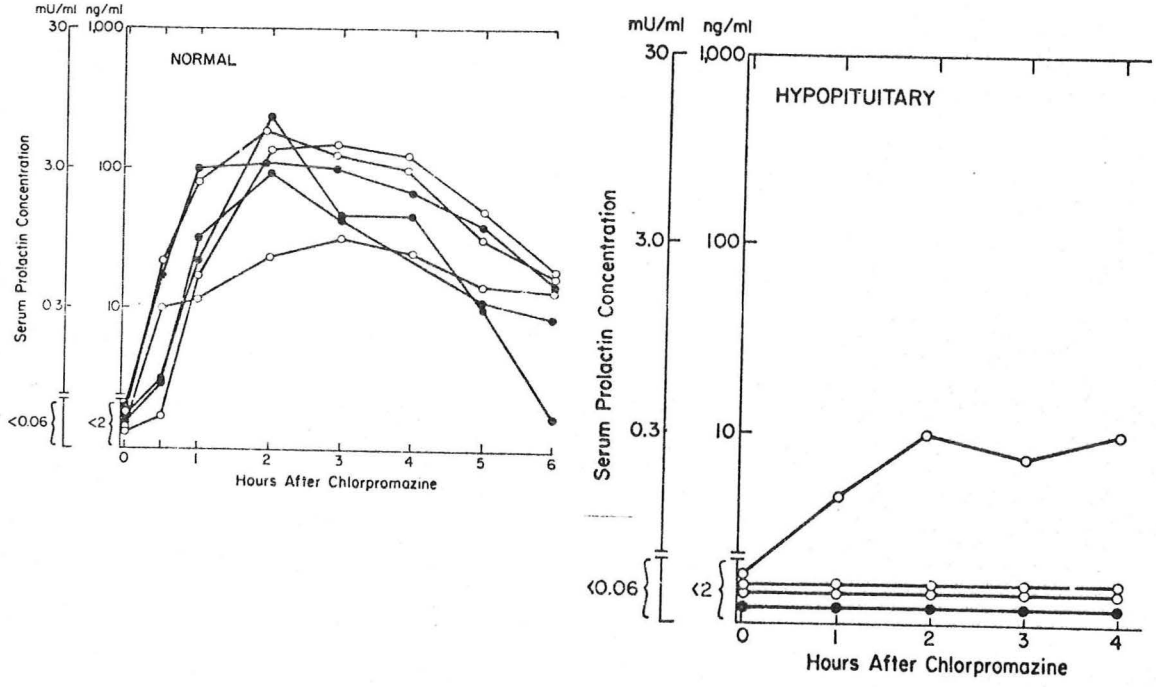

Figure 11. Time course of prolactin release in blood in response to an intramuscular injection of chlorpromazine (Ref. 36)

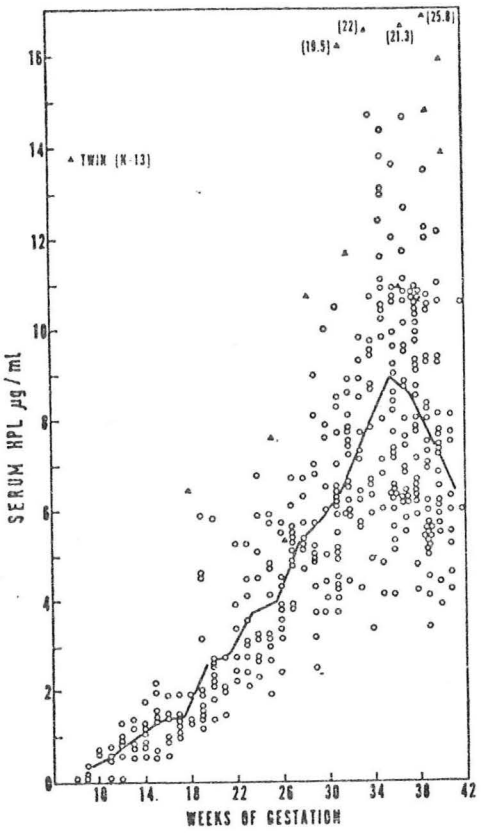

Figure 12. Levels of serum HPL in normally pregnant women and 13 twin pregnancies. (Ref. 47)

	Number of subjects	*Serum prolactin ng/ml*	
		Mean	*Range*
Children	36	11	0–17
Adults (males)	42	10	0–28
Menstrual cycle	9		
Follicular		10	4·2–21
Luteal		11	4·9–42
Acromegaly	13	16	3–26
Galactorrhoea	21	100	12–1800
Idiopathic hypopituitary	14	10	0–32
Pregnancy			
First trimester	24	25	7–47
Second trimester	96	50	6–350
Third trimester	102	134	36–600
Term	19	207	44–600
Postpartum (6 weeks)	25	10	0–14
Newborn			
Cord blood	19	258	120–500
One week	7	192	40–400
Nursing mother			
1–3 weeks			
Before suckling	6	14	8–20
30 min after		259	175–400
60 min after		133	75–200
3–5 days			
Before suckling	2	130	120–140
30 min after		230	200–260
60 min after		185	180–190
Insulin (10 patients)	No response		
(2 patients)	Maximum increment of 20 ng/ml		
Arginine (6 patients)	No response		
Anaesthesia and surgery			
Human subjects	4		6–150
Pregnant monkeys	6		30–1000
Non-pregnant monkeys	4		2–60

Figure 13. Serum prolactin values measured by radioimmunoassay (Ref. 66)

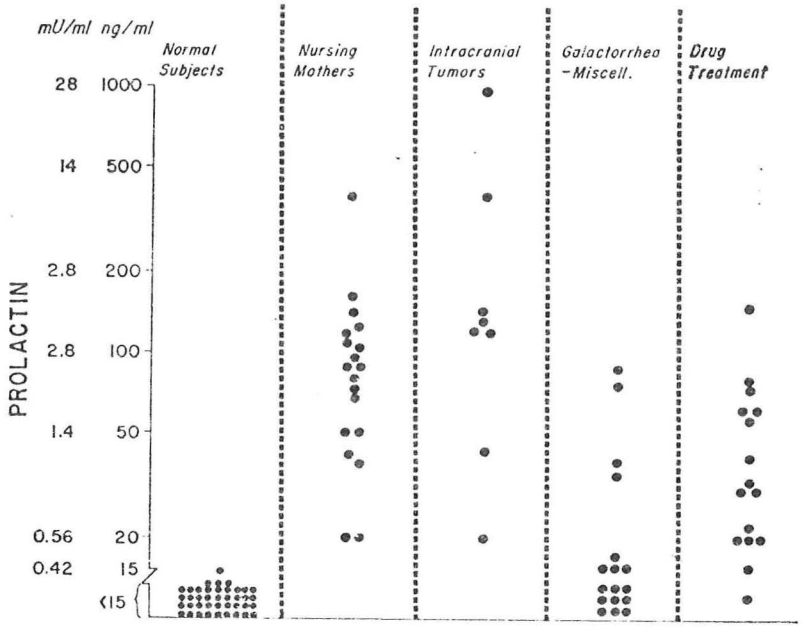

Figure 14. Serum prolactin values measured by bioassay (Ref. 65)

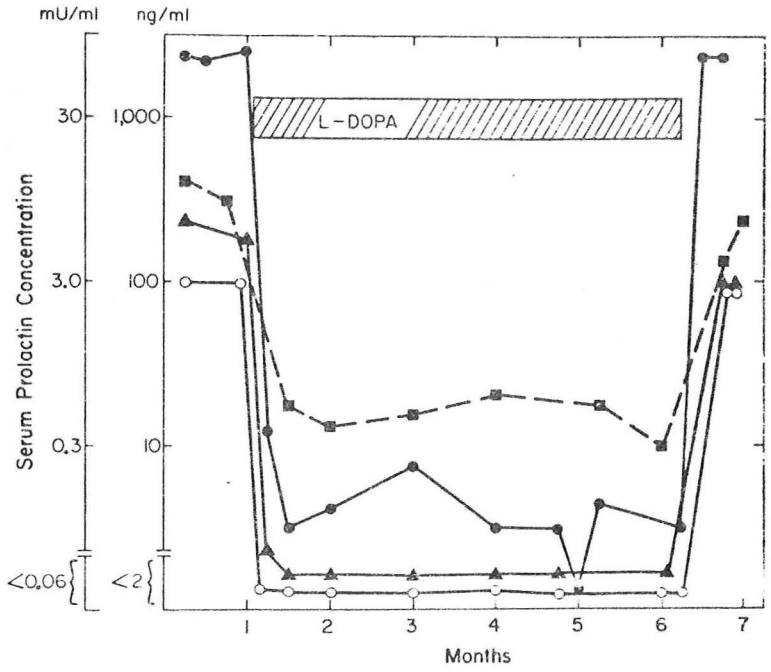

Figure 15. Effect of L-dopa therapy over a five month period on serum prolactin levels in four patients with the Forbes-Albright syndrome (Ref. 87)

REFERENCES

I. GENERAL

1. Kon, S. K. and A. T. Cowie. Milk: The Mammary Gland and Its Secretion. 2 volumes. New York: Academic Press, 1961.

2. Zaks, M. G. The Motor Apparatus of the Mammary Gland. Springfield: Charles C. Thomas, 1962.

*3. Cowie, A. T. and J. S. Tindal. The Physiology of Lactation. Baltimore: The Williams and Wilkins Co., 1971.

4. Reynolds, M. and S. J. Folly, editors. Symposium on Lactogenesis: The Initiation of Milk Secretion at Parturition. Philadelphia: University of Pennsylvania Press, 1969.

5. Sulman, F. G. Hypothalamic Control of Lactation. New York: Springer-Verlag, 1970.

*6. Wolstenholme, G. F. W. and J. Knight, editors. Lactogenic Hormones. London: Churchill Livingstone, 1972.

II. EMBRYOLOGY AND ANATOMY OF THE BREAST

7. Raynaud, A. Morphogenesis of the Mammary Gland. Ch. in Milk: The Mammary Gland and its Secretion. Vol. I. Ed. by Kon, S. K. and A. T. Cowie. New York: Academic Press, 1961, p. 3.

Although the embryogenesis of the human breast is fundamentally the same as in other species, there is no working hypothesis as to why the mammary line (well developed in the 7 mm embryo) shortens and condenses to give rise to only one functional mammary bud on each side. Between 20 and 30 mm the epithelial bud assumes a globular shape, and the breast is well differentiated by the end of the second month of intrauterine life. Very little change occurs between the 2nd and 5th months, but during the 5th month (120 to 150 mm) both the nipple and the secondary epithelial buds develop. During the remainder of embryonic life ductular proliferation continues so that by the time of birth 15-25 glands are present, each of which opens to the exterior. Although the secretion of testosterone by the fetal testis clearly inhibits embryogenesis of the mammary bud in males of several species (and is presumed to do so in the case of man) this has never been clearly documented to be the case in man, and any histological differences between the breasts are slight in children of both sexes prior to puberty.

8. Meites, Joseph. Control of Mammary Growth and Lactation. Ch. in Neuroendocrinology. Vol. I. Edited by L. Martini and W. F. Ganong. New York: Academic Press, 1966, p. 669.

Also Ref. 2 and 3.

At the time of female puberty extensive branching of the ducts occurs in most animals in conjunction with the estrous cycle; however, the greatest development of the mammary glands occurs during gestation and the early postpartum period and is characterized by alveoli and lobules forming a compound tubuloalveolar structure. The alveoli are the milk secreting units, and a group of alveoli constitute a lobule.

9. Borgmann, W. and U. Welsch. On the Ultrastructure of the Mammary Gland. Ch. in Symposium on Lactogenesis: The Initiation of Milk Secretion at Parturition. Ed. by M. Reynolds and S. J. Folly. Philadelphia: Univ. of Penn. Press, 1969, p. 14.

Also Ref. 3.

The alveolar cells not only contain the enzymatic machinery for the synthesis of the various milk constituents but assemble the milk into droplets that are extruded from the surface of the cell encased in delicate walls of endoplasmic reticulum. These globules coalesce, the lining membrane becoming the "microsomes" of milk, and are stored in the lumen of the alveolus and the various intralobular ducts. Although the myoepithelial superstructure is admirably designed to aid in the extrusion of the stored milk upon demand, in virtually all species emptying requires the application of either negative or positive pressure.

III. MILK FORMATION

10. Kronfeld, D. S. Biosynthesis of Milk Constituents at Lactogenesis. Ch. in Symposium on Lactogenesis: The Initiation of Milk Secretion at Parturition. Ed. by M. Reynolds and S. J. Folly. Philadelphia: Univ. of Penn. Press, 1969, p. 109.

Also Ref. 1.

Fundamentally, milk can be looked upon as containing three major constituents - lactose, casein, and triglyceride. There is now abundant evidence that lactose is formed in the alveolar cell from blood glucose and that milk proteins (with the exception of small quantities of immunoglobulins) are synthesized de novo from amino acids. The origin of the fatty acids of milk is not entirely clear. Although the short chain fatty acids are clearly synthesized predominantly by the alveolar cell itself, such fatty acids are only minor constituents of human milk. It seems likely that a large portion, possibly the major portion of the predominant C18 fatty acids of milk are transported from

blood, and as much as 25% of the total may arise from the diet. This machinery is capable during the mature post-gestational stage of secretion up to a liter of milk per day containing approximately 71 kilocalories of food (38 grams of fat, 70 grams of lactose, and 12 grams of protein).

IV. ENDOCRINOLOGICAL CONTROL OF BREAST DEVELOPMENT AND LACTATION

11. Lyons, W. R., C. H. Li, and R. F. Johnson. The Hormonal Control of Mammary Growth and Lactation. Recent Progress in Hormone Research 14: 219, 1958.

12. Lyons, W. R. Hormonal Synergism in Mammary Growth. Proc. Roy. Soc. Series B. 149:303, 1958.

13. Clifton, K. H. and J. French. Ducto-alveolar Growth in Mammary Glands of Adreno-gonadectomized Male Rats Bearing Mammotropic Pituitary Tumors. Endocrinol. 66:893, 1960.

14. Talwalker, P. K., J. Meites, and C. S. Nicoll. Effects of Hydrocortisone, Prolactin, and Oxytoxin on Lactational Performance of Rats. Am. J. Physiol. 199:1070, 1960.

15. Cowie, A. T., G. S. Knaggs, and J. S. Tindal. Complete Restoration of Lactation in the Goat after Hypophysectomy. J. Endocrin. 28:267, 1964.

16. Talwalker, P. K. and J. Meites. Mammary Lobulo-alveolar Growth in Adreno-Ovariectomized Rats Following Transplantation of "Mammotropic" Pituitary Tumors. Proc. Soc. 117:121, 1964.

Although estrogen is clearly the important hormone that causes ductal proliferation and elongation (and probably maturation of the nipple as well) there is no evidence that estrogens play a direct role in lactogenesis itself. Indeed, as the result of quantitative studies in hypophysectomized, castrated, adrenalectomized animals of a variety of species it is well established that prolactin and adrenal steroids are the major hormones that induce milk secretion and that insulin and thyroxine are required at least in a permissive way. It is doubtful that oxytoxin is required absolutely since in hypophysectomized, castrated, adrenalectomized rats implanted with prolactin secreting tumors the administration of glucocorticoid alone is sufficient to maintain maximal milk production, suggesting that the major role of oxytocin is to enhance prolactin secretion.

17. Rivera, E. M. Differential responsiveness to hormones of C^3H and A Mouse Mammary Tissues in Organ Culture. Endocrinol. 74:853, 1964.

18. Turkington, R. W. Hormonal Regulation of Cell Proliferation and Differentiation. Ch. in Developmental Aspects of the Cell Cycle. Ed. by I. L. Cameron, G. M. Padilla, and A. M. Zimmerman. New York: Academic Press, 1971, p. 315.

19. Turkington, R. W. Hormone-dependent Differentiation of Mammary Glands In Vitro. Current Topics in Developmental Biol. 3:199, 1968.

The studies of the endocrinological requirements for lactation in intact animals have been supplemented by studies from several laboratories of milk formation in explants of mammary gland grown in organ culture. Rivera documented clearly that adrenal steroid and insulin are required for survival and differentiation of the alveolar cell but that milk formation itself occurs only when prolactin is added to the culture system. These findings have been amply confirmed.

V. PROLACTIN PHYSIOLOGY

20. Niall, H. D., M. I. Logan, R. Saver, I. Y. Rosenblum, and F. C. Greenwood. Sequences of Pituitary and Placental Lactogenic and Growth Hormones: Evaluation from a Primordial Peptide by Gene Reduplication. PNAS 68:866, 1971.

21. Li, C. H. Recent Knowledge of the Chemistry of Lactogenic Hormones. Ch. in Lactogenic Hormones. Ed. by G. E. W. Wolstenholme and J. Knight. London: C. Livingston, 1972, p. 7.

Prolactin is a peptide from the pituitary gland, approximately 20,000 in MW. This hormone, certainly one of the most extensively studied of all hormones, shares remarkable structural homologies both with growth hormone and with the placental lactogen.

A. EFFECTS ON TISSUES OTHER THAN BREAST

22. Bern, H. A. and C. S. Nicoll. The Comparative Endocrinology of Prolactin. Recent Progress in Hormone Research 24:681, 1968.

23. Nicol, C. S. and H. A. Bern. On the Actions of Prolactin Among the Vertebrates: Is There a Common Denominator? Ch. in Lactogenic Hormones. Ed. by G. F. W. Wolstenholme and J. Knight. London: C. Livingston, 1972, p. 299.

24. Horrobin, D. F., I. J. Lloyd, A. Lipton, P. G. Barstyn, N. Durkis, and K. L. Muinuri. Actions of Prolactin on Human Renal Function. Lancet 2:352, 1971.

Furthermore, it is possibly the most widely dispersed of all hormones in the animal kingdom, and in lower species it plays a vital role in the regulation of many diverse functions including the adaptation of euryholine fish to fresh water, the regulation of

thyroid function in some fish and amphibia, regulation of growth in reptiles, fat deposition in birds, and hair and sebaceous gland maturation in mammals. Furthermore, when administered to man ovine prolactin causes decreased renal excretion of water, Na^+, and K^+ as well as increased plasma osmolality.

B. EVIDENCE FOR PROLACTIN IN MAN

25. Rimoin, D. L., T. J. Merimee, and V. A. McKusick. Growth Hormone Deficiency in Man: An Isolated, Recessively Inherited Defect. Science 152:1635, 1966.

26. Spellacy, W. N., W. C. Buhi, and S. A. Birk. Normal Lactation and Blood Growth Hormone Studies. Am. J. Obstet. Gynecol. 107:244, 1970.

It is interesting in retrospect that unequivocable evidence for the existence of prolactin in man has been obtained only recently. However, a variety of types of indirect evidence have indicated for several years that growth hormone could not be the human lactogenic hormone. Not only do ateliotic dwarfs with complete absence of growth hormone lactate normally, but in addition growth hormone is not involved in lactation in the post-gestational state.

27. Frantz, A. G. and D. L. Kleinberg. Prolactin: Evidence that it is Separate From Growth Hormone in Human Blood. Science 170:745, 1970.

28. Channing, C. P., M. Taylor, E. Knobil, C. S. Nicoll, and C. W. Nichols, Jr. Secretion of Prolactin and Growth Hormone by Cultures of Adult Simian Pituitaries. PSEBM 135:540, 1970.

29. Hwang, P., H. Friesen, J. Hardy, and D. Wilansky. Biosynthesis of Human Growth Hormone and Prolactin by Normal Pituitary Glands and Pituitary Adenomas. J. Clin. Endocrinol. 33:1, 1971.

30. Lewis, U. J., R. N. P. Singh, and B. K. Seavey. Human Prolactin: Isolation and Some Properties. Biochem. Biophys. Res. Comm. 44: 1169, 1971.

31. Guyda, H., P. Hwang, and H. Friesen. Immunologic Evidence for Monkey and Human Prolactin. J. Clin. Endocrinol. 32:120, 1971.

However, it has only been during the past two years that direct evidence has been obtained that the human pituitary secretes a distinct prolactin of MW 20,000 and that this hormone circulates in the blood.

C. REGULATION OF PROLACTIN SECRETION

32. Labella, F., M. Krass, W. Fritz, S. Vivian, S. Shiv, and G. Queen. Isolation of Cytoplasmic Granules Containing Growth Hormone and Prolactin from Bovine Pituitary. Endocrinol. 89:1094, 1971.

33. Pasteels, J. L. Morphology of Prolactin Secretion. Ch. in Lactogenic Hormones. Ed. by G. E. W. Wolstenholme and J. Knight. London: C. Livingstone, 1972, p. 241.

Prolactin is stored in the pituitary in acidophilic granules, as is growth hormone. The evidence seems conclusive that each of these hormones is packaged in a specific granule derived from a specific cell type.

34. Macleod, R. M. and J. E. Lehmeyer. Regulation of the Synthesis and Release of Prolactin. Ch. in Lactogenic Hormones. Ed. by G. E. W. Wolstenholme and J. Knight. London: C. Livingstone, 1972, p. 53.

35. Friesen, H., C. Belanger, H. Guyda, and P. Hwang. The Synthesis and Secretion of Placental Lactogen and Pituitary Prolactin. Ch. in Lactogenic Hormones. Ed. by G. F. W. Wolstenholme and J. Knight. London: C. Livingstone, 1972, p. 83.

Also Ref. 3 and 22 and a review by R. Guillemin in Recent Progress in Hormone Research, 1972, in Press.

As is true for MSH but not for other pituitary hormones, the predominant regulation of prolactin secretion by the pituitary in negative, e.g. under ordinary basal conditions, the hypothalamus secretes a peptide hormone, Prolactin Inhibitory Factor (PIF), which is delivered to the pituitary via the portal system and which inhibits the release of prolactin into the blood. Many, if not most, physiological factors that influence prolactin release are thought to do so by affecting the synthesis or release into the hypophyseal-portal system of PIF. Thus, when pituitary gland explants are cultured in vitro, prolactin is spontaneously released into the medium whereas other pituitary hormones such as growth hormone tend to be retained within the cells.

36. Turkington, R. W. Phenothiazine Stimulation Test for Prolactin Reserve: The Syndrome of Isolated Prolactin Deficiency. J. Clin. Endocrinol. 34:247, 1972.

For example, phenothiazines are thought to enhance prolactin secretion by inhibiting at a hypothalamic level the synthesis and/or release of PIF. In contrast to several of the releasing hormones, however, PIF has apparently neither been characterized in detail (it is a peptide) nor synthesized.

37. Ameromani, Y., C. L. Chen, and J. Meites. Serum Prolactin Levels in Rats During Different Reproductive States. Endocrinol. 86:506, 1970.

38. Bryant, G. D., J. I. Linzell, and F. C. Greenwood. Plasma Prolactin in Goats Measured by Radioimmunoassay: The Effects of Test Stimulation, Mating Behavior, Stress, Fasting, and of Oxytoxin, Insulin, and Glucose Injections. Hormones 1:26, 1970.

39. Chen, C. L. and J. Meites. Effects of Estrogen and Progesterone on Serum and Pituitary Prolactin Levels in Ovariectomized Rats. Endocrinol. 86:503, 1970.

40. Voogt, J. L., C. L. Chen, and J. Meites. Serum and Pituitary Prolactin Levels Before, During, and After Puberty in Female Rats. Am. J. Physiol. 218:396, 1970.

41. McAtee, J. W. and A. Trenkle. Effects of Feeding, Fasting, Glucose, or Arginine on Plasma Prolactin Levels in the Bovine. Endocrinol. 89:730, 1971.

However, it is likely that a specific prolactin releasing hormone is also of physiological importance, and it has not been established that all the physiologic stimulae that influence prolactin release act via PIF. For example, the sucking reflex results both in enhanced oxytoxin release and in the enhanced synthesis and release of prolactin in the steady state. While the effect of sucking may in part be mediated by oxytoxin (the evidence for this is still controversial) the precise mechanism of the sucking effect is unsettled. Estrogen clearly enhances prolactin release, probably acting both at a hypothalamic level and directly on the pituitary itself. In contrast to growth hormone, prolactin does not appear to be influenced by blood glucose levels, but in some species at least arginine infusions cause striking increases in the blood concentration.

42. Bowers, C. Y., H. G. Finesen, P. Hwang, H. J. Guyda, and K. Folkers. Prolactin and Thyrotropin Release in Man by Synthetic Pyroglutamyl-Histidyl-Prolin Amide. Biochem. Biophys. Res. Comm. 45:1033, 1971.

At least one prolactin releasing factor has been identified, however; thyrotropin releasing hormone releases prolactin as well as TSH from the pituitary. This phenomenon may be of physiologic importance under some circumstances.

To summarize, prolactin release by the pituitary appears to be under predominantly negative control by the hypothalamus, but it remains to be established that this is the only important control mechanism for this process.

D. MECHANISM OF PROLACTIN ACTION

43. Turkington, R. W., K. Brew, T. C. Vanaman, and R. L. Hill. The Hormonal Control of Lactose Synthetase in the Developing Mouse Mammary Gland. J. Biol. Chem. 243:3382, 1968.

44. Turkington, R. W. and R. L. Hill. Lactase Synthetase: Progesterone Inhibition of the Induction of α-Lactalbumin. Science 163:1458, 1969.

45. Majumder, G. C. and R. W. Turkington. Hormonal Regulation of Protein Kinases and Adenosine 3'-5'-Monophosphate Binding Protein in Developing Mammary Gland. J. Biol. Chem. 246:5545, 1971.

46. Turkington, R. W. Molecular Biological Aspects of Prolactin. Ch. in Lactogenic Hormones. Ed. by G. E. W. Wolstenholme and J. Knight. London: C. Livingstone, 1972, p. 111.

The current model for the mechanism of prolactin action can be summarized as follows:

1.) Prolactin interacts with and attaches to specific receptors on the cell surface.

2.) By an as yet unidentified mechanism the altered state of the cell membrane is translated into an intracellular signal to the nucleus.

3.) Enhanced intranuclear transcription of RNA that is coordinated to provide the ribosomal, transfer, and messenger RNA's required for synthesis of milk proteins and for the synthesis of the enzymes necessary for lactose and fat production.

4.) Synthesis and secretion of the milk products.

This entire process has been shown to take place in vitro within 2-4 hours after the addition of prolactin to appropriately primed cells.

VI. LACTATION IN MAN

A. PHYSIOLOGICAL LACTATION DURING THE PUERPERIUM

47. Spellacy, W. N. Immunoassay of Human Placental Lactogen: Physiological Studies in Normal and Abnormal Pregnancy. Ch. in Lactogenic Hormones. Ed. by G. E. W. Wolstenholme and J. Knight. London: C. Livingstone, 1972, p. 223.

48. Hwang, P., H. Guyda, and H. Friesen. A Radioimmunoassay for Human Prolactin. PNAS 68:1902, 1971.

Also Ref. 3 and 5.

In the initiation and maintenance of physiological lactation, two additional hormones play a significant role - humen placental lactogen (HPL) and oxytoxin. Starting at the 10th week HPL rises from non-detectable levels in the serum to exceedingly high values (between 6 and 10 µg/ml) during the last 4 weeks of pregnancy, falling slightly prior to delivery. The magnitude of this rise is correlated roughly with the health of the mother and of the placenta. The exact role of this hormone, as compared with the other hormones of pregnancy, in determining the changes of the breast during pregnancy are not entirely settled. While it is not required absolutely for lactation or its initiation (e.g. the castrated, adrenalectomized, hypophysectomized goat) it is present in all placental mammals studied to date. From studies done in experimental animals, it is likely that high circulating levels of progesterone may be the critical factor that retards milk secretion in the primed gland during pregnancy. The role of estrogen in this regard is likely although unsettled.

Following delivery HPL disappears rapidly from the maternal circulation, and progesterone and estrogen levels also fall, at a time when hydrocortisone secretion is usually enhanced. These factors, combined with the sucking reflex which promotes the release of oxytocin and of prolactin are thought to be the primary factors that result in the initiation and maintenance of milk flow. Two reservations about this model are appropriate: 1.) Most of the work has been done in experimental animals, and the results may not be entirely applicable to man, and 2.) Present explanations for the sucking reflex do not seem entirely adequate, and it seems likely that some unrecognized smooth muscle hormone such as prostaglandin may well be involved in the ejection process which is so critical for the maintenance of milk secretion.

49. Hwang, P., H. Guyda, H. Friesen, and J. Tyson. Studies of Human Prolactin by Radioimmunoassay. Abstracts of the Endocrine Soc. June 1971, p. A-43.

It is exceedingly interesting that the first nursing of the day appears to be more effective in releasing prolactin than does the third.

50. El-Minawi, M. F. and M. S. Foda. Postpartum Lactation Amenorrhea. Am. J. Obstet. Gynecol. 111:17, 1971.

Among the unexplained features of normal lactation is the postpartum amenorrhea that according to these authors is more common in breast feeding mothers. Although this phenomenon may well be nutritional, it

is clear that careful studies of LH-FSH and gonadal physiology during the puerperium are needed and could possibly shed light on the amenorrhea that so often accompanies galactorrhea.

B. GALACTORRHEA

51. Argonz, J. and E. B. del Castillo. A Syndrome Characterized by Estrogenic Insufficiency, Galactorrhea, and Decreased Urinary Gonadotropin. J. Clin. Endocrinol. 13:79, 1953.

52. Forbes, A. P., P. H. Henneman, G. C. Griswald, and F. Albright. Syndrome Characterized by Galactorrhea, Amenorrhea and Low Urinary FSH: Comparison with Acromegaly and Normal Lactation. J. Clin. Endocrinol. 14:265, 1954.

53. Chiari, J., C. Braun, and J. Spaeth. Johann Chiari, Richard Frommel and the Chiari-Frommel Syndrome. Ch. 46 in Obstetrics and Gynecological Milestones. H. Speert, ed. New York: MacMillan, 1958.

54. Rankin, J. S., A. F. Goldfarb, and A. E. Rakoff. Galactorrhea-Amenorrhea Syndromes: Postpartum Galactorrhea-Amenorrhea in the Absence of Intracranial Neoplasm. Obstetrics and Gynecology 33:1, 1969.

55. Young, R. L., E. M. Bradley, J. W. Goldzieher, P. M. Myers, and F. R. Lecoq. Spectrum of Nonpuerperal Galactorrhea. J. Clin. Endocrinol. 27: 461, 1967.

56. Thompson, J. P. and R. D. Kempers. Amenorrhea and Galactorrhea. Am. J. Ob. Gyn. 93:65, 1965.

On clinical grounds it has been apparent for many years that the attempts to categorize idiopathic galactorrhea into nosologic entities (as to whether occurring after pregnancy, with or without a pituitary tumor, and whether accompanied by amenorrhea) make no sense. Not only is the overlap enormous but over the years many patients shift from one category to another. What will be attempted here is a classification of the clinical syndromes based on the recent studies of prolactin physiology in various disease states.

57. Canfield, C. J. and R. W. Bates. Nonpuerperal Galactorrhea. New England J. Med. 273:897, 1965.

58. Kleinberg, D. L. and A. G. Frantz. Human Prolactin: Measurement in Plasma by an In Vitro Bioassay. J. Clin. Invest. 50:1557, 1971.

59. Forsyth, I. A., G. M. Besser, C. R. W. Edwards, L. Francis, and R. P. Mynes. Plasma Prolactin Activity. Brit. Medical J. 3:225, 1971.

60. Sherwood, L. M. Human Prolactin. New England J. Med. 284:774, 1971.

61. Lead Article. Human Prolactin. Brit. Med. J. 3:201, 1971.

62. Loewenstein, J. E., I. K. Moriz, G. T. Peake, and W. H. Daughaday. Prolactin Bioassay by Induction of N-Acetyllactosamine Synthetase in Mouse Mammary Gland Explants. J. Clin. Endocrinol. 33:217, 1971.

63. Turkington, R. W. Measurement of Prolactin Activity in Human Serum by the Induction of Specific Milk Proteins in Mammary Gland In Vitro. J. Clin. Endocrinol. 33:210, 1971.

64. Turkington, R. W. Human Prolactin. Amer. J. Med. 53:389, 1972.

65. Frantz, A. G., D. L. Kleinberg, and G. L. Noel. Physiological and Pathological Secretion of Human Prolactin Studied by In Vitro Bioassay. Ch. in Lactogenic Hormones. Ed. by G. E. W. Wolsterholme and J. Knight. London: C. Livingston, 1972, p. 137.

66. Bryant, G. D. and F. C. Greenwood. The Concentrations of Human Prolactin in Plasma Measured by Radioimmunoassay: Experimental and Physiological Modifications. Ch. in Lactogenic Hormones. Ed. by G. E. W. Wolsterholme and J. Knight. London: C. Livingston, 1972, p. 197.

67. Turkington, R. W. Measurement of Prolactin Activity in Human Serum by the Induction of Specific Milk Proteins In Vitro: Results in Various Clinical Disorders. Ch. in Lactogenic Hormones. Ed. by G. F. W. Wolsterholme and J. Knight. London: C. Livingston, 1972, p. 169.

68. Besser, C. M. and C. R. W. Edwards. Galactorrhea. Brit. Med. J. 2:280, 1972.

The thesis that underlies all these papers (stated most explicitly in Ref. 68) is that all galactorrhea is due to enhanced prolactin secretion but that galactorrhea is less common than is elevated blood prolactin. The latter is hardly surprising since milk production requires a complex developmental gestalt and other hormones as well, but the central thesis is as yet unproved. Although most patients with galactorrhea do in fact have elevated serum prolactin, some have levels that are in the normal range even upon repeated testing. The proponents argue that with present methodology blood prolactin levels even in puerperal lactation are occasionally

normal and that if the assays were sensitive enough, abnormal prolactin secretion could probably be documented in all cases.

I. FAILURE OF NORMAL HYPOTHALAMIC INHIBITION OF PROLACTIN RELEASE BY THE PITUITARY

a. Pituitary Stalk Section

69. Turkington, R. W., L. E. Underwood, and J. J. VanWyk. Elevated Serum Prolactin Levels After Pituitary-Stalk Section in Man. New England J. Med. 285:707, 1971.

Perhaps the strongest evidence that the normal CNS control mechanism is inhibitory in character is that stalk section in man results in a striking increase in prolactin release by the pituitary (in 11 of 15 patients in this particular study). If pituitary infarction that sometimes results is extensive enough, however, blood prolactin falls, as do the other pituitary trophic hormones.

b. Drugs

70. Relkin, R. Galactorrhea: A Review. New York State J. Med. 65:2800, 1965.

(Also Ref. 36 and Ref. 60-68)

For all practical purposes virtually all drugs that influence the CNS result in enhanced prolactin release, presumably due to the inhibition of PIF synthesis or release. This includes serpasil, chlorpromazine, aldomet, stelazine, compazine, equanil, mellaril, prolixin, and tofranil. The response to chlorpromazine is so predictable that Turkington (36) has proposed using the prolactin response as a test of normal hypothalamic reserve capacity.

c. Central Nervous System Disease

71. Turkington, R. W. Secretion of Prolactin by Patients with Pituitary and Hypothalamic Tumors. J. Clin. Endocrinol. 34:159, 1972.

72. Turkington, R. W. Hyperprolactinemia in Sarcoidosis. Ann. Int. Med. 76:545, 1972.

Although galactorrhea is known to be a frequent sequela of a multitude of extrapituitary CNS diseases, including craniopharyngioma, pinealoma, encephalitis, meningitis, hydrocephalus, following pneumoencephalogram, etc., documentation of enhanced prolactin secretion is clear-cut only in hypothalamic tumors and in sarcoidosis of the CNS. Other CNS diseases are presumed to act in the same fashion.

2. ENHANCED RELEASE OF PROLACTIN INDEPENDENT OF THE NORMAL INHIBITION MECHANISM

a. Anterior Chest Wall Stimulation

See Ref. 60-68.

Chest wall stimulation of a variety of types - nipple stimulation, chest surgery, unilateral mastectomy, breast abscess, herpes zoster, dermatitis, and burns of the chest wall - is associated with a significant incidence of galactorrhea. It is possible that the increased prolactin release following nipple stimulation might be due to inhibition of PIF, but the remarkable rapidity of the phenomenon suggests the possibility of enhanced release mechanism. (It is thought that enhanced prolactin release cannot be mediated by oxytocin alone.) That this mechanism for inducing milk secretion can be a very powerful one is attested to by the fact that several authors state that a nursing baby can induce milk secretion in women not in the puerperium (even occasionally in post menopausal women) for example when a mother dies and the baby is given to another woman in the family for nursing. It is a common clinical impression that manipulation of the breast is a common cause of galactorrhea.

b. Pituitary Tumors

73. Racadot, J., E. Vila-Porcile, F. Peillon, and L. Olivier. Adenoma Hypophysaines ā Cellules a Prolactine: Etude Structurale Correlative Anatomo-Cliniques. Annales d'endocrinologie 32:298, 1971.

Fundamentally three types of pituitary tumor may be associated with galactorrhea; pure prolactin secreting tumors and chromophobe adenomas that contain prolactin cells in small quantities have been studied most carefully. The question that is unresolved is that of acromegaly; some acromegalies have both elevated GH levels and prolactin levels whereas others have only elevated GH. It is not clear at present whether excessive GH in the absence of prolactin can support lactation, but most workers in the field seem to believe that growth hormone in man is probably not a lactogenic hormone. In retrospect, it seems likely that Forbes and Albright actually described the syndrome that results from prolactin secreting pituitary tumors and that the amenorrhea may well be the result of secondary effects of the tumor. It is interesting that in their original paper, the suggestion was advanced that the disorder is in fact due to enhanced prolactin secretion.

74. Mahesh, V. B., S. D. Pria, and R. B. Greenblat. Abnormal Lactation with Cushing's Syndrome - a Case Report. J. Clin. Endocrinol. 29: 978, 1969.

It is not clear whether the galactorrhea of Cushing's disease is due to enhanced glucocorticoid secretion or to the presence of some prolactin secreting cells in the pituitary tumors.

c. Ectopic Secretion of Prolactin by Other Tumors

75. Turkington, R. W. Ectopic Production of Prolactin. New England J. Med. 285:1455, 1971.

As is true with other hormones, prolactin can be secreted on occasion by other malignancies; in this report bronchogenic carcinoma and hypernephroma were both associated with elevated prolactin secretion and gynecomastia.

d. Human Placental Lactogen Secretion

Although elevated placental lactogen secretion and galactorrhea can occur in hydatidiform moles and in chorionepitheliomas it is interesting that this phenomenon is not too common. This is said to be because HPL secretion per unit mass of tumor is low in contrast to the phenomenally high rates of chorionic gonadotropin secretion, e.g. the tumor tends to mimic the placenta of early rather than late pregnancy.

e. Hypothyroidism

76. Ross, F. and M. L. Nusynowitz. A Syndrome of Primary Hypothyroidism, Amenorrhea and Galactorrhea. J. Clin. Endocrinol. 28:591, 1968.

77. Bayliss, P. F. C. and W. VantHoff. Amenorrhea and Galactorrhoea Associated with Hypothyroidism. Lancet 2:399, 1969.

78. Edwards, C. R. W., I. A. Forsyth, and G. M. Besser. Amenorrhea, Galactorrhea and Primary Hypothyroidism with High Circulating Levels of Prolactin. Brit. Med. J. 3:441, 1971.

The galactorrhea of hypothyroidism is important for two reasons: 1.) It is cured by thyroid replacement, and 2.) It is almost certainly due to TRH mediated release of prolactin - the only clear-cut evidence for physiologically important prolactin releasing activity in man.

3. IDIOPATHIC

When all the known causes are excluded, there are still a large number of patients with galactorrhea of unknown etiology. It is strongly suspected by many students of the problem that a

significant fraction of these patients will prove to have subtle disorders of the hypothalamus that will have to be elucidated by careful dissection of the regulation of prolactin release in such patients. What is clear is that early ovarian failure is a frequent accompaniment of the disorder, and it is conceivable that such failure might be primary rather than secondary in the disorders. What does seem clear is that several syndromes are almost certainly lumped together into this category at present.

C. THE CONTRACEPTIVE PROBLEM

79. Gregg, W. I. Galactorrhea After Contraceptive Hormones. New England J. Med. 274:1432, 1966.

80. Friedman, S. and A. Goldfien. Breast Secretions in Normal Women. Am. J. Obstet. Gynecol. 104:846, 1969.

81. Friedman, S. and A. Goldfien. Amenorrhea and Galactorrhea Following Oral Contraceptive Therapy. J. A. M. A. 210:1888, 1969.

82. Gambrell, R. D., Jr., R. B. Greenblatt, and V. B. Mahesh. Post-Pill and Pill Related Amenorrhea-Galactorrhea. Am. J. Ob. Gyn. 110:838, 1971.

83. Shevach, A. B. and W. N. Spellacy. Galactorrhea and Contraceptive Practices. Obstetrics and Gynecology 38:287, 1971.

Although contraceptive steroids (with and without estrogens) have been reported to cause galactorrhea, it is clear from these studies that the incidence is the same in women on mechanical as on oral contraceptives, that the galactorrhea can begin either while the patient is on the pill or on cessation of therapy, and that the natural history and course is amazingly similar to that of the idiopathic disorder (Chiari-Frommel syndrome). Indeed, Friedman and Goldfien concluded that the incidence of galactorrhea may actually be decreased in women on the pill (80). It seems fairly safe to conclude that, despite occasional striking association, contraceptive steroids do not play a major role in causative agents for galactorrhea. (They are also generally ineffective agents in the treatment of galactorrhea in galactorrhea-amenorrhea syndromes.)

VII. TREATMENT OF GALACTORRHEA

Management of galactorrhea is frequently frustrating, and it is not uncommon after a negative diagnostic work-up to be left with no form of therapy to offer the patient other than avoidance of chest wall stimulation. It is clear that the main therapeutic hope is for a PIF hormone that would be therapeutically useful. In the interim, two other forms of therapy offer some promise.

84. Kamberi, I. A., R. S. Mical, and J. C. Porter. Effect of Anterior Pituitary Perfusion and Intraventricular Injection of Catecholamines on Prolactin Release. Endocrinol. 88:1012, 1971.

85. Kleinberg, D. L., G. L. Noel, and A. G. Frantz. Chlorpromazine Stimulation and L-DOPA Suppression of Plasma Prolactin in Man. J. Clin. Endocrinol. 33:873, 1971.

86. Turkington, R. W. Inhibition of Prolactin Secretion and Successful Therapy of the Forbes-Albright Syndrome with L-DOPA. J. Lab. Clin. Med. 78:824, 1971.

87. Turkington, R. W. Inhibition of Prolactin Secretion and Successful Therapy of the Forbes-Albright Syndrome with L-DOPA. J. Clin. Endocrinol. 34:306, 1972.

Following up on the report from Porter's laboratory that dopamine caused accelerated PIF release, two groups of investigators have treated patients with L-DOPA (0.5 g q6h). Of 14 patients treated by Turkington (86) 11 had dramatic decrease in blood prolactin to normal or near normal levels within 48 hours. Several patients had complete cessation of galactorrhea for as long as they took the medicine (up to 6 mos.), and the improvement was associated with increased gonadotropin secretion. Two of the 3 patients who did not respond proved ultimately to have chromophobe adenomas.

88. Luttinbeck, P. M., J. S. Pryor, L. Varga, and R. Wenner. Treatment of Non-Puerperal Galactorrhea with an Ergot Alkaloid. Brit. Med. J. 3:228, 1971.

Ergot alkaloids, which are also potent inhibitors of prolactin release resulted in dramatic relief of galactorrhea in 3 patients, but unfortunately unpleasant side effects caused discontinuation of the drug.

VIII. POSSIBLE ROLE OF PROLACTIN IN CARCINOMA OF THE BREAST

89. Salih, H., W. Branden, H. Flax, and J. R. Hobbs. Prolactin Dependence in Human Breast Cancers. Lancet 2:1103, 1972.

90. Lead Article. Prolactin and Breast Cancer. Lancet 2:1129, 1972.

It is of interest that as many as a third of all breast carcinoma may be prolactin dependent, and it is possible that the same effect as following hypophysectomy would be obtained if an effective means of inhibiting prolactin release were available.