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Abnormal lactation

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PHYSIOLOGY OF LACTATION

Knowledge of the physiology of the mammary gland has been acquired mainly since the turn of the century. Recent developments are due primarily to progress in the field of endocrinology.

Mammary Gland Growth

1. Before Puberty: Mammary growth is intimately dependent upon the activity of the ovaries for it is minimal in the male and completely arrested by oophorectomy. In the immature animals the primary mammary ducts grow isometrically, but about the time of puberty it becomes significantly faster, allometric (88). Duct growth occurs chiefly in the follicular phase in the ovarian cycle; and during the luteal phase in ovulatory cycles, alveoli and alveolar ducts may be formed as well (88).

2. Hormonal Control of Mammary Growth:

Ovarian Hormones: Both estrogens and progesterone stimulate mammary development in both males and females, whether or not the gonads are present. Estrogen causes the growth of the ducts, stroma and nipple, while estrogens plus progesterone causes the formation of the lobular-alveolar system.

Most workers state that an intact anterior lobe of the pituitary is essential for the stimulating action of the ovarian hormones upon mammary growth (15). More recent experiments conclude that ovarian hormones normally act synergistically with those from the anterior pituitary and do not stimulate that gland to make and release special mammary-developing hormones (88). Several groups of

workers have been able to show that the steroid hormones can cause mammary growth in hypophysectomized animals if certain of the six well-known anterior pituitary hormones are given as well.

Anterior Pituitary Hormones: As stated above it now appears certain that the pituitary hormones act synergistically with the ovarian hormones to produce mammary growth. When the pituitary is removed in males as well as in females, growth hormone and adrenocorticotrophic hormone must be given in addition to prolactin to get normal mammary development with ovarian hormones. In order to mimic normal duct development in hypophysectomized, oophorectomized and sometimes adrenalectomized rats, growth hormone and corticoids need be administered with an estrogen (88). To obtain full lobulo-alveolar development such as occurs by mid-pregnancy, prolactin and progesterone are needed as well. To start lactation the ovarian hormones are unnecessary, and only prolactin and corticoids are needed (88). Thyrotropic hormone was not found necessary to obtain normal mammary growth, but the effect of the sex hormones is enhanced by administration of the thyroid hormone which appears to be essential for the action of estrogen (15). Thus, at least five of the recognized anterior pituitary hormones have a mammotrophic action, but not one of them had that action as its only effect. Of the five, prolactin appears to have a double action. It may stimulate the secretion of progesterone by the corpus luteum and it augments the action of the ovarian steroid hormones in forming alveoli, and so controls mammary growth directly and indirectly (88, 91).

It is also the only pituitary hormone capable of starting lactation in developed glands (88). Growth hormone can exert a direct mammogenic effect, as well as probably influencing mammogenesis by its general effect on bodily metabolic processes (91).

Placenta: The placenta can produce estrogen, progesterone, gonadotropic and luteotropic factors. Lyons and his colleagues have shown that in the rat placental extracts can replace prolactin in producing mammary growth with estrogen and progesterone in hypophysectomized animals (91). It is not known whether this substance is identical with prolactin of pituitary origin (91). A substance similar to growth hormone may also be secreted by the placenta.

Other Endocrine Glands: Most workers believe that both the thyroid and the adrenal influence mammary growth only in a secondary or indirect manner. The effect of insulin appears to be due to generally improving the metabolic condition of the animal. No fetus is necessary for full mammary development, at least in the rabbit prolonged luteal action appears to be adequate (25, 109).

Lactation

1. Initiation of Lactation: The initiation of lactation has been called lactogenesis. This cannot take place in the absence of the anterior pituitary gland and is to a greater or lesser extent inhibited by removing either the posterior pituitary, the adrenal cortex or the thyroid (88). Most of the mammary growth is complete by half to two-thirds of the way through pregnancy with

histologic signs of some secretion, the formation of specific milk constituents such as casein and fatty acids have been detected. Thus, the glands in the last trimester of pregnancy can be stimulated to full activity not only by normal parturition but by abortion. It seems unlikely that the fetus plays any role in preventing lactation while it is present. The removal of the placenta is an obvious change taking place at parturition but there are also possible changes in the pituitary, the ovaries, and the adrenals. The sensory stimulation of the nipples causes the release of posterior and possibly anterior pituitary hormones responsible for milk discharge and secretion, in addition, the psychological effect on the mother of seeing and feeling the young suckle is of no small import, particularly in man.

The theory of Nelson that placental estrogens inhibit lactation during pregnancy which promptly starts as soon as their influence is removed at parturition, stems from the observation that estrogens cause mammary growth in guinea pigs which secrets milk as soon as treatment stops. Human clinical findings may be irrelevant here because large doses are used and the effects may be indirect. A number of workers report that estrogens do not inhibit lactation if suckling is kept up. It seems unlikely that estrogens alone hold milk secretion in check until parturition. There is no evidence that they ever occur alone in nature.

While estrogens and progesterone on the one hand can inhibit lactation, prolactin and possibly other anterior pituitary hormones

can start it in suitably developed glands, on the other. It seems reasonable to assume, therefore, that at parturition lactation starts because the inhibiting action of the steroids is reduced and the stimulatory action of the prolactin increases (88,83). The assumption that prolactin alone is responsible for the initiation of milk secretion is not held by all workers. There is some evidence that the adrenal cortex may play some role (15). Lyone and coworkers found that any combination of hormones that excluded both prolactin and cortisol failed to initiate lactation (17).

It is highly probable that the inhibiting influence of ovarian hormones upon lactation is exerted by way of the hypophysis rather than by direct action on the mammary glands (134). The decrease in the circulating ovarian hormones may act as a stimulus to the hyphophysis to produce prolactin. Lactation is not initiated during pregnancy principally because the amount of lactogenic hormones produced by the pituitary is too low to support lactation (97). Also in parturient women, the amount of lactogenic hormone found in the urine is 8 - 16 times as much as can be obtained during pregnancy (97). This theory of initiation of lactation is also supported by Meites and Turner. They postulate it is the progesterone-estrogen ratio that stimulates the pituitary to produce prolactin. The progesterone-estrogen ratio is believed to be such that progesterone overrides the lactogen-stimulating effects of estrogen. As a result, the amount of lactogenic hormone in the pituitary during pregnancy remains insufficient to initiate an abundant lactation.

There is some disagreement as to the exact role the placenta places in initiation or prevention of lactation. One group states that the placenta does not inhibit lactation (134), and another group states that the flow of milk is not established until after the birth of the young and the expulsion of the placenta (15).

Peterson maintains that secretion of milk begins before parturition and that the question is not a matter of secretion after childbirth but one of discharge or ejection of milk. Colostrum being a concentrated milk supports his theory.

There is some evidence both experimental and clinical that suckling alone may initiate lactation under certain conditions (97).

Oxytocin, progesterone, adrenal cortical extracts, tissue extracts and desoxycorticosterone acetate have been shown to have no effect on the lactogen content of the pituitary (97). The thyroid is not necessary for the initiation of lactation, but it can exert a definite supplementary influence on lactation.

2. Maintenance of Lactation:

a. Anterior Pituitary: Milk secretion ceases abruptly if the anterior pituitary is removed (134, 17). In the rat, after removal of the pituitary during lactation, prolactin is the only pure hormone capable of partially preventing the fall in milk yield, although its action is often improved by giving adrenocorticotrophic hormone and growth hormone as well (88). There appears to be an anterior pituitary hormone complex responsible for lactation. The crude anterior lobe extract is more effective in stimulating already established

lactation (galactopoiesis) than is prolactin (154) but prolactin is necessary for the continuance of lactation. Clinical studies have shown that injections of prolactin, especially the larger doses, appear to increase slightly the secretion of breast milk (123). Folley concludes from his studies that partially purified prolactin will not initiate lactation unless adrenal cortical extract is given at the same time (47). Prolactin has no effect on the fat protein and ash content of the breast milk (123).

The exact mechanism by which prolactin is released from the acidophilic cells of the anterior pituitary is not known. One theory states that there is a center in the hypothalamus which, when stimulated, causes the release of prolactin from the pituitary. Another possibility is that there is an inhibitory center in the hypothalamus which normally supresses prolactin production and/or release from the pituitary. When this center is depressed as by suckling stimulus the pituitary releases prolactin. This theory has some clinical support as seen in the cases when reserpine is given to women they sometimes lactate. Although the exact site on which resperine has its effect is not known there is some evidence that it has its effect on mesencephalic centers (155). Benson has found that prolactin is released as a result of reserpine treatment (13). Since this drug apparently has a depressant effect on other centers in this area it seems logical to assume that some inhibitory center for lactation is depressed.

Although the somatrophic hormone appears to have some effect on mammary gland growth there is no evidence that it has an effect on lactation except in a nonspecific manner. Adrenocorticotropic hormone and thyroid stimulating hormone have their effects on lactation through their target organs.

b. Adrenal Cortex: Milk secretion is seriously impaired by adrenalectomy (88). It has not been clearly decided whether this is due to removal of steroids acting directly on the mammary glands or is secondary to the serious disturbance of general carbohydrate and mineral metabolism. Meites and Turner conclude that the adrenals have their favorable effect on lactation by their effect on salt, carbohydrate and mineral metabolism rather than by any direct effect on the mammary gland (97). The increase in adrenal cortical activity during lactation may reflect the over-all increase in metabolic activity required to provide the mammary glands with substrates used in milk secretion. Brownell and coworkers discovered a hormone separate from cortin which supports lactation and for which they suggest the name cortilactin (29).

c. Thyroid: Thyroid activity increases during lactation in proportion to the yield of milk (88). Throidectomy and the administration of methyl thiouracil lower the yield of milk but there is some reason to believe that the former may be due in part to the simultaneous removal of the parathyroids. There are no clear indications to oppose the simple view that the thyroids influence milk secretion as part of their control of general metabolism.

d. Suckling: Suckling is absolutely essential for the maintenance of lactation, since without the stimulus of nursing the high postpartum lactogen production of the pituitary is not maintained (97). The exact mechanism involved in the release of prolactin following suckling stimulation is not entirely understood. The most likely explanation is that the plexus of nerves in the nipple and areola are stimulated and afferent nerve impulses travel via the dorsal roots to the cord (40). Their pathway in the brain stem is not known. These impulses cause the release of oxytocin and some workers believe this hormone in turn causes the release of prolactin from the acidophilic cells of the anterior pituitary (88). This theory gains support from the clinical observation that drugs which have a general depressant action in the central nervous system, such as reserpine and phenobarbital, can cause persistant lactation in women (101, 155).

The evidence to support the theory that oxytocin causes the release of prolactin is that oxytocin injections will delay mammary gland involution in the rat but only if the anterior pituitary is present (88, 13). This may be interpreted to mean that oxytocin is the neurohumor carried in the hyphophysial portal vessels from the posterior to the anterior pituitary, to release prolactin.

Mammary Involution

This has been hardly studied at all experimentally. Histologic studies show that in the early stages when the alveoli are grossly distended with milk the capillaries are collapsed, suggesting

a reduced blood flow. No attempts have been made to see if any process actively affects involution.

Milk Ejection

Milk leaves the gland, once it is secreted, chiefly due to the interesting neurohormonal reflex known as milk ejection which takes place within a minute of the start of suckling or milking. All the milk that can be removed by suckling is present as such in the gland at the start and is not, as was once widely thought, partly secreted slowly between milkings and partly secreted rapidly in response to stimulation of the nipples (88).

The evidence is almost overwhelmingly for the view that this rapid transference of milk from the alveoli and small ducts to the large ducts and cisterns is due to the contraction of the mammary myoepithelial cells in response to oxytocin release into the blood stream by the posterior pituitary gland under the influence of afferent nervous impulses from the nipples. The long latent period between stimulation of the nipple and the flow of milk is not characteristic of a purely nervous reflex (88, 11).

By the direct observation of living mammary tissue of small laboratory animals, the alveoli, when containing milk, can be seen to contract and squeeze their contents into the ducts, in response to oxytocin reaching them via the blood stream or applied topically to the scanty connective tissue (88). Histologic studies show clearly that the only possible contractile cells around alveoli are the myoepithelial cells, these observations that living alveoli

contract can only mean that the myoepithelium is contractile. There is also evidence confirming the original hypothesis of German histologists that the myoepithelial cells along ducts are also contractile.

The Nervous System and Lactation

Nerve endings are most abundant at the tip of the nipple and around the teat sphincter where one could expect them to be maximally stimulated during suckling. There is also much evidence that the stimulation of these endings is important in maintaining lactation and at the moment we know of two possible ways in which this could be so. First, as has already been discussed the sensory impulses from the nipple release oxytocin, which after reaching the glands in the blood stream causes the ejection of milk and thus aids in the complete emptying of the glands. Eayrs inferred from his findings that the pathway by which the suckling stimulus maintains lactation enters the central nervous system by the dorsal roots and ascends in the spinal cord deep in the lateral funiculus of the same side (40). This pathway to the diencephalon is either indirect, unmyelinated, or not fasiculated but widely dispersed throughout the reticular formation. Second, there is the suggestion that such impulses also release prolactin and possibly other anterior pituitary hormones, which of course would tend to maintain lactation (88). Some workers have associated these two processes by suggesting that in fact oxytocin releases prolactin, readhing the anterior pituitary via the hypophyseal portal vessels.

The mammary glands receive only adrenergic vasoconstrictor sympathetic fibers and similar fibers to the smooth muscle in the nipple.

Probably the most interesting thing about the mammary sympathetic nerves is that they are capable of reducing the blood flow to zero on stimulation and that the mammary blood vessels are very sensitive to the vasoconstrictor actions of adrenalin and noradrenalin (38). This is the postulated mechanism by which adrenalin inhibits the action of oxytocin, by reducing the blood supply to the extent that oxytocin does not reach the mammary gland in sufficient concentration to cause its effect (1).

There is much evidence against the presence of specific secretory nerves in the mammary gland (88).

ABNORMAL LACTATION

Introduction

Abnormal lactation is milk secretion persisting longer than two years in the postpartum female breast, occuring in the non-puerperal female breast, and occurring in the male breast. From the earliest time (Hippocrates) lactation was known to occur in virgins, but it is nevertheless a rare event (50).

Etiology

1. Endocrine Etiology:

a. Ovarian Insufficiency: This condition as a cause of galactorrhea is most easily demonstrated in the cases reported following castration and partial ovarian resection. The drop in estrogens allowing the anterior pituitary prolactin hormone to have free play is postulated as the basic cause of the galactorrhea. Estrogen administration to some of these patients resulted in cessation of the milky discharge which further supports this postulate. Abnormal lactation was produced following castration in women who had previously borne children (63) as well as in nulliparous women (126, 57). The onset of galactorrhea occurred from one day to three weeks (57) after the operation and varied in duration from a few days (63) to several years (125). The amount of secretion varied from copious galactorrhea to small quantities obtained only by manual expression. Post partum lactation and amenorrhea as a cause of galactorrhea is included under the ovarian insufficiencies. Laboratory data to support the conclusion of ovarian insufficiency

was not reported in all of these articles but in some cases was presumed to be present because of the amenorrhea. Pituitary tumors were demonstrated by skull X-rays in some cases (50,64). Ovarian insufficiency was postulated to be present secondary to lack of pituitary FSH stimulation from the pituitary. The case of the Balzek sisters is included under this category. They were conjoined twins and had a common circulation but separate nervous systems. Pregnancy and parturition in one was followd by mammary secretion in both (23). The duration of lactation varied from two years to 47 years (132). The amount of flow varied from a small amount which had to be expressed manually to amounts of secretion that flowed constantly.

	Ovarian Insufficiency
	Bibliography Numbers
Castration	10, 50, 57, 63, 81, 82, 125, 126
Postpartum	4, 5, 23, 31, 50, 51, 64, 70, 76, 98, 106, 132, 141

b. Utero-ovarian Tumors with or Without Endocrine Function and Surgery Related to These Disorders:

Carcinoma and leimyomata uteri; ovarian cystoma, carcinoma and dermoids; adrenal tumors and hysterectomy are etiologies considered. C.W. Johnson reports a case of a female with mammary secretion and retroflexion of the uterus. When the uterine malposition was corrected, milk secretion ceased (73).

Saenger reports two cases of carcinoma of the ovary with secretion of milk by the breasts (127). Welter reports a case of a mammary secretion occuring in a 26 year old woman who had a dermoid and corpus luteum cyst of the ovary (159). Engstrom reports a case of a woman secreting black milk from both breasts three years following removal of a tubal abscess. The possibility of the breast being infected with Aspergillus niger was not excluded (45). Total hysterectomy as a cause of mammary secretion is postulated to be related to the drop in estrogens allowing prolactin a free play. The indication for the hysterectomy was not always reported. Two case reports stated the operation was performed because of fibroids (126, 57). Foss reports a case in which the hysterectomy was done for metrorrhagia (50).

Utero-Ovarian Tumors

	Bibliography Numbers
Carcinoma and leiomyonata of the uterus and retroflexion	73, 126, 140
Ovarian cystoma, carcinoma and dermoids	127, 150
Adnexal tumors	45
Hysterectomy	10, 125, 126, 50, 63, 57, 151

c. Other Functioning Endocrine Tumors:

Functioning endocrine tumors other than those directly related to the female genital tract are also a cause of galactorrhea. Lisser reports a case of a 33 year old male with an adrenal cortical tumor who had gynecomastia and milk secretion. He postulated the

milk secretion was due to cortilactin being produced in excess amounts by the tumor cell (89). Holl reports a similar case in which regression of the gynecomastia and feminine changes occurred after removal of the tumor (66). Bittorf reports a similar case of a male, age 26, on whom the histogic diagnosis of hypernephroma was made (18). Three cases of gynecomastia with milk secretion in men with choriocarcinoma were found in the literature (20, 34). In one report the milk secretion decreased when the tumor was removed but increased again as the metastasis increased (34). In the latter case no information was given as to whether metastisis to the brain were present or not.

Other Functioning Endocrine Tumors

	Bibliography Numbers
Adrenal carcinoma	18, 66, 89
Testicular choriocarcinoma	20, 34

d. Pituitary Disease:

This was one of the most common conditions associated with abnormal lactation. Acromegally associated with abnormal lactation is usually seen in females but Roth (124) gives an account of the condition in two males. Chromophobe adenoma with galactorrhea was described in five cases. One case of basophilic adenoma of the pituitary and galactorrhea was described by Toaf (146). The galactorrhea ceased after removal of the tumor. Histologic diagnosis was made on the above cases either from surgical specimens or at autopsy. There is a considerable number of reports of galactorrhea

associated with X-ray evidence of an enlarged pituitary but without histologic evidence as to the type of tumor.

Pituitary stalk section was performed on one patient with metastatic breast cancer and she began to lactate postoperatively and was still lactating seven months later (42). The hypermormotrophic syndrome described by Zondek (153) is considered under diseases of the pituitary. This syndrome is characterized by symptoms of galactorrhea, thyrotoxicosis, excessive utering bleeding and a flat glucose tolerance curve with low blood sugar. The sella tursica was normal in all five cases reported. The author assumes that the primary defect is excess FSH which stimulates the follicles to hyperproduction of estrogen which in turn stimulates the pituitary to replace excess hormonotrophic factors (153).

Pituitary Disease

	Bibliography Numbers
Acromegally	28, 37, 50, 52, 92, 93, 124, 125, 142, 135
Chromophobe adenoma	26, 64, 125, 151
Basophilic adenoma	146
Pituitary tumor	49, 50, 60, 61, 71, 75, 79, 84, 95, 100, 125, 146
Section of pituitary stalk	42
Hyperhormonotrophic syndrome	153

e. Hypothalamic and Related Disorders:

Hypothalamic lesions have been implicated as the etiology of abnormal lactation. Reise decribes a case of abnormal lactation and

and parkinsonism following an attack of epidemic encephalitis. He concluded the mammary activity resulted from a disturbance of the vegetative nuclei (120).

Dadey describes a case of abnormal lactation, amenorrhea and diabetes insipidus. These symptoms came on following an attack of encephalitis (36).

Pseudocyesis as a cause of abnormal lactation is described by three authors. Engstrom describes a case in a multiparous woman (45). Gellhorn cites several cases of phantom pregnancy with mammary secretion. These were due either to the desire or the fear of pregnancy and in one case, to the sight of milk secretion (56). Reeb describes the case of a 19 year old multiparous female who feared she was pregnant and as a result of the psychic trauma started to produce milk from both breasts (118).

Hypothalamic and Related Disorders

	Bibliography Numbers
Postencephalitic Parkinsonism	120
Pseudocyesis	45, 56, 118

2. Local Factors:

a. Mechanical Stimulation: Mechanical stimulation is believed to be one of the primary factors in initiating and maintaining mammary secretion in the normal post partum breast. This is discussed under physiology of lactation.

Briehl describes one of the most interesting and unusual cases of autostimulation with resultant lactation in a virgin (27).

Baudelocque describes a case of an eight year old girl suckling her brother (59). There are numerous examples of post-menopausal women nursing their grandchildren. The development of gynecomastia with lactation in men following suckling stimulation is reported by several authors (59, 77).

b. Disturbances of the Chest Wall: Other than infectious processes of the chest wall there are two main types, thoracic surgery and burns of the chest. Grossman (62) presents and discusses four cases of abnormal lactation following thoracoplasty. Aufses (6) reports a case of abnormal lactation in the left breast of a female following a right radicle mastectomy. Vogt describes a case of third degree burns over the entire chest which was followed by profuse milk secretion which did not stop until the wound was healed. The patient also had amenorrhea (147).

Local Factors

Bibliography Numbers

Mechanical Stimulation	27, 50, 54, 59, 77, 96, 107, 137
Disturbances of Chest Wall	
Thoracic Surgery	6, 61, 62, 128
Burns of the Chest	147

3. Drugs:

Drugs other than hormonal agents which cause abnormal lactation are the phenathiazine group of drugs and Rauwolfia alkaloids. The drug most frequently reported as causing abnormal lactation is chlorpromazine. This is followed by Resperine and

then one report was due to Temaril (72). The mechanism by which these drugs cause lactation is not fully known as the action of these drugs on the hypothalamic centers is unknown. It is generally believed these drugs have a depressing action on the central nervous system. This fact is used to postulate that the drug depresses a center in the hypothalamus which acts as an inhibitor to the release of prolactin.

Drugs	Bibliography Numbers
Chlorpromazine	7, 30, 32, 74, 94, 102, 103, 104, 113, 121, 152
Temaril	72
Reserpine	112, 139
Stilbestrol	69

4. Infections:

Infectious diseases have been reported in association with abnormal lactation. Central nervous system, syphilis, herpes zoster, and encephalitis are three diseases for which reference could be found. The mechanism of action in these cases is believed to be due to stimulation of the afferent nerve pathway involved in the neurohormonal reflex of lactation.

Infections

Bibliography Numbers

Syphilis	16, 21, 39
Herpes Zoster	61
Encephalitis	36, 120
Tuberculosis	87

5. Miscellaneous:

Miscellaneous other conditions have been associated with abnormal lactation. As can be seen on Chart #9 the list is fairly long and heterogenous. In these cases it is difficult from reading the literature to acertain of some if these are incidential to the galactorrhea or if they contribute to it.

Miscellaneous

Bibliography Numbers

Teratoma Testis	46, 34
Carcinoma of Prostate	69
No Apparent Cause	2, 50, 44, 49, 151, 22
Metastatic Carcinoma to pituitary from breast	55
Malignant hypernephroma	110
Following pneumoencephalography	12
Hyperostosis Frontalis Interna	24
Surgical Removal of Thyroid and Parathyroid	70
Following Prostatectomy	78
Psommosarcoma of Pineal Gland	108

6. Syndromes:

Of the syndromes the most frequently reported is the Chiari-Frommel Syndrome. This syndrome involves post partum amenorrhea, uteroovarian atrophy and galactorrhea. Two cases were reported by Chiari in 1855 and later in 1882. Frommell reported another case and gave a clinical recapitulation of Chiari's syndrome. In 1932, Schiller (130) described the syndrome again and used the term "Chairi-Frommel's Syndrome". Christiansen reviewed the literature of this syndrome in 1957 and stated there were 15 previously known cases and added another in his report (31). Potter (114) and Ashkar (5) describe cases of Chiari-Frommel's Syndrome who subsequently became pregnant.

The Forbes Albright Syndrome is galactorrhea, amenorrhea, and low urinary FSH. This essentially does not differ from the Argonz Castillo Syndrome, estrogenic insufficiency, galactorrhea and low urinary follicle stimulating hormone. Forbes concludes the cause of the syndrome was hypophyseal in origin, the contribution of the hypothalamus being the unknown factor. Argonz also concluded the cause was in the hypophysis. Argonz described his syndrome in 1953 and Forbes reported her cases in 1954.

Syndromes

Bibliography Numbers

Forbes Albright	26, 48
Hyperhormotrophic Syndrome	153
Chiari Frommel Syndrome	5, 31, 51, 58, 64, 98, 114, 122, 135, 136, 138, 146
Argonz del Castillo Syndrome	3

Treatment

The treatment of cases of abnormal lactation has been unsatisfactory. In cases where the lactation was due to mechanical stimulation, drug administration, tumors, or other causes, the removal of the causative factor results in the cure of the galactorrhea. In the majority of cases the etiology of the galactorrhea is basically unknown, therefore, the treatment is empirical and the results are variable. Stilbestrol has probably been the most widely used hormone and, as can be seen from the chart, the results have been variable.

Combinations of the above therapeutic measures have been used with the same degree of success as with the drugs used individually. Combinations of the gonadotrophic and estrogenic or progestational agents have been used and the proponents claim good results but other workers do not get the same degree of success. Treatment will remain empirical until the etiology of abnormal lactation is further elucidated.

Treatment

Bibliography Numbers

Mode of Therapy	Increased Lactation	No Effect on Lactation	Decreased Lactation
Stilbestrol	39, 57	36, 51, 60, 62, 69, 125, 135, 151, 153	10, 50, 61, 98
Progesterone		36, 97, 153	
Corpus Luteum Extract			28
X-ray to Pituitary		79, 95, 153	39, 69, 99, 125, 146
Cortisone	39		
Belladonna and Glycerine Locally		149	77, 141
Castration			46
Testosterone		70, 153	
Chorionic Gonadotropin	51	31, 64, 153	
Follicle Stimulating Hormone		51	
Thyroid Extract			36

Laboratory Results

Laboratory data as a general rule was not reported in most of the cases. The more recent reports give details of the laboratory work with description of techniques and the results obtained. Earlier workers do not give laboratory data, especially the urinary steroid levels or blood chemistry studies. Because of the variability of reporting laboratory results no attempt will be made to chart these results. The one result which is lacking in all these reports is an accurate measurement of prolactin levels.

Case Reports

No. 1

Patient: L.M. Age: 37 Race: White Sex: F

The patient was admitted to the hospital on 6-22-61 with chief complaint of urinary stress, incontinence, frequency, dysuria and occasional nocturia for the past four months.

Past medical history: Childhood diseases: Rheumatic fever without sequalae. Pneumonia, age 5. Adult Illness: Thyroid deficiency. Operations: Tonsillectomy at age 8, appendectomy at age 17, suspension of female organs at age 25, hysterectomy and left oopherectomy at age 34 (1958) because of leiomyofibroma which was causing menometorrhagia.

Social History: High school graduate. Smokes cigaretts and drinks occasionally.

Family History: Mother has colon trouble and tuberculosis. Grandmother had cancer of the uterus. No history of breast disease.

Systemic Review:

HEENT: The patient has worn glasses since age 9. No blurring of vision or double vision. Thyroid within normal limits.

Chest: No history of abnormality.

Breasts: The patient complains of persistent secretion of a milky fluid from both breasts since the birth of her last child in 1956. She states her breasts did not enlarge or change during the last pregnancy but she had enlargement, tenderness and

secretion of a few drops of milky fluid after the delivery. There has been no bloody discharge.

Heart: Shortness of breath with exertion since 1960. No orthopnea or nocturnal dyspnea.

G.I.: Appetite good with 14 pound weight gain in the past year.

G.U.: No history of polydipsia or polyuria. No venereal diseases.

Menstrual History: Menarche, age 12. Periods regular every 28 days with 5 - 7 days of moderate flow with cramping the first 2 - 3 days. Surgical menopause in 1958. Para 2-3-2-5.

Allergies: None known.

Physical Examination: Teeth in poor state of hygiene.

Breasts: Tender and a few drops of white liquid could be expressed bilaterally. Left axillary node palpable. Nipples small and moderately pigmented.

Pelvic Examination: Cervical stump intact, no apparent lesions. Whitish secretion seen.

Clinical Record:

5-20-60: Patient started on luteotrophic hormone, 10 mgm. daily for 2 weeks and a temperature chart kept for three months. Lactation ceased on the luteotrophic hormone for 2 - 3 weeks but then resumed.

7-6-60: Cystic right ovary palpated.

4-14-61: Stilbestrol 5 mgm/day for three weeks started.

5-5-61: The patient states she has had no lactation for two months.

No. 2

Patient: L.R. Age: 31 Race: White Sex: F

The patient is considered reliable.

C.C.: She has had pain in her abdomen and neck since the birth of her child 16 months earlier (8-8-58).

History of the Present Illness: The back pain has occurred intermittently since February, 1957. She has pain in the lumbar region and flanks with occasional migration to abdominal region. The pain is cramping in nature. She complains of pain over upper ant. chest wall, aching in nature. She gets no relief from aspirin. This occurs at night when in bed. It is not related to exertion or cold. She also complains of pain in extension of her neck, which occurs toward the end of the day.

The patient has complained of "dizzy spells" since October, 1957. She states that they occur at no specific time and are not accompanied by tinnitus or headaches. She states that she remains still and the objects around her spin. There is no history of related convulsions or syncope.

She has headaches that occur 2 - 3 days prior to menstrual period. They occur suboccipital radiate to temporal and frontal regions, and occur always bilaterally. They are dull aching in character, and are not relieved by aspirin. There is no time relationship and no aura.

The patient has blurring of vision when reading.

S.R.: No significant history except above.

Breasts: The patient did not ever nurse.

Menstrual History: Menarche, age 10. Cycle, 25-30 days regular with 5 days of moderate flow. She has had cramps occurring 3 days after period for the past 9 months.

Para: 4-0-0-4 1945, 1946, 1949, 1958. All of the deliveries were full term and vaginal. There were no hospitalizations or operations.

Physical Examination: Weight, 159; Height, 5'4"; B.P., 120/80; R. - 16 P. - 68.

The physical examination was within normal limits except for the spleen being down one finger breadth. Also the patient had a grade 2 rectocoele and cystocoele. She had diastasis recti as well. Also, uterine myomata were thought to be present. The patient was also thought to have a psychoneurotic overlay (anxiety reaction).

No breast secretion was expressed.

July 22, 1960: The patient mentioned she had not quit lactating since her last delivery and milk could be expressed from the breast.

August 22, 1960: The patient was seen in the endocrine clinic. She has been taking Equanil two times a day for the past month.

October 28, 1960: The patient took stilbestrol from 10-6-60 to 10-12-60 without effect on lactation.

No. 3

Patient: R. H. Age: 28 Race: White Sex: F

The patient is a 28 year old para 2-0-0-2 white female who is very obese. Her weight has ranged from 189½ to 202 pounds. Her obesity is generalized with no hirsutism or purple striae.

She was seen at the University of Nebraska Hospital for the first time on 1-27-58 with a c. c. of rupture of her naval. She was also found to be hypothyroid, amenorrheic and lactating. She was admitted to the University of Nebraska Hospital on 3-27-58 for evaluation of her condition.

Her amenorrhea had persisted since the birth of her last child in 1955 (3-19-55). Both her pregnancies and deliveries were normal. She was given 50 mg. progesterone I.M. on 3-13-58 and 5 days later she had a "normal"period. It was repeated on 1-20-59 and she bled from 1-24-59 to 1-29-59. She has a chronic foul smelling vaginal discharge.

Her lactation was bilateral and was first noted on 1-27-58. The patient stated it was intermittent and slight in amount.

Evaluation of her thyroid revealed that she suffers from primary hypothyroidism. She has been on as much as 4 grain thyroid without effect on her periods or weight. She has been on thyroid since age 9.

The patient states she had a normal period without medication on 4-15-59 lasting 5 - 7 days.

No. 4

Patient: R.M. Age 18 Race: Negro Sex: F

C.C.: Bleeding from the breast for past three weeks.

History of the Present Illness: The patient first noted a bloody and oily yellow-green fluid exuding from her right breast after taking a shower. She denies tenderness, trauma to the breast, lumps, or any abnormalities of her breasts.

In addition, she had a complaint of a dull, aching, non-radiating pain of the left lateral abdomen. She denies any symptoms referrable to the kidney or genitalia.

Past Medical History: The patient has been followed at the University Hospital since birth and has been seen on numerous occasions for minor childhood diseases. The past history is essentially negative.

Systemic Review: Essentially negative except for history of present illness.

Physical Examination: Pulse 70. Blood Pressure 110/70.

HEENT: Negative

Respiratory and Cardiovascular System: No significant abnormalities.

Breasts: Serosanguinous discharge after manipulation. No masses or areas of tenderness palpable.

Abdomen: Spleen palpable 2-3 cm. below left costal margin.

Genitalia: Normal nulliparous female.

Menstrual History: Menarche, age 13. Periods regular every

28-32 days lasting four days.

Neurologic: No significant abnormalaties

Impression: Intraductal papilloma.

Clinical course: The patient was seen in the clinic regularly and the discharge from her right breast continued. On one occasion, pelvic examination revealed a small uterus, no ovarian enlargement and no adnexal masses. On 7-20-61, intranasal oxytocin was given and a serous discharge was expressed from both breasts.

On 9-21-61, the patient had an endometrial biopsy showing proliferative endometrium. She was started on 10 u. luteotrophic hormone and maintained on this for ten days. At the end of this time she was still lactating.

On 11-20-61, the patient was started on 25 mgm. prolactin I.M. She was maintained on this for 14 days, and she had no lactation while on the drug but lactation started again two days after prolactin was stopped.

On 12-14-61 it was decided to discontinue treatment.

No. 5

Patient: R.S. Age: 32 Race: White Sex: F

C.C.: Polydipsia, anorexia, backache, extreme restleness and poor control of hypoparathyroidism.

Past Medical History: The patient was first seen at the University Hospital Clinic because of an enlarged thyroid on 2-25-55. A biopsy of the thyroid revealed papillary adenocarcinoma. A total thyroidectomy and radical neck dissection was done on 5-27-55. The patient has had difficulty with hypothyroidism, and hypoparathyroidism ever since. She has been maintained on Vitamin D, calcium gluconate and thyroid extract.

She gave birth to a normal infant in August of 1958. On January 8, 1959, the patient was seen in the Gynecology Clinic with a chief complaint of bloody, spotty discharge necessitating the wearing of a pad. She had been seen in the Obstetrics Clinic on 12-8-58 and given 50 mgm. Progesterone I.M. On 12-12-58 she began to bleed until 12-16-58. She had more spotting on 12-26-58 to 12-31-58. Her last flow began on 1-5-59 and has lasted until this clinic visit. She also complained of a thin white secretion from both breasts which started on 12-8-58 while taking a bath. Since then, she has been able, on several occasions, to express a watish discharge from her breasts. She did not breast feed her last child.

Pelvic Examination was normal.

Lactation has continued to the present time, 7-11-60.

Menstrual History: Menarche, age 13 with 21 day cycle with seven days of moderate flow.

Pregnancies: Para 4-0-0-4. All deliveries were normal term without complication.

Physical Examination: B.P. 126/80. The patient was a well-developed, poorly nourished, somewhat pigmented, pleasant white female with a well-healed thyroidectomy scar in the right side of her neck. The heart and lungs were normal. The Chovestek and Traussau signs were negative. There was no evidence of lenticular opacity, corneal opacification, or metastatic calcification of the eyes. Pelvic and rectal examinations were within normal limits.

No. 6

Patient: C.J. Age: 21 Race: Negro Sex: F

C.C.: Persistent lactation since birth of her first child in September, 1957.

History of the Present Illness: The patient had no difficulty with pregnancy or delivery. Her last pregnancy delivered a hydatid mole in September, 1960. She had anemia due to hemorrhage at this time and endometritis was diagnosed. She also had bilateral luteum cysts of her ovaries.

Past Medical History: Menarche, age 10 years, with 30 day periods, irregular, with three days of light flow. Her periods have been irregular, 18-30 days, since her second pregnancy.

Physical Examination: Height, 5'5½"; Weight, 130 pounds, B.P., 120/80.

The physical was normal except for milky discharge from both nipples with pressure. Her breasts were small, pendulous, non-tender, and symmetrical. She had a retrovereted retroflexed uterus and the right ovary was palpable.

Clinical Course: The patient has been treated for ten months with 5 - 15 mgm/day of stilbestrol and 100 mgm. provera I.M. every two weeks without effect on her lactation.

LABORATORY DATA

	#1	#2	#3
CBC	Hb.14.7 gm. WBC 10,600 Normal Dif.	Hb.11.2 gm. RBC 4.74 WBC 6,600	
U.A.	Normal	30-40 RBC/hpf.	Normal
BMR			-25 -21%
Serology	Negative	Negative	
Blood Glucose	74 mgm%		86 mgm%
Glucose Tolerance Test			Normal
BUN	1.5 mgm%		
PBI	6.4 mcgm%		1.7 mcgm% 4.2 mcgm%
I^{131} Uptake			6.6%/4 hrs. 4.4%/24 hrs.
Cholesterol Total:	195 mgm%		325 mgm% 202 mgm%
Ester:			
BSP		2% Ret. in 5 minutes	
EKG	Normal		
Visual Field	Normal	Normal	Normal
Cervical Cytology	Normal on Repeated Occasion	Normal	Normal
TSP	7.19 gm.%		
Albumin	4.66 gm.%		
Globulin	2.53 gm.%		
Urinary 17 KS	3.2 mg/24 hr. 3.1 mg/24 hr.	2.7 mgm/24 hr.	4.0 mgm/24 hr.
Urinary 17 Hydroxy	2.3 mg/24 hr. 2.7 mg/24 hr.		
FSH	1-3 lab.units (N)	4 units (high)	0 (low)
Endometrial Biopsy			
Skull X-ray	Normal	Normal	Normal
Urinary Pregnanetriol	3.3 mgm/ 24 hr.		

	#4	#5	#6
CBC		Hb.12.7 gm.	Hb.11.7 gm.
U.A.			
BMR			
Serology		Negative	Negative
Blood Glucose			
Glucose Tolerance Test			
BUN	7.5 mgm%		
PBI	8.0 mcgm%		
I^{131} Uptake			
Cholesterol Total:	193 mgm%		
Ester:			
BSP			
EKG			
Visual Field	Normal	Normal	
Cervical Cytology	Normal	Normal	Normal
TSP			
Albumin			
Globulin			
Urinary 17 KS			5, 4.9, 3, 3.7 mg/24 hr.
Urinary 17 Hydroxy			1.0 mg/24 hr.
FSH			1-3 lab units (N)
Endometrial Biopsy	Secretory & Prolif.		
Skull X-ray	Normal	Normal	Normal
Urinary Pregnanetriol			12, 14, 6 mgm/ 24 hr. (high)

Comments

Abnormal lactation or galactorrhea is the formation and secretion of milk or colostrium from the nonpuerperal breasts of female and male mammae. This is a relatively rare occurance yet it has been reported in association with numerous diversified conditions.

After castration and in cases of precocious and physiologic menopause, galactorrhea is sometimes found; in these conditions urinary gonadotropins are always increased (3).

Galactorrhea has been reported in acromegalic females and rarely in acromegalic males (124). Galactorrhea with no interference with menstruation in apparently normal females has been observed. Galactorrhea sometimes occurs as one of the endocrinologically abnormal features of Simmond's Disease (3).

In 1855, Chiari reported two cases of persistent lactation and amenorrhea following parturition. In each of these cases, there was associated utero-ovarian atrophy. Frommel, in 1882, found one such case in 3,000 gynecological patients in Vienna. Since then the syndrome characterized by persistent lactation, amenorrhea following delivery, and utero-ovarian atrophy, has been referred to as the Chiari-Frommel Syndrome. This syndrome is not always a functional disorder with a tendency to spontaneous cure as supposed by Chiari and Frommel, because reports of its association with pituitary tumors have been dislosed by Greenblatt (10) and Toaff (146).

Forbes and her co-workers (49) introduced another syndrome characterized by galactorrhea, amenorrhea and low urinary FSH in their presentation of 15 cases of amenorrhea and persistent lactation not associated with a recent pregnancy or acromegally. Deficiency of endogenous estrin was demonstrated in the majority of Forbes' patients as well as in the four patients with the syndrome (estrogenic insufficiency, galactorrhea, and decreased urinary gonadotropins) reported by Argonz and del Castillo (3).

Krestin (79) pointed out that mammary secretion of colostrum has occurred in chorio-epithilioma of the testes with metastases as well as psammosacroma of the pinal body.

Galactorrhea occurred for 36 hours following pneumo-encephalography in a menstruating 43 year old woman described by Bellut (12). Four cases of lactation following thoracoplasty in nonpregnant multiparous women have been presented by Grossman (62) et al. Partial ovarian resection was followed by galactorrhea in two cases reported by Labry and Gabriel (81).

The use of endocrine substances in the treatment of cancer has resulted in lactation. In Huggins (69) a case of a 64 year old man with carcinoma of the prostate and osseous metastesis, who had taken stilbestrol for two years, creamy milk was expressed from both breasts following administrations of prolactin for five days.

Other recently introduced drugs such as chlorpromazine and Rauwolfia have been associated with the development of abnormal

lactation. Winnick and Tennebaum (152) studied 21 women who had galactorrhea while on chlorpromazine therapy in a psychiatric hospital in Jerusalem. In these patients whose ages varied from 21 to 95 there had been no previous pathologic lactation. The occurrence of lactation in women receiving Rauwolfia has recently been reported by Platt and Sears (112).

In 1928 Riese (120) published a case report of a 25 year old woman who developed galactorrhea and parkinsonism following epidemic encephalitis in 1919.

In discussing the pathophysiology of abnormal lactation one can only theorize since the mechanism of normal lactation is not completely understood. Forbes, et al. presumed that in view of the incidence of pituitary tumor in some of their cases of galactorrhea, amenorrhea and low urinary follicle stimulating hormone, the syndrome is due to pituitary dysfunction, even when no tumor is demonstrable, with production of an excess of some hormone. There is either an abundance of a hormone responsible for lactation (prolactin) or interference with the production of a pituitary hormone which normally inhibits lactation. They tentatively propose that all of their patients had an overproduction of prolactin by the pituitary.

Argonz and Castillo suggested that a modification of the estrogenic level and an unknown hypothalmic influence, which affected the pituitary, may be factors operative in this syndrome (3). They seem to feel that there is an eosinophilic hyperfunction of

the anterior pituitary lobe where prolactin presumably is elaborated. This may explain the occurrence of galactorrhea in some acromegalics. Conceivably the production of an excess amount of prolactin may lead to a pituitary unbalance resulting in diminished secretion of one or more of the other pituitary hormones in the Chiari-Frommel Syndrome of galactorrhea, amenorrhea, and low urinary follicle stimulating hormone. At any rate, galactorrhea is obviously a manifestation of polyglandular dysfunction in many instances (84). Apparently the male and even infant breasts are capable of responding to the proper hormonal stimulation as is evident in the secretion of the so-called "witch's milk" in newborn infants (95).

The lactogenic action of chlorpromazine and Rauwolfia is probably mediated through their action on the hypothalamus. Likewise, the occurrence of galactorrhea after pneumoencephalography resulted from hypophysial or midbrain damage. The occurrence of diabetes insipidus further tends to incriminate the hypothalamic-hypophysial axis in the physiology of abnormal lactation. Whether the action of these conditions and drugs is due to the stimulation of a neurosecretory center or due to the depression of an inhibitory center in the hypothalamus is not known.

Summary

The normal physiology of lactation was discussed briefly.

An attempt was made to review the world literature for the purpose of disclosing all the etiologic conditions associated with abnormal lactation. These conditions plus treatment programs were summarized in bibliographical charts.

A review of six cases of abnormal lactation observed at the University of Nebraska College of Medicine was presented.

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