endocrine

PROLACTIN-SECRETING PITUITARY ADENOMAS

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"If a woman have milk, who is not with child, nor has brought forth, her menses are obstructed."

Hippocrates: Aphorism 39, Section V

It is only within the past 10 years that the spectrum of disorders associated with prolactin (PRL) hypersecretion has begun to be elucidated. Indeed, it was not until 1970 that PRL was demonstrated as a hormone distinct from growth hormone in human blood (1). The following year a sensitive and specific radioimmunoassay for human PRL was developed (2), and by 1977 its entire 198 amino-acid sequence had been established (3). As the result of the availability of the PRL radioimmunoassay, it is now recognized that PRL is the most frequently hypersecreted hormone in patients with hypothalamic-pituitary disease. Of patients with pituitary tumors, as many as 70% harbor prolactinomas (4). Equally staggering is the high frequency of PRL-secreting adenomas among women with secondary amenorrhea (approximately 15%), particularly among those with concomitant galactorrhea (at least 35%, but probably 50% or more) (5-7). Definition of the magnitude of the "prolactinoma problem" has relied not only on the ability to measure PRL in serum, but also on parallel advances in radiology, surgery, and pharmacology. A rational approach to the evaluation and management of patients with prolactinomas requires an understanding of normal PRL physiology and the regulation of its secretion, the various physiologic and pathologic conditions associated with hyperprolactinemia, possibilities as to the pathogenesis of PRL-secreting adenomas, the clinical manifestations of prolactinomas, and the natural history of these tumors.

Normal Prolactin Physiology

Although PRL has a wide range and diversity of biologic actions among vertebrate species (including influences on behavior, osmoregulation, and differentiation and development of the female breast), its only recognized physiologic role in humans is the promotion of tubuloalveolar proliferation in the breast and stimulation of milk production during pregnancy and the postpartum period. Increased secretion of PRL by the pituitary begins early in pregnancy under the stimulation of high estrogen levels, and is evident histologically as hyperplasia of the pituitary lactotrophs. The serum PRL concentration increases steadily through gestation, reaching a level 10 to 20 times that found prior to pregnancy. Although estrogen and progesterone are also essential in milk formation, primarily by synergizing with PRL in promoting ductular and alveolar proliferation in the breast, they inhibit actual milk secretion during pregnancy. Following parturition and the abrupt decline in estrogen and progesterone levels, secretion of milk is no longer restrained and lactation ensues under the stimulus of suckling. Suckling, by means of neural pathways originating in the nipple, results in increased secretion of both PRL (necessary for continued milk production) and oxytocin (essential for milk ejection). The serum levels of PRL begin to decline immediately postpartum but its persistent secretion is absolutely essential for lactation to continue. By 2 to 3 months postpartum circulating levels of PRL are usually within the normal range in the absence of the suckling stimulus, and are normal by 6 to 12 months even in the presence of continued nursing. Thus, although hyperprolactinemia is necessary for the initiation of lactation, normal PRL levels may sustain lactation for long periods subsequently (8, 9).

Neuroendocrine Regulation of Prolactin Secretion

PRL is synthesized in the lactotroph cells of the anterior pituitary and is stored in acidophilic granules. Like other anterior pituitary hormones, its secretion is modulated by the hypothalamus. In the case of PRL this modulation is predominantly inhibitory and not stimulatory as is the case with regulation of the other pituitary trophic hormones.

Stimuli from the hypothalamus are relayed to the anterior pituitary by those hypothalamic neurosecretory cells (the tuberoinfundibular neurons) whose axonic terminals abut the hypophyseal portal system (Fig. 1). Some of these neuro-

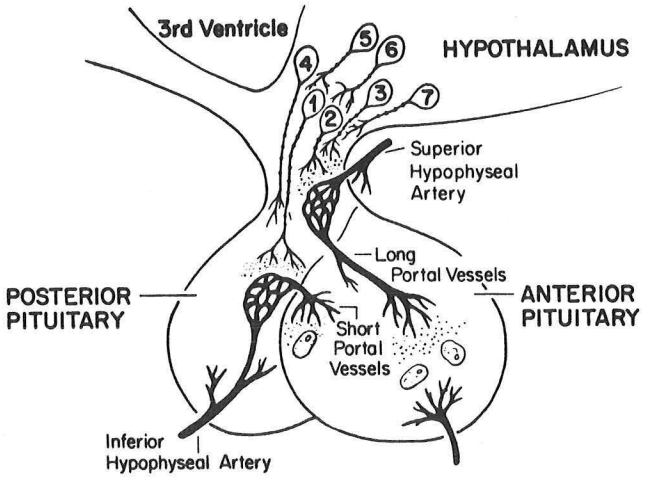


Fig. 1. Hypothalamic regulation of trophic hormone secretion by the anterior pituitary.

secretory terminals contain dopamine; others contain small peptides, each of which controls the secretion of specific anterior pituitary hormones. The secretion of PRL is controlled directly by secretory activity of the dopaminergic tuberoinfundibular neurons (10-13). However, the activity of these neurosecretory neurons is also under regulation by impulses arriving via synapses with other hypothalamic and extrahypothalamic neurons. Neurotransmission at this level is mediated by biogenic amines, including dopamine, norepinephrine, and serotonin (5-hydroxytryptamine), as well as by histamine, acetylcholine and opioid peptides. Dopamine that is secreted directly from the terminals of the tuberoinfundibular neurons into capillaries of the portal circulation is transported to the anterior pituitary. At this level dopamine binds to specific receptors on the pituitary lactotrophs and thereby inhibits PRL secretion (14). An endogenous hypothalamic prolactin inhibitory peptide has not been characterized to date. Histamine however appears to be a second regulatory factor that results in inhibition of PRL secretion, independent of central nervous system dopaminergic pathways (15-16). The existence of endogenous, physiologically important prolactin releasing factors has not been established. Although thyrotrophin-releasing hormone (TRH), the hypothalamic tripeptide that stimulates secretion of thyrotrophin (TSH), does stimulate PRL secretion when injected into normal individuals (via TRH receptors located on the pituitary lactotroph itself), evidence suggests that it is not a physiologic regulator of PRL. Serotoninergic, cholinergic, and endorphinergic/enkephalinergic stimuli also result in increased PRL secretion, but again, their physiologic importance is unknown. The effect of estrogen in stimulating PRL secretion is most likely the result of an intrinsic antidopaminergic activity (17) and/or its effect in inducing lactotroph hyperplasia.

PRL also regulates its own secretion via a short-loop feedback mechanism (Fig. 2) (18). Retrograde flow of PRL through the hypophyseal portal system to the hypothalamic tuberoinfundibular neurons probably results in increased dopamine secretion by these neurons and subsequent inhibition of PRL secretion.

NORMAL FEEDBACK REGULATION OF PROLACTIN SECRETION

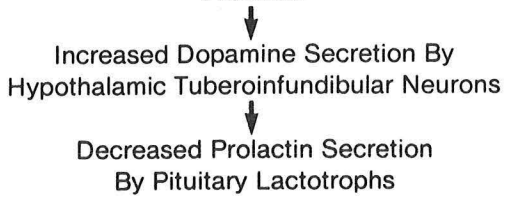


Fig. 2

The net effect of these neuroregulatory pathways is a mean serum PRL level of approximately 8 ng/ml in women (range 1 to 25ng/ml) and 5 ng/ml in men (range 1 to 20 ng/ml) (8). However, because of a short circulating half-life (approximately 15 to 20 minutes) and of episodic secretory bursts, the actual serum level may vary by 5 to 10 ng/ml over a period of 1 hour (5). Further variability in PRL levels in normal individuals is related to sleep, stress, and exercise as described below.

Hyperprolactinemia

Hyperprolactinemia may be transient or persistent. Transient elevations of PRL are most frequently associated with various physiologic stimuli of PRL secretion. More persistent elevations are typically associated with administration of certain drugs, with various nonpituitary diseases, and with several primary pituitary disorders (Table I). The most common of the latter is the PRL-secreting adenoma.

Physiologic Conditions Associated with Hyperprolactinemia. Numerous physiologic conditions are known to increase PRL secretion. The effect of the marked hyperestrogenism of pregnancy on PRL secretion has already been described. Estrogens also modulate the mean basal serum levels of PRL in nonpregnant women and the response of PRL to various secretory stimuli; this effect accounts for the slightly higher basal PRL levels seen in women as compared to men. When exogenous estrogens are administered PRL levels rise after several days of therapy. When the estrogen dose is less than 50 µg of ethinyl estradiol per day (or its equivalent), the rise in PRL is usually not outside the normal range. At doses of 400 µg of ethinyl estradiol per day, however, a persistent increase in serum PRL concentration throughout the day is observed (19). A modest increase in PRL secretion with breast stimulation is seen in approximately one-third of normally menstruating, non-postpartum women, but in the majority of normal women and in men there is no effect of breast stimulation on PRL release (5, 8). Thus, the reflex mediating the marked increase in PRL secretion with breast stimulation in postpartum women is suppressed in men and in most non-postpartum women. However, chest wall and cervical spinal cord lesions occasionally result in hyperprolactinemia via the same neural arc that is activated by breast and nipple stimulation. Sleep and stress also increase PRL secretion, possibly on the basis of

Table I

FACTORS AFFECTING PROLACTIN SECRETION

Physiologic

- Pregnancy
- Estrogens
- Neurogenic
  - Breast Stimulation
  - (Chest Wall Lesions)
  - (Spinal Cord Lesions)
- Sleep
- Stress
- Exercise
- Hypoglycemia

Pharmacologic Agents

- Neuroleptics
  - Phenothiazines
  - Butyrophenones
- Metoclopramide
- α-Methyldopa
- Reserpine
- Cimetidine (intravenous)
- Opiates

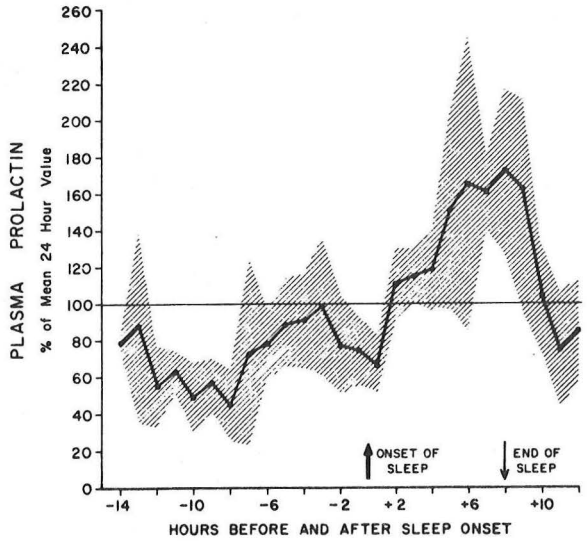
Nonpituitary Disorders

- Chronic Renal Failure
- Polycystic Ovarian Disease
- Hypothyroidism
- Hypothalamic Disease
  - Craniopharyngioma
  - Sarcoidosis

Pituitary Disorders

- Prolactinomas
- Acromegaly
- Empty Sella Syndrome
- Pituitary Stalk Section

increased serotoninergic and/or cholinergic stimulation. A 50% to 100% rise in serum PRL typically is seen within 4-6 hours of the onset of sleep (Fig. 3). Strenuous exercise and hypoglycemia are modest stimuli of PRL secretion (8).



Plasma Prolactin in Six Normal Subjects, Measured throughout a 24-Hour Period, Expressed as a Percentage of the 24-Hour Mean Plasma Level for Each Subject. Shaded area represents 1 standard deviation. A night-time peak, beginning after the onset of sleep, is evident.

Ref. 8

Fig. 3

Hyperprolactinemia Associated with Pharmacologic Agents. Hyperprolactinemia is frequently associated with administration of various pharmacologic agents that antagonize endogenous dopaminergic neurotransmission. The site of antagonism may be the hypothalamus or the pituitary. The action of drugs restricted from the CNS is confined to the pituitary. Drugs that do penetrate the blood-brain barrier, such as the neuroleptics, block dopaminergic receptors in the hypothalamus and/or the pituitary. The site of dopaminergic blockade induced by other dopamine receptor blockers such as metoclopramide and sulpiride is unknown. Following administration of a neuroleptic drug, PRL levels increase within a few hours but fall to lower, though still elevated levels during the course of long-term treatment. PRL levels in patients taking these medications are usually less than 150 ng/ml but may reach 300 ng/ml (9). PRL levels usually are normal within 48 hours of discontinuation of neuroleptic drug therapy. α-Methyldopa and reserpine may also lead to hyperprolactinemia by interfering with dopaminergic transmission. Drugs that result in increased PRL levels largely independent of dopaminergic pathways are the H_2-receptor blocker cimetidine (when administered as an intravenous bolus) (15, 16) and the opiates.

Hyperprolactinemia Due to Nonpituitary Disease. Several nonpituitary disorders may cause hyperprolactinemia. Decreased clearance of PRL accounts for the hyperprolactinemia seen in patients with chronic renal failure. The hyperprolactinemia described in some patients with polycystic ovarian disease is most likely due to chronic hyperestrogenism, although a PRL-secreting adenoma may be responsible in others. The slight increase in PRL seen in approximately 40% of patients with primary hypothyroidism (20) is primarily secondary to an increased sensitivity of the lactotroph TRH receptor in the setting of decreased levels of thyroid hormone. Increased release of TRH into the hypophyseal portal system may also contribute to the hyperprolactinemia in these patients. Intrinsic hypothalamic disease, such as craniopharyngioma (21, 22) and granulomatous involvement by sarcoidosis (23), also occasionally results in hyperprolactinemia. Most instances of idiopathic hyperprolactinemia are probably the result of disturbances in hypothalamic regulation of PRL secretion or of occult pituitary prolactinomas.

Pituitary Disorders Resulting in Hyperprolactinemia. The PRL-secreting adenoma is the most common primary pituitary disorder resulting in hyperprolactinemia, and accounts for the highest levels of serum PRL observed. The hyperprolactinemia associated with acromegaly (24-28) and the empty-sella syndrome (29-34) is frequently secondary to the concomitant presence of a prolactinoma. Interruption of the hypophyseal portal circulation by non-PRL producing pituitary tumors also results in hyperprolactinemia, but the serum PRL in these cases is almost always less than 100 ng/ml (35).

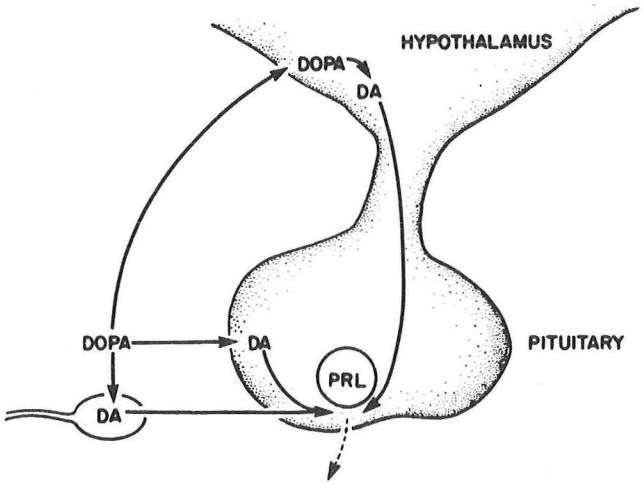
Pathogenesis of Prolactin-Secreting Adenomas

A PRL-secreting adenoma can theoretically arise by one of 2 mechanisms. A primary hypothalamic defect can be envisioned as resulting in decreased dopamine secretion by the hypothalamic tuberoinfundibular neurons with consequent chronic, unrestrained PRL secretion and possible adenomatous transformation of some of the lactotrophs. Alternatively, a primary pituitary disorder may be postulated in which there is either a deficiency of dopamine or an insensitivity to dopamine that is localized to the lactotrophs in that area of the pituitary in which the prolactinoma has formed.

Attempts have been made to differentiate between these two possibilities by examining the serum PRL response to various pharmacologic stimuli in patients with small PRL-secreting adenomas (in whom it is extremely unlikely that interruption of the hypophyseal portal system is contributing to the hyperprolactinemia).

-- PRL response to L-dopa (36-39).

The serum PRL is reduced by 33% or more within 90 minutes of the oral administration of L-dopa (500 mg) in most patients with prolactinomas. This response resembles that observed in normal control individuals and indicates that there are dopamine receptors on the adenomatous lactotrophs. Before L-dopa is able to exert any neurotransmitter or neuroendocrine activity, it must undergo decarboxylation to dopamine. Since this decarboxylation takes place in peripheral nerve terminals (giving rise to circulating dopamine) as well as in the pituitary and the CNS (including the hypothalamus), the suppressive effect of L-dopa on PRL secretion could conceivably be mediated by direct stimulation of dopamine receptors in the pituitary and/or via stimulation of hypothalamic tuberoinfundibular neurons to release endogenous dopamine into the portal circulation (Fig. 4). In either case, the inhibitory effect of L-dopa indicates that patients with prolactinomas do respond appropriately to increased dopaminergic tone.



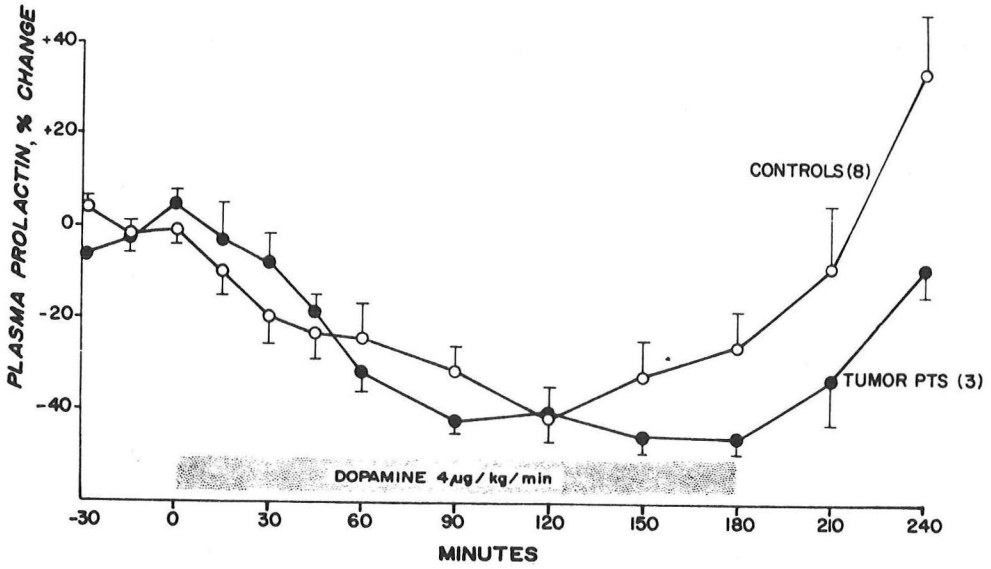
Ref. 44

Fig. 4. Inhibition of prolactin by L-dopa.

-- PRL response to intravenous infusion of dopamine and dopamine receptor blockers (Figs. 5-8) (40-44).

Patients with prolactinomas respond to dopamine infusion with a fractional decline in serum PRL similar to that seen in controls (Fig. 5). When the response to dopamine infusion is examined in terms of the absolute PRL decrement, a strong positive correlation is observed between the basal PRL level and the magnitude of the decrement during dopamine infusion (Fig. 6) (43). Dopamine, unlike L-dopa, does not cross the blood-brain barrier. Its effect on PRL secretion therefore must be exerted directly at the level of the pituitary. (The pituitary lies outside the blood-brain barrier.) Thus, dopamine insensitivity of the adenomatous lactotrophs is not a likely explanation for the pathogenesis of prolactinomas. This observation is supported by in vitro studies in which no difference in the number or affinity of

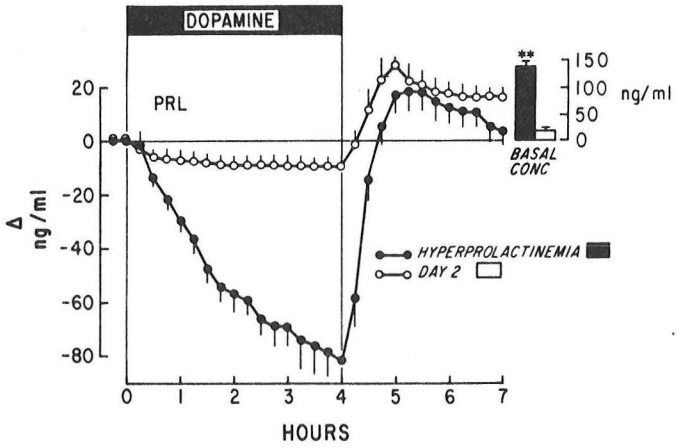
dopamine receptors between adenomas and normal pituitary can be demonstrated (45). Furthermore, L-dopa and dopamine reduce in vitro secretion of PRL by adenomas in tissue culture (46).



Ref. 44

Percent change from basal PRL levels (±SEM) in control and tumor patients during and after dopamine infusion. Dopamine was infused (intravenously) for 180 min.

Fig. 5

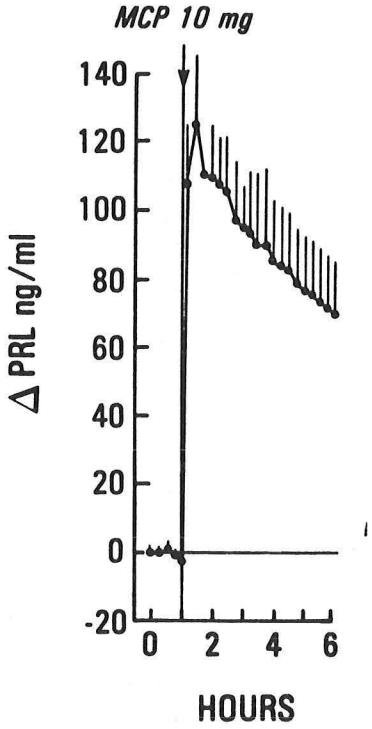


Ref. 43

The mean (±SE) basal serum PRL (mean of five samples) and their Δ (±SE) responses to dopamine infused at 4 μg/kg·min for 4 h in six normal women during the early follicular phase of the cycle and nine hyperprolactinemic women with pituitary prolactinoma. **, $P < 0.001$.

Fig. 6

In contrast to the similarities in PRL responses to L-dopa and dopamine in normal individuals and patients with prolactinomas, there is a discordance in PRL responses to dopamine receptor blockers such as metoclopramide and sulpiride. A marked increase in PRL secretion is seen in normal individuals following an intravenous injection of metoclopramide (Fig. 7). This contrasts to the very small increase in PRL following metoclopramide injection in patients with prolactinomas

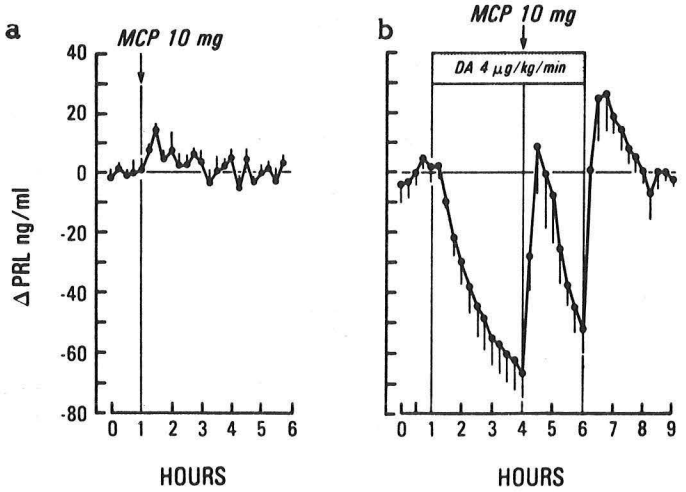


Ref. 43

The Δ (±SE) serum PRL (in nanograms per ml; mean of five basal samples) in four normal women during the early follicular phase of the cycle after an iv bolus of MCP (10 mg)

Fig. 7

(Fig. 8a). When dopaminergic tone at the adenomatous lactotrophs is increased by dopamine infusion, the PRL response to metoclopramide is restored and resembles the response of normal controls (Fig. 8b). In addition to endogenous dopamine deficiency at the adenomatous lactotrophs these results suggest: (1) near maximal



Ref. 43

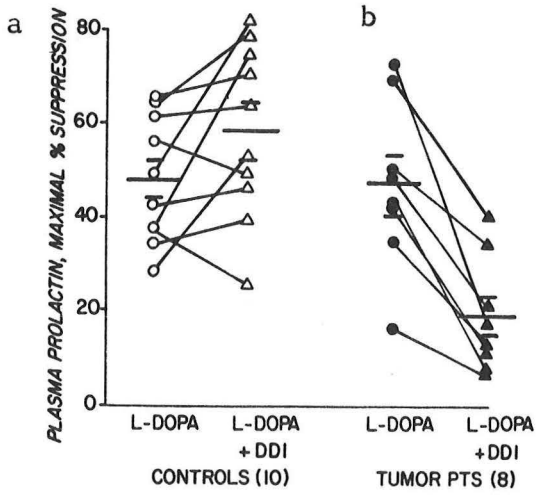
The Δ (±SE) serum PRL (in nanograms per ml; mean of five basal samples) in five prolactinoma patients after an iv bolus of MCP (10 mg) alone and then at the 3-h mark of a 5-h dopamine (DA) infusion (4 μg/kg·min) in four of the five patients on a separate occasion at least 1 week later.

Fig. 8

endogenous dopaminergic inhibition of PRL secretion in normal pituitaries (Fig. 6), and (2) suppression of PRL secretion from nonadenomatous lactotrophs in pituitaries harboring small prolactinomas (Fig. 8a). That PRL secretion by nonadenomatous lactotrophs is indeed impaired in patients with small PRL-secreting adenomas is supported by the observation that responses of PRL to stimulation by TRH (which acts via specific TRH receptors on the lactotroph) are almost uniformly attenuated (47). Furthermore, the PRL responses to TRH as well as to metoclopramide in patients who have undergone removal of small prolactinomas return only after a period of several months following surgery (48). Thus PRL-mediated short-loop feedback suppression of PRL secretion by nonadenomatous lactotrophs results in a prolonged functional impairment of these cells following reversal of the hyperprolactinemia.

-- PRL response to administration of L-dopa plus carbidopa (Fig. 9) (44, 49).

Carbidopa is an inhibitor of L-dopa decarboxylase that in low doses does not cross the blood-brain barrier. Any suppressive effect of L-dopa on PRL secretion when administered with carbidopa must therefore be mediated by CNS dopaminergic pathways. When an appropriate combination of drugs (e.g. carbidopa 50 mg po every 6 hours for 24 hours followed by L-dopa 100 mg po) is administered to normal individuals, the degree of PRL suppression resembles that seen when L-dopa is administered alone (Fig. 9a). Therefore, even though peripheral conversion of L-dopa to dopamine has been blocked, its conversion to dopamine within the CNS and hypothalamus maintains the same degree of PRL suppression observed with L-dopa alone. This contrasts with the result obtained in most patients with prolactinomas (Fig. 9b). Whereas L-dopa administration alone results in a degree of



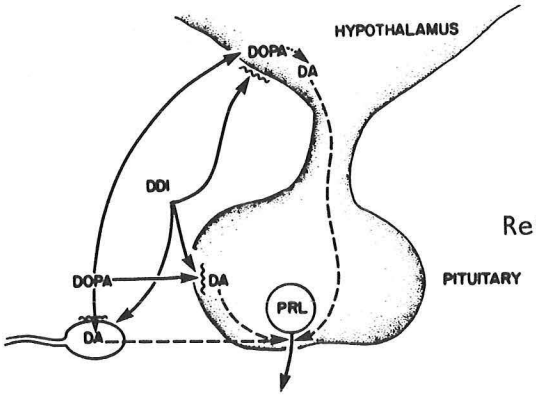
Ref. 44

Maximal percent suppression of plasma PRL in control and tumor patients after L-dopa administration, either alone or after carbidopa pretreatment. Control subjects are represented by open symbols and tumor patients by closed symbols. The circles and triangles represent the maximal percent suppression after L-dopa alone, and after carbidopa plus L-dopa, respectively. The mean maximal percent suppression (±SEM) in the two groups are represented by the horizontal lines.

Fig. 9

PRL suppression similar to that seen in the controls, co-administration of L-dopa and carbidopa results in a reversal of PRL suppression in the patients with prolactinomas. Reversal of the L-dopa suppression of PRL by carbidopa in these patients implies the presence of either a hypothalamic defect in the conversion of L-dopa to dopamine (Fig. 10) or decreased delivery of dopamine to the lactotrophs that comprise the adenoma [for example, due to an aberrant vascular arrangement of the portal vessels (43)] (Fig. 11).

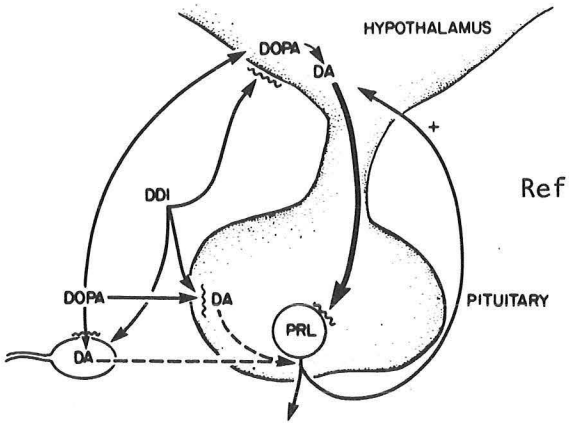
PRL-SECRETING TUMORS
PRIMARY NEUROENDOCRINE DISEASE



Ref. 44

Fig. 10

PRL-SECRETING TUMORS
AUTONOMOUS PITUITARY DISEASE



Ref. 44

Fig. 11

These studies do begin to approach the problem of distinguishing a hypothalamic versus a pituitary defect as the primary event in the pathogenesis of a prolactinoma. If the defect were at the level of the hypothalamus one would expect to find (1) hyperplasia of the nonadenomatous lactotrophs and (2) a persistent abnormality in the PRL responses to TRH, metoclopramide, and L-dopa + carbidopa, as well as eventual recurrence of hyperprolactinemia following removal of the prolactinoma. On the other hand, a pituitary defect resulting in decreased delivery of dopamine to the adenomatous lactotrophs would be predicted to result in (1) a suppression of nonadenomatous lactotrophs (via short-loop feedback by PRL) and (2) normalization of the PRL responses to TRH, metoclopramide, and L-dopa + carbidopa, as well as permanent resolution of hyperprolactinemia following adenomectomy.

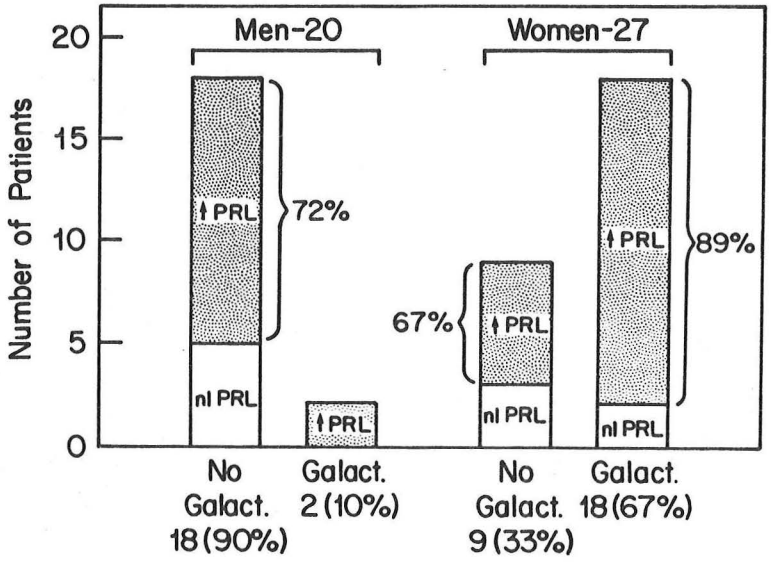
Most patients with PRL-secreting adenomas do not have hyperplasia of the nonadenomatous lactotrophs (6,25), and do demonstrate a return of normal PRL responses to TRH and metoclopramide following surgical removal of their tumors (48,50). Furthermore the PRL responses to these pharmacologic stimuli in many patients with idiopathic hyperprolactinemia are similar to those described in patients with prolactinomas (39, 49, 51-53). This has led to the widespread belief that most of these individuals with "functional" hyperprolactinemia in fact have adenomas that are too small to be detected radiographically (54-58). Although heterogeneity in the etiology of prolactinomas undoubtedly exists, a primary pituitary defect appears to be responsible in the majority of patients. Other nonhypothalamic-pituitary factors, principally hyperestrogenism related to oral contraceptive use and pregnancy, may result in the growth of a pre-existent PRL-secreting adenoma but there is no evidence that they result in de novo adenoma formation (59). Although the use of oral contraceptives is generally reported to be

higher among women with prolactinomas than among age-matched control groups (5, 60-63), many of these women have been given contraceptives because of menstrual abnormalities that may be secondary to pre-existent hyperprolactinemia. Based on the estimated high prevalence of PRL-secreting microadenomas in the general population, it may be predicted that clinically silent microadenomas occur in many other women who are given oral contraceptives. With long-term use, this stimulus is sufficient to cause growth and clinical expression of the tumor. Thus, a primary deficiency of dopamine may be exacerbated by the antidopaminergic activity of estrogen. This probably explains most cases of post-oral contraceptive galactorrhea-amenorrhea as well as persistent galactorrhea-amenorrhea following pregnancy (59).

Clinical Manifestations of Prolactinomas

Secretory adenomas of the pituitary create problems in 2 ways. Common to all tumors (secretory and nonsecretory) are effects of the tumor mass itself as it grows and compresses surrounding pituitary and extrasellar tissues. Specific syndromes such as acromegaly and Cushing's disease are the consequence of the secretory product of the tumor. Unrestrained PRL secretion results in hypogonadotrophism and, in the presence of appropriately primed alveoli in the breast, galactorrhea.

Prior to the availability of a radioimmunoassay for PRL all non-growth hormone and non-ACTH producing pituitary tumors were considered to be functionless. Hypogonadism and galactorrhea in patients with "chromophobe" pituitary adenomas were attributed to mass effects of the tumor -- destruction of pituitary gonadotrophs and interruption of the hypophyseal portal circulation. It is now clear that most of these tumors -- as many as 35% to 80% -- secrete PRL (4, 64-66). In the study summarized in Fig. 12, 72% of all men and 67% of all women with documented pituitary tumors unassociated with galactorrhea had hyperprolactinemia (8). Among patients with galactorrhea, hyperprolactinemia was found in 100% of the men and 89% of the women. Histological confirmation that



Differences in Sex, Presence or Absence of Galactorrhea (Galact.) and Elevation of Serum Prolactin (PRL) in 47 Untreated Patients with Documented Pituitary Tumors

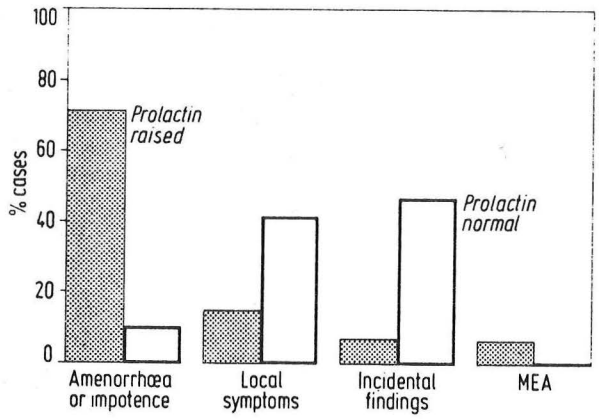
Ref. 8

Fig. 12

tumors removed from these patients are in fact prolactinomas can be demonstrated by histochemical immunoperoxidase staining for PRL (6, 25, 26, 67). Electron microscopy of most chromophobe tumors reveals abundant Golgi structures consistent with secretory activity despite a paucity of granules. Thus "chromophobe" and "nonsecretory" are not synonymous (24,65, 66, 68-70).

In the PRL era, with increased awareness of the clinical effects of hyperprolactinemia, PRL-secreting tumors are being diagnosed much earlier in their course. As a result, at least in women, prolactinomas are frequently diagnosed before tumor growth has caused any enlargement of the sella. At this stage the adenoma is still less than or equal to 10 mm in diameter and is designated a microadenoma. Thus, as is the case in patients with microadenomas secreting growth hormone or ACTH, presenting symptoms in patients with PRL-secreting microadenomas are related directly to the secretory product of the tumor.

A comparison of presenting symptoms in patients with prolactinomas and those with nonsecretory tumors is depicted in Fig. 13 (64). Seventy-one percent of all patients with hyperprolactinemia present with primary complaints related to hypogonadism. When the frequency of presenting complaints among patients with hyperprolactinemia is examined for men and women separately, 38% of men and 87% of women present because of hypogonadism. Thus in women, amenorrhea or oligomenorrhea, frequently with concomitant galactorrhea, usually prompts the



Ref. 64

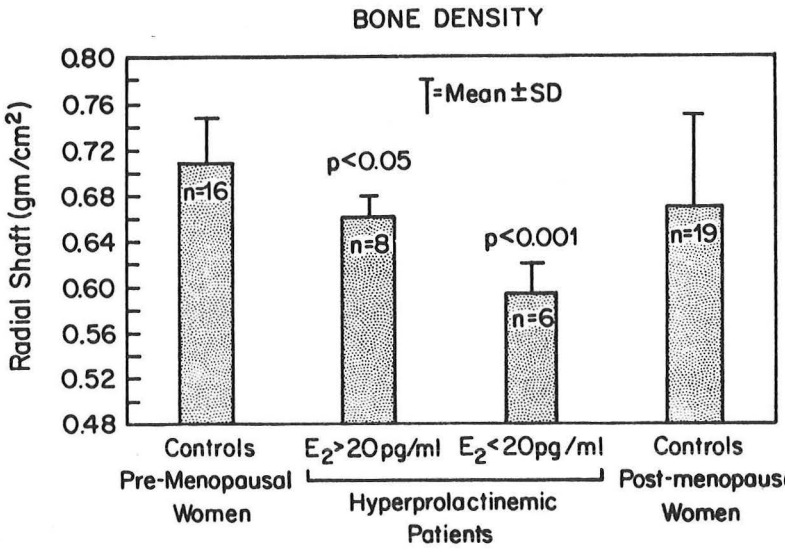
—Presenting symptoms in 64 untreated patients.

The mode of presentation in the group of 45 hyperprolactinæmic patients is compared with that in the group of 19 with normal prolactin levels. (MEA=multiple endocrine adenomata.) The difference between the groups is significant (χ^2 =23 ·0, P=<0·001).

Fig. 13

initial evaluation (71-75). Infertility due to a short luteal phase is also suggested to be an early feature of hyperprolactinemia (9,76). Preservation of entirely normal menstrual function is very unusual in women with PRL-secreting adenomas (less than 10%) (5). Because of this sensitivity of menstrual function to hyperprolactinemia, medical attention is generally sought relatively soon following the onset of the PRL excess. A prolactinoma at this stage is most likely to be a microadenoma (6, 50, 54, 55, 63). Consequently, symptoms and signs of an expanding mass lesion are infrequent in women with prolactinomas. A history of decreased libido and of symptoms related to atrophic genital changes may also be obtained. Accelerated osteoporosis, secondary to chronic anovulation with loss of

the six-fold or greater monthly increase in estrogen secretion that occurs during the late follicular, mid-portion, and luteal phases of the normal menstrual cycle, is of potential concern. Decreased bone density has been documented in women with hyperprolactinemia and correlates with the level of estrogen deficiency as assessed by the serum estradiol level (Fig. 14) (77).



Ref. 77

Bone Density in Hyperprolactinemic Women with Detectable and Undetectable Serum Estradiol (E_2) Concentrations and in Premenopausal and Postmenopausal Controls.

Fig. 14

Galactorrhea is reported in between 30% and 90% of all women with hyperprolactinemia (5, 78, 79). This wide range in incidence is most likely due to the vigor with which the presence of galactorrhea is sought and in the reluctance by many physicians to report galactorrhea as a finding on physical examination unless the breast secretion is copious. However even the expression of very small amounts of milk from one or both breasts justifies the diagnosis of galactorrhea. If the material expressed looks like milk, it probably is milk. When the nature of the nipple discharge is in doubt, the finding of fat globules with Sudan IV staining is diagnostic of galactorrhea (80). Lactation that persists for more than 1 year following parturition and cessation of breast feeding, or that occurs at any time outside the immediate postpartum period, should be considered to be inappropriate.

Although only approximately 40% of men with PRL-secreting tumors present primarily because of symptoms related to hypogonadism (64), more than 90% admit to decreased libido and impotence at the time the diagnosis is made (81-83). The incidence of infertility due to impaired spermatogenesis in men with PRL-secreting adenomas is undoubtedly increased, but its frequency in a large series of patients has not been reported. However, as many as 11% of men with oligospermia but no evidence of pituitary tumor have been reported to have hyperprolactinemia (84). Gynecomastia, present in 30% or less of men with prolactinomas, is not the effect of PRL excess on the breast, but a secondary effect of diminished testosterone production. Galactorrhea may occur in men with hyperprolactinemia but only after the appearance of gynecomastia (85,86). Prolactinomas in men at the time of diagnosis are almost always macroadenomas that declare themselves by their mass effects -- visual field and acuity defects, headache, or enlargement of the sella

turcica detected as an incidental finding on x-rays of the skull or sinuses obtained for unrelated reasons. Hypogonadism at this advanced stage is likely to be due to destruction of pituitary gonadotrophs by the tumor. However, PRL excess in men also probably results in disturbances in sexual function at earlier stages of the tumor (87); unlike amenorrhea, which does prompt early evaluation, these early disturbances in male sexual function must often remain unacknowledged by the patient and unrecognized by the physician.

There are at least 4 potential mechanisms to explain the pathogenesis of hypogonadism in patients with hyperprolactinemia. A large macroadenoma (PRL-or non PRL-secreting) may either (1) interrupt the hypophyseal portal circulation, resulting in decreased delivery of gonadotrophin-releasing hormone as well as of dopamine to the pituitary, or (2) it may destroy the pituitary gonadotrophs directly by tumor compression. In the case of smaller macroadenomas or microadenomas, however, other mechanisms must be responsible. (3) Patients with hyperprolactinemia secondary to primary hypothalamic disease, for example sarcoidosis or craniopharyngioma, may have compromise in the synthesis or release of gonadotrophin-releasing hormone as well as of dopamine. None of these first 3 mechanisms requires any specific effect of PRL excess per se to explain the hypogonadism. The fourth mechanism, and the one that is most likely responsible for hypogonadism in patients with microadenomas and small macroadenomas, involves specific effects of hyperprolactinemia. There are 2 possibilities by which PRL excess can potentially result in hypogonadism: either PRL has direct inhibitory effects on gonadal function and/or it affects the production or release of gonadotrophins. Although there is evidence that PRL does inhibit the production of progesterone by the corpus luteum, the explanation of hypogonadism in most patients with microprolactinomas or small macroadenomas is a PRL-mediated inhibition of the release or synthesis of gonadotrophin-releasing hormone by the hypothalamus (88,89). The evidence for this is 3-fold. First, basal levels of LH and FSH in both men and women with prolactinomas are in the low-normal to normal range (Table II) (90). Evaluation of the 24-hour secretory pattern of gonadotrophins

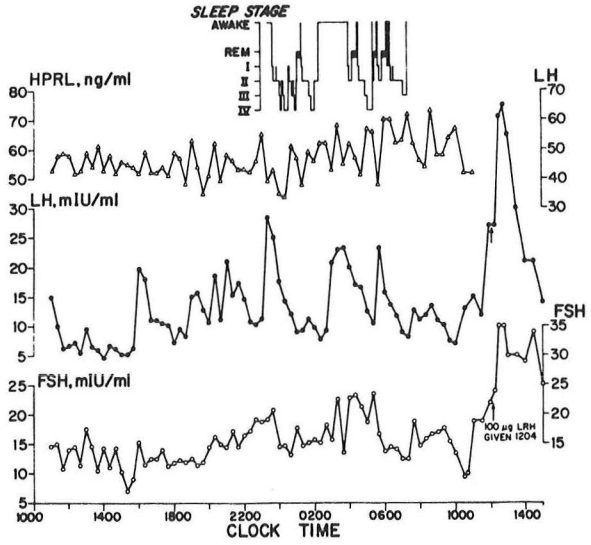
Table II

VALUES OF SERUM FSH, LH AND ESTRADIOL AS COMPARED TO NORMAL VALUES DURING THE FOLLICULAR PHASE OF THE MENSTRUAL CYCLE*

Hormone	Patients Mean	Normal Subjects† Cycle Phase	Mean
Serum FSH (μg/dl)	19.5	Follicular	21.8
Serum LH (μg/dl)	7.6	Follicular	6.9
Serum Estradiol (μg/dl)	3.3	Early Follicular	1.5
		Mid-Late Follicular§	9.7

*Comparisons are made with follicular phase since all patients were anovular.
†Healthy ovulatory women ages 20-29. Ref. 90
§Excludes pre-ovulatory peak levels.

in patients with hyperprolactinemia by some investigators has revealed absence of normal secretory bursts (91), whereas others report secretory patterns indistinguishable from normal (Fig. 15) (71). Basal levels of testosterone in men and of estradiol in women are also in the low or low-normal range. (In the case of estradiol, levels are seldom above early follicular phase concentrations.) The finding of low or low-normal testosterone and estradiol levels in the setting of low-normal or even normal levels of gonadotrophins is characteristic of hypo-



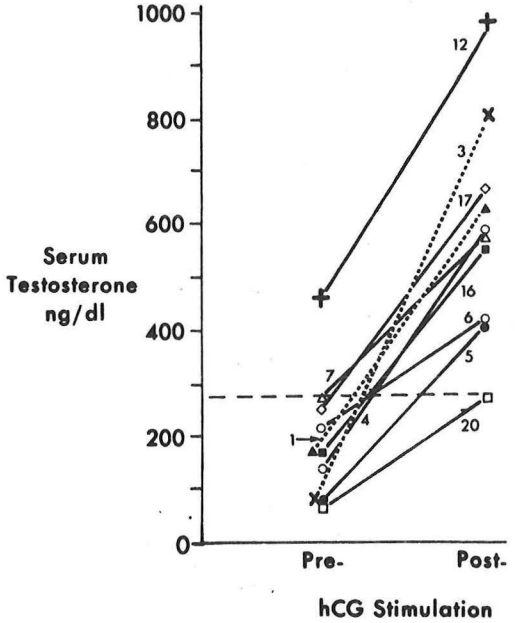
Ref. 71

Twenty-four Hour Pattern of Prolactin (HPRL) (△), Luteinizing Hormone (LH) (●) and Follicle-Stimulating Hormone (FSH) (○) in Case 1, with a Pituitary Microadenoma.

The sleep-stage histogram is indicated above the period of nocturnal sleep; 100 µg of luteinizing-hormone-releasing hormone was given at 1204, with the plasma luteinizing hormone and follicle-stimulating hormone responses shown.

Fig. 15

gonadotrophic hypogonadism. Second, the gonadal response in patients with microprolactinomas or small macroadenomas to gonadotrophin stimulation (Fig. 16) (81) or to stimulation by gonadotrophin-releasing hormone (92) is normal. This is strong evidence against a primary gonadal defect. Third, direct evidence of a



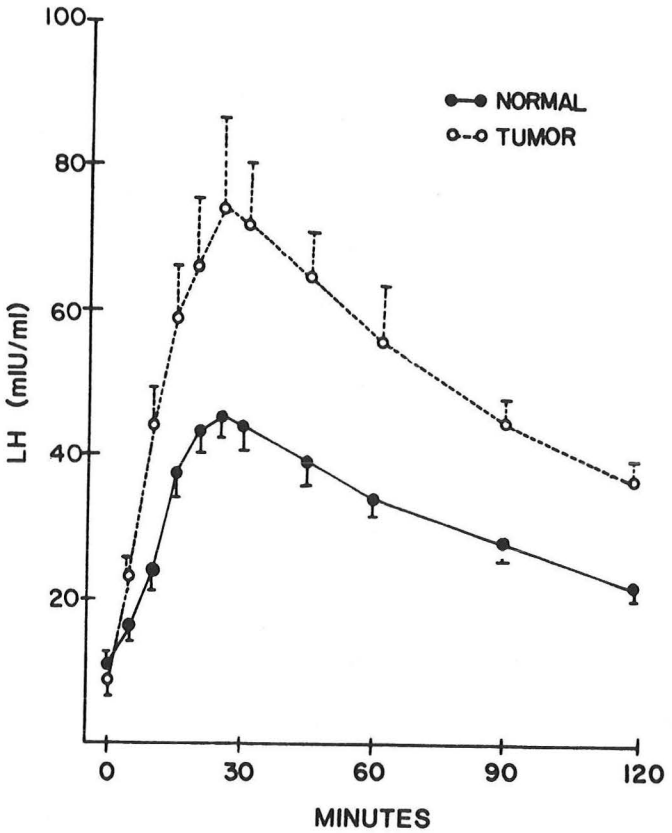
Testosterone Responses before Initiation of Therapy before and after Stimulation with Human Chorionic Gonadotropin (hCG).

Each symbol represents a different patient. The solid and broken lines represent the responses to an intramuscular dose of human chorionic gonadotropin of 5000 IU per square meter, or 2000 IU daily for three days, respectively. Patient numbers are indicated. The horizontal dashed line represents the lower limit of normal for testosterone in our laboratory.[26]

Ref. 81

Fig. 16

hypothalamic defect in these patients is provided by a normal (or even exaggerated) gonadotrophin response to gonadotrophin-releasing hormone (Fig. 17) (93); by an absent response of gonadotrophin levels to the administration of the anti-estrogen clomiphene citrate, a drug that acts at the hypothalamic level to release gonadotrophin-releasing hormone (94,95); and finally, by a loss of the positive

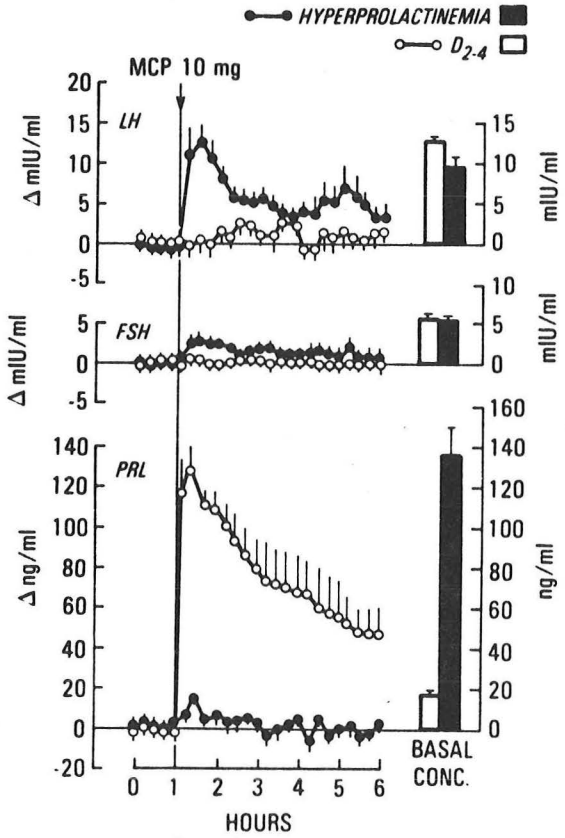


Ref. 93

Mean ± SE LH concentrations in 24 women with a PRL-secreting pituitary adenoma and in 8 normal women (controls) tested during the early follicular phase. Each woman received a 100-μg iv bolus of GnRH at zero time.

Fig. 17

feedback effect of estradiol on LH release in women (96). This effect of hyperprolactinemia may be mediated via a short-loop feedback mechanism leading to increased hypothalamic dopamine secretion. Increased hypothalamic dopamine is believed to inhibit synthesis or secretion of gonadotrophin-releasing hormone, which in turn results in decreased secretion of LH and FSH and finally, in decreased gonadal function. Evidence that increased dopaminergic tone may cause inhibition of gonadotrophin-releasing hormone in women with PRL-secreting adenomas has been described (Fig. 18) (97). An increase in LH release follows administration of the dopamine receptor antagonist metoclopramide in women with hyperprolactinemia but not in normal controls.



Mean (± SE) basal LH, FSH and PRL levels (mean of 5 samples) and their Δ responses to iv bolus of 10 mg of MCP in 5 hyperprolactinemic patients with documented pituitary microadenoma and 4 cycling women on day 2-4 of their cycle.

Ref. 97

Fig. 18

A specific sequence in the development of amenorrhea in women with hyperprolactinemia has been proposed (9). At an early stage excess PRL suppresses follicular maturation. As a result, inadequate corpus luteum function manifested as a short luteal phase ensues. Although at this stage preovulatory estradiol and LH peaks are preserved, progesterone production by the corpus luteum is deficient. Sustained hyperprolactinemia eventually leads to a loss of the preovulatory estradiol peak and consequent prolongation of the follicular phase. This results in oligomenorrhea. Finally, the hypothalamus becomes acyclic and does not respond to the positive feedback effect of estradiol, and amenorrhea ensues.

The clinical manifestations of PRL-secreting tumors due to effects of the tumor mass itself are the same as those observed in patients with other secretory or non-secretory pituitary tumors. Headache, visual field and acuity defects, extraocular motor deficits, and diabetes insipidus are absent in patients with microadenomas, but may begin to develop relatively soon after parasellar extension of an enlarging macroadenoma. Clinical hypopituitarism occurs only in patients with very large tumors that have destroyed more than 80 to 85% of the normal pituitary. Patients with microprolactinomas have normal anterior pituitary function except for the gonadotrophin defect previously described and a lower maximal response of growth hormone to insulin-induced hypoglycemia (6, 98). Deficiencies of TSH, ACTH, and growth hormone in patients with large tumors correlate with the area of the tumor as assessed radiographically (99,100).

Evaluation of Patients for a Suspected Prolactin-Secreting Adenoma

Clinical Findings. The initial evaluation of all women with galactorrhea or amenorrhea and of men with impotence or infertility should include the consideration of hyperprolactinemia. In women the risk of hyperprolactinemia and pituitary tumor is related directly to the clinical findings at the time of presentation. Galactorrhea in a patient with regular menses is not likely to be associated with hyperprolactinemia. The actual frequency of galactorrhea in the population of otherwise normal women is difficult to assess from various reports, but may be as high as 45% (5). Women with galactorrhea and regular menses comprise the largest group (approximately one-third) among all patients with galactorrhea; 75% to 85% have normal PRL levels (80). The abnormality in most of these patients is therefore most likely to be increased sensitivity of the breast to PRL, such that maintenance of galactorrhea is analogous to the situation in nursing mothers many months postpartum in whom lactation continues despite normal PRL levels. When however galactorrhea is accompanied by amenorrhea the situation changes dramatically. Approximately 80% of patients with both galactorrhea and amenorrhea have hyperprolactinemia, and of these as many as 68% have radiographic abnormalities consistent with a pituitary adenoma. The corresponding frequencies of hyperprolactinemia and sellar abnormalities in patients with amenorrhea alone are 13% and 2%, respectively. Among all women with secondary amenorrhea (with and without galactorrhea) the incidence of hyperprolactinemia is as high as 30%; 50% of these patients demonstrate radiographic abnormalities consistent with a pituitary adenoma. These data are summarized in Table III (5). Thus, the occurrence of galactorrhea in a patient with amenorrhea significantly increases the likelihood of hyperprolactinemia and of the presence of a pituitary adenoma. Furthermore, the frequency of hyperprolactinemia and pituitary adenoma increases with increasing duration of the amenorrhea (101).

Table III Ref. 5

INCIDENCE OF HYPERPROLACTINEMIA AND ABNORMAL SELLA X-RAY FINDINGS IN PATIENTS PRESENTING WITH AMENORRHEA ALONE, GALACTORRHEA ALONE, OR GALACTORRHEA AND AMENORRHEA

	AMENORRHEA ALONE	GALACTORRHEA ALONE	GALACTORRHEA-AMENORRHEA
Total Number Of Cases	654	163	423
Elevated Prolactin	12.8%	25.8%	77.5%
Sellar Abnormalities	1.8%	11.7%	40.9%

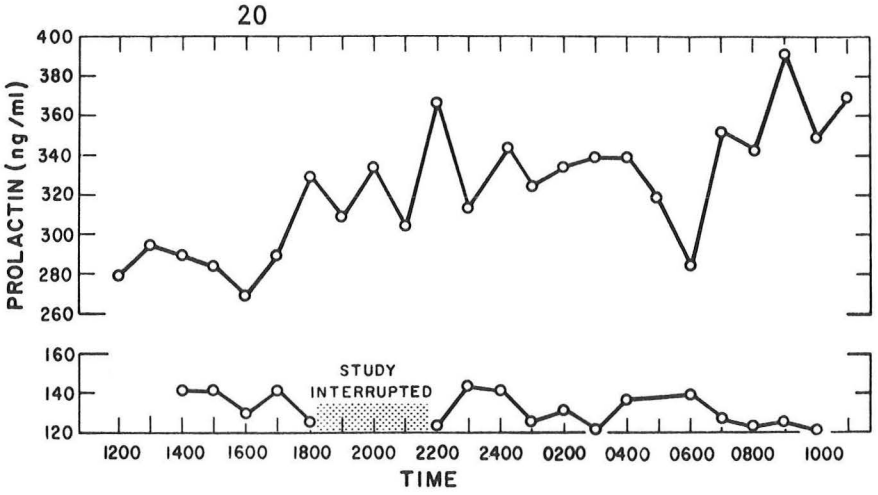
As stated previously, men with prolactinomas usually present at a more advanced stage in the course of their disease. Thus a microprolactinoma is an uncommon cause of isolated impotence or infertility in men. Although decreased libido, impotence, or infertility may be the only presenting complaints in men with prolactin-secreting adenomas, evidence of a mass effect of the tumor, including asymptomatic expansion of the sella turcica, is usually apparent at the time of initial evaluation.

Other syndromes associated with PRL-secreting adenomas have been described. These include coexistent secretion of PRL and growth hormone by the same tumor in patients with acromegaly (24-28); the presence of a PRL-secreting adenoma in an empty sella (29-34); a prolactinoma associated with von Recklinghausen's disease (102); and a PRL-secreting adenoma as a component of the multiple endocrine neoplasia I syndrome (103-108).

Serum PRL. A basal serum PRL determination should be obtained as part of the initial evaluation of every patient with galactorrhea, amenorrhea, infertility, decreased libido, impotence, or symptoms or signs of a sellar or parasellar mass. If the PRL level is normal (less than 25 ng/ml) in a woman with galactorrhea but regular menses, no further evaluation is indicated. The serum PRL should be remeasured at 1- to 2-year intervals subsequently for as long as the galactorrhea persists because of the uncertainty of the natural history of normoprolactinemic galactorrhea. A woman with amenorrhea, no galactorrhea, and a normal PRL level should have further evaluation of pituitary-gonadal function, but there is no need to continue evaluation for a PRL-secreting adenoma. Patients with galactorrhea and amenorrhea associated with a normal PRL level should undergo further evaluation for exclusion of other possible pituitary or hypothalamic lesions. If the initial evaluation is negative, these patients should be followed with yearly determinations of serum PRL as well as with monitoring for development of symptoms or signs of hypothalamic-pituitary disease. Men with isolated impotence or infertility and normal PRL levels are evaluated further for their primary problems. PRL measurements in men however are usually obtained because of other evidence of hypothalamic-pituitary disease (for example headache or decreased libido associated with an enlarged sella). Thus an enlarged sella on a plain skull film is usually the indication for which the PRL level is measured; if the PRL is normal, further evaluation must be directed towards ruling out a hypothalamic or non-secretory pituitary tumor, a parasellar mass mimicking a pituitary tumor, or the empty sella syndrome.

If the basal PRL is marginally elevated, the determination should be repeated on a serum specimen obtained by pooling 3 separate samples drawn through an intravenous catheter 20 minutes apart. This technique reduces the effects on a random serum PRL determination of intermittent secretory bursts of PRL that characterize the normal 24-hour secretory profile. It also reduces the effect of venipuncture or PRL secretion, a stress that has been reported to result in a serum PRL as high as 100 ng/ml (95). Patients with hyperprolactinemia associated with PRL-secreting adenomas have sustained hyperprolactinemia regardless of the degree of PRL elevation (Fig. 19) (31). Although breast manipulation does not cause PRL elevation in the majority of women (including those with galactorrhea and normal PRL levels), a small, transient increase may occur in up to a third of all nonpostpartum, regularly menstruating women (8). Therefore if a slightly elevated PRL level is measured in a patient shortly following breast examination, a repeat determination should be made. If sustained hyperprolactinemia is documented the

Ref. 31



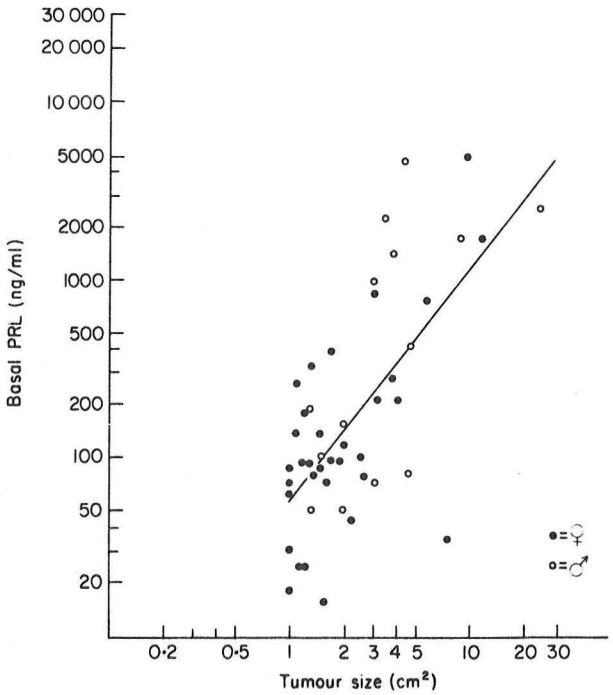
Twenty-four hour serum prolactin (hPRL) values on two separate hospital admissions, Patient AC.

Fig. 19

possibilities of a drug effect (particularly a history of phenothiazine ingestion), primary hypothyroidism, and renal insufficiency must be ruled out before further evaluation of the hyperprolactinemia. Even if primary hypothyroidism is documented, the serum PRL should be repeated after restoration of normal thyroid status since thyroid disease and prolactinomas may coexist (5). In none of these instances however is the serum PRL likely to be greater than 100 ng/ml (although levels as high as 300 ng/ml have been reported in patients with chronic renal failure being treated with drugs that have antidopaminergic activity) (9). Obviously the possibility of pregnancy should have been considered in the appropriate patient with amenorrhea and ruled out before a serum PRL is ever measured.

All patients with sustained hyperprolactinemia unassociated with medication, hypothyroidism, or renal failure require further evaluation. The degree of elevation of the serum PRL may provide insight into the underlying etiology. Although a PRL-secreting adenoma may cause only a slight increase in serum PRL, it is with few exceptions virtually the only cause of a serum PRL greater than 200 ng/ml. Moreover, if the hyperprolactinemia is due to hypothalamic or other pituitary disease, the serum PRL is usually less than 100 ng/ml (35, 109, 110). Among patients with documented adenomas, the degree of PRL elevation correlates to some extent with tumor size, although frequent exceptions are noted (Fig. 20) (65, 100).

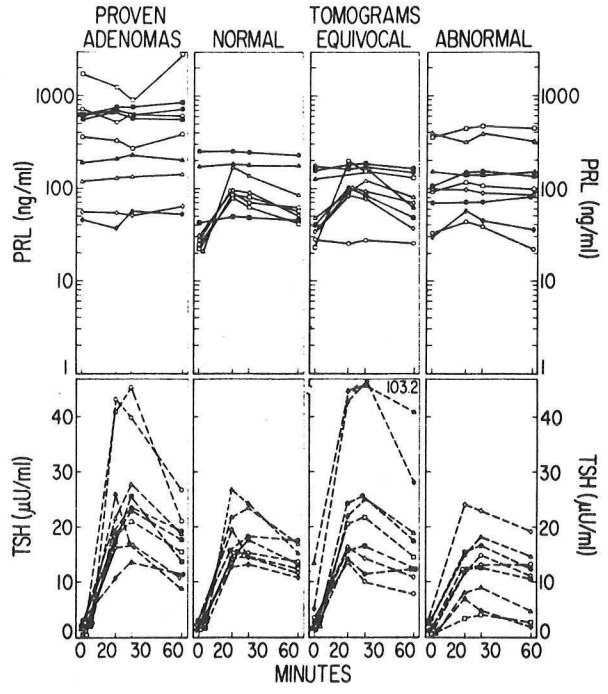
Ref. 100



Correlation between (log) tumour size (=lateral area of the sella plus extrasellar tissue) and (log)basal prolactin level in forty-seven untreated patients ($r=0{\cdot}68$, $P<0{\cdot}0005$). Closed symbols represent female patients.

Fig. 20

PRL Suppression and Stimulation Tests. Various dynamic tests of PRL secretion have been proposed to assist in the evaluation of patients with hyperprolactinemia. These include responses of PRL to suppression by L-dopa or the dopamine agonist bromocriptine, and to stimulation by chlorpromazine, TRH, or metoclopramide (36-38, 48-51, 111-115). Administration of dopaminergic drugs to patients with hyperprolactinemia almost invariably results in PRL suppression regardless of the etiology of PRL excess. These tests therefore are not useful in differentiating among the various causes of hyperprolactinemia. An exception may be the combined L-dopa - carbidopa test described earlier, although it appears that in individual patients this test also appears to be of limited discriminatory value (56). Likewise results of stimulation tests of PRL secretion are in general similar in patients with hyperprolactinemia of diverse etiologies, and usually demonstrate either no or only a small increase in PRL following administration of the drug (51, 58). In Fig. 21, the response of serum PRL to TRH in women with surgically documented PRL-secreting adenomas is compared to the response observed in women with normal, equivocal, or abnormal tomograms of the sella (113). Although in this study, no normal responses to TRH (defined as a 200% increase in PRL) were found among patients with adenomas or with clearly abnormal tomograms, many series report at least some patients with prolactinomas who do have normal responses (49, 50, 116). Thus, in the individual patient being evaluated for hyperprolactinemia, the PRL response to TRH stimulation does not appear to be of use in distinguishing among the causes of PRL excess.



Ref. 113

Plasma PRL and TSH concentration after TRH stimulation in patients with elevated PRL baseline and normal, equivocal, or abnormal tomograms.

Fig. 21

CSF Levels of PRL. The concentrations of anterior pituitary hormones in the CSF is a function of their molecular weight and plasma concentration. Patients with suprasellar extension of secretory pituitary tumors have been reported to have disproportionate elevations of hormone levels in the CSF (117). More recent studies indicate that CSF PRL levels correlate only with serum levels. No significant differences were observed in the ratio of CSF to serum levels of PRL among patients with normal serum PRL levels, physiological hyperprolactinemia, drug-induced hyperprolactinemia, and hyperprolactinemia associated with prolactinomas (including patients with and without suprasellar extension) (118). Thus CSF PRL levels are of no diagnostic importance.

Radiographic Evaluation. Of primary concern in the patient with hyperprolactinemia unrelated to drugs, thyroid or renal disease is the possibility of a hypothalamic or pituitary (PRL or non-PRL secreting) tumor. Radiographic evaluation is therefore of paramount diagnostic importance. Prior to 1974 the only radiographic procedure commonly used in screening for abnormalities of the pituitary fossa was the plain anteroposterior and lateral skull film with coned views of the sella. This is a simple and inexpensive procedure and delivers minimal radiation to the patient. It is also an insensitive means of detecting early signs of a pituitary adenoma.

An increase in the linear dimensions of the sella due to an intrasellar tumor is not detectable by plain radiography until the diameter of the tumor is greater than 10 mm. Because the effects of PRL hypersecretion result in early screening for pituitary disease, approximately 50% of all prolactinomas at the time of clinical presentation are less than or equal to 10 mm in diameter (i.e. are microadenomas) (5, 119). Thus, a substantial number of patients with surgically documented tumors have normal coned views of the sella.

More sensitive radiographic procedures are therefore required to detect pituitary microadenomas. Multidirectional (hypocycloidal) polytomography of the sella at 1 to 2 mm section intervals enables evaluation for focal changes in the lamina dura that are not detected by plain radiography (120, 121). Findings considered compatible with changes secondary to an adenoma are localized thinning or erosion of the lamina dura of the anterior wall or floor of the sella and focal bulging of the sellar floor. This technique is capable of detecting adenomas as small as 5 mm. By the time the adenoma has reached this size approximately 25% to 50% of the sellar contents have been replaced by tumor (55). Recently however both radiological-surgical and radiological-autopsy correlative studies have cast doubt on the usefulness of sellar polytomography in the routine assessment of microadenomas. In a comparison of the radiological changes in the sella found on polytomography and the location of pituitary microadenomas at surgery, over 25% of patients with microadenomas had either normal to equivocal radiographic findings or findings that had no relationship to the location of the tumor at all (122). Two other studies addressed this issue by examining sphenoid specimens containing the pituitary that had been removed by block dissection at autopsy (67, 123). No known history of pituitary disease was present in any of the subjects. The sphenoid-pituitary specimens were first examined by hypocycloidal tomography at 2 mm intervals and then decalcified and sectioned for histological study of the pituitary. A total of 220 specimens were examined in both series (Table IV). Forty-six tumors were identified histologically but only 12 were recognized by tomography (false-negative rate of 74%). In 174 specimens no tumor was identified but 28 had abnormal tomograms consistent with an adenoma (false-positive rate of 16%). The explanation of the false-negative tomographic studies may be attributed

to the location of the tumor, since no bony erosion may develop if the microadenoma is not near the sellar cortex. False-positive studies are most likely due to developmental variations in the sellar floor that simulate changes of a microadenoma (122).

Table IV Refs. 67 and 123

DETECTION OF PITUITARY ADENOMAS BY POLYTOMOGRAPHY IN AUTOPSY SPECIMENS

Series	Adenoma Identified	Tomography Positive	No Adenoma Identified	Tomography Positive
Turski, et al.(1981)	14	6	86	8
Burrow, et al.(1981)	32	6	88	20
Total	46	12	174	28

The inherent limitations of hypocycloidal polytomography appear to be circumvented by high-resolution computed tomography (CT) (124, 125). With the newest generation of CT scanners 1.5 mm tomographic sections through the sella can be taken. This technique not only examines the bony sella but also the intrasellar contents. Moreover, unlike polytomography, CT imaging identifies suprasellar and parasellar pathology (including supra- and parasellar extension of pituitary tumors) and the presence of an empty sella. Also the amount of radiation to the lens of the eye is considerably less with CT (0.5 to 2.5 rads) than with polytomography (approximately 6 to 12 rads). Intrasellar pathology with high resolution CT is reflected by an abnormal shape or height of the pituitary and by focal areas of heterogeneous alterations in density within the gland (125). These differences in density are accentuated by contrast enhancement. In one series of 12 consecutive patients with a PRL-secreting microadenoma, the high resolution, contrast-enhanced CT scan in the coronal plane identified the tumor in all cases, the smallest being 3.5 mm in diameter (125). Hypocycloidal polytomography in this series correctly identified the tumor in only 8 of the 12 patients. Even further detail of the relationship of lesions with the optic chiasm, hypothalamus, and internal carotid arteries is achieved by high resolution CT performed following introduction of the contrast agent metrizamide into the subarachnoid space (126, 127). High resolution CT is currently the procedure of choice in this and other institutions for the evaluation of patients with suspected microadenomas (128). With the advent of CT, pneumoencephalography is not required in the diagnostic evaluation of hypothalamic-pituitary disease, and preoperative carotid arteriography is usually necessary only in patients who have very large tumors with suprasellar extension or in those who have had prior radiation therapy (129).

The radiographic evaluation of the patient with hyperprolactinemia should proceed as follows. A coned view of the sella is obtained initially to determine whether or not there is diffuse sellar enlargement or bony erosion. Patients with an enlarged sella should next be evaluated with CT to distinguish among the possibilities of a primary empty sella, a pituitary macroadenoma, and a primary suprasellar or parasellar tumor. If the lesion is a macroadenoma, suprasellar

extension of the tumor is also detected by CT. The distinction of an empty sella from a partially empty sella containing a hypodense pituitary tumor requires CT with metrizamide cisternography (126). No patient with an abnormal sella on plain radiography should undergo hypocycloidal polytomography since polytomography in these patients is invariably abnormal as well (130).

Hyperprolactinemic patients with a normal coned view of the sella should be examined with high resolution CT to evaluate for a microadenoma. Most such patients will have presented with symptoms for which definitive treatment is indicated. Definition of a microadenoma in these individuals is of particular importance. The incidence of false-negative and false-positive studies with high resolution CT is not yet well defined but preliminary studies indicate they are acceptably low. Hypocycloidal polytomography is not as reliable as high resolution CT in the screening evaluation of hyperprolactinemic patients with normal plain anteroposterior and lateral radiography of the sella. If high resolution CT is not available and it is elected to evaluate these patients with polytomography, interpretation of the study should be tempered by the recent reports that challenge the diagnostic specificity and sensitivity of the procedure (67, 123). If no abnormality is demonstrated on high resolution CT or, if this procedure is unavailable, on polytomography, guidelines for further follow-up are not well defined. Determination of serum PRL at 6-to 12-month intervals and radiographic evaluation (with CT) at 1- to 3-year intervals have been advocated (5). The uncertainty as to the optimal means of following these patients will be dispelled only after the natural history of the PRL-secreting adenoma has been more precisely defined (see below).

Evaluation of Visual Fields and Pituitary Trophic Hormone Status. The routine testing of visual fields and of anterior pituitary hormone reserve in patients with microadenomas is not recommended as part of the initial evaluation. Visual-field examinations are normal in the case of microadenomas and offer no additional information. In patients with larger tumors suprasellar extension does compress the optic chiasm, usually resulting in bitemporal visual-field deficits. However, monocular and binasal deficits have been described in some patients with pituitary tumors (131). Goldmann perimetry is appropriate in the preoperative evaluation of these patients. ACTH, growth hormone, TSH, and gonadotrophin reserve are normal in essentially all patients with microprolactinomas (58). Patients with macroadenomas have variable deficits of anterior pituitary hormones and hormonal reserve, the extent of which correlates with the size of the tumor (99, 100). Most such patients undergo adenomectomy soon after diagnosis and receive large doses of glucocorticoid during the neurosurgical procedure; therefore it is only necessary to establish preoperative thyroid status so that hypothyroidism can be treated prior to surgery. As in patients with nonsecretory pituitary tumors or tumors secreting ACTH or growth hormone, evaluation of adrenal status is deferred until the postoperative period. If radiation therapy is necessary postoperatively because of incomplete tumor resection, glucocorticoids are continued through this period of treatment. Gonadal function in patients with prolactinomas is essentially always disturbed because of the hyperprolactinemia. Formal evaluation of gonadal function is reserved for those patients with evidence of persistent hypogonadism following specific therapy (132).

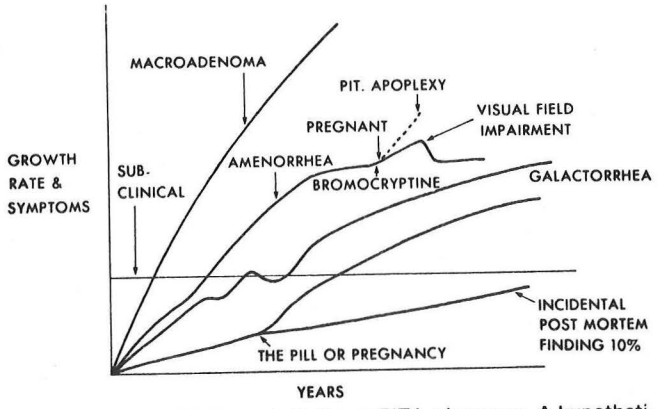
Other Findings. It should be remembered that a prolactinoma may be a feature of the multiple endocrine neoplasia I syndrome. Hypercalcemia, hypoglycemia, or peptic ulcer disease associated with hyperprolactinemia should prompt investigation for hyperparathyroidism and/or an islet cell neoplasm.

Natural History of Prolactin-Secreting Adenomas

Uncertainty as to the natural history of PRL-secreting microadenomas accounts for much of the current debate regarding optimal management of patients with these tumors. In large autopsy series the prevalence of occult pituitary microadenomas is between 9% and 25% (68, 133, 134). When specific immunoperoxidase histochemical staining for PRL is performed, approximately 40% to 50% of these adenomas are found to contain PRL (59, 67). Thus, as many as 10% of all individuals have incidental microprolactinomas when they die.

In a longitudinal study, 43 women with galactorrhea, hyperprolactinemia, and radiographic evidence of a pituitary microadenoma were followed for 3 to 20 years without long-term medical treatment (128). Asymptomatic tumor progression (suprasellar extension detected by high resolution CT) occurred in only 2 patients, both of whom underwent transsphenoidal adenomectomy without complications. Three patients had spontaneous resolution of their amenorrhea, galactorrhea, and hyperprolactinemia. Eleven women became pregnant after receiving bromocriptine, gonadotrophins, or clomiphene, and all of these had an uneventful course. Several other large series of patients with PRL-secreting microadenomas confirm the lack of significant tumor growth during pregnancy (135-139). In one large review of 91 pregnancies in women with PRL-secreting microadenomas, only 3 patients developed headache during the pregnancy, 1 developed headache and a visual-field defect, and 1 developed diabetes insipidus -- a total incidence of complications of 6% (136). Four of the 5 patients required no treatment and were delivered at term. Symptoms disappeared after delivery. The 1 patient with headache and visual-field defect underwent transsphenoidal adenomectomy postpartum. Reports of symptomatic enlargement of prolactinomas during pregnancy with development of severe headaches and visual-field deficits are essentially confined to patients with larger tumors (140-149).

Figure 22 depicts a hypothetical scheme of the natural history of pituitary adenomas (150). In this example, a figure of 10% is used for the prevalence of microadenomas as an incidental postmortem finding. The growth rate of individual tumors varies. Adenomas that grow very rapidly present as large macroadenomas soon after the development of symptoms. Other tumors have intermediate growth rates. In this instance symptoms such as galactorrhea and/or amenorrhea develop after a critical point of PRL production is reached. Estrogen stimulation associated with pregnancy or the use of oral contraceptives may trigger a more rapid rate of growth of some adenomas but does not result in de novo adenoma formation.



Natural history of pituitary *(PIT.)* adenomas. A hypothetical scheme of the development and growth of pituitary adenomas.

Ref. 150

Fig. 22

Thus, a tentative natural history of PRL-secreting adenomas can be constructed. (1) Most PRL-secreting microadenomas do not become macroadenomas. (2) Exposure to increased estrogen results in hyperplasia of normal lactotrophs and may cause growth of pre-existent prolactinomas. However, (3) pregnancy rarely causes appearance of symptoms of tumor growth in women with microprolactinomas. These observations should influence the approach to the treatment of these tumors.

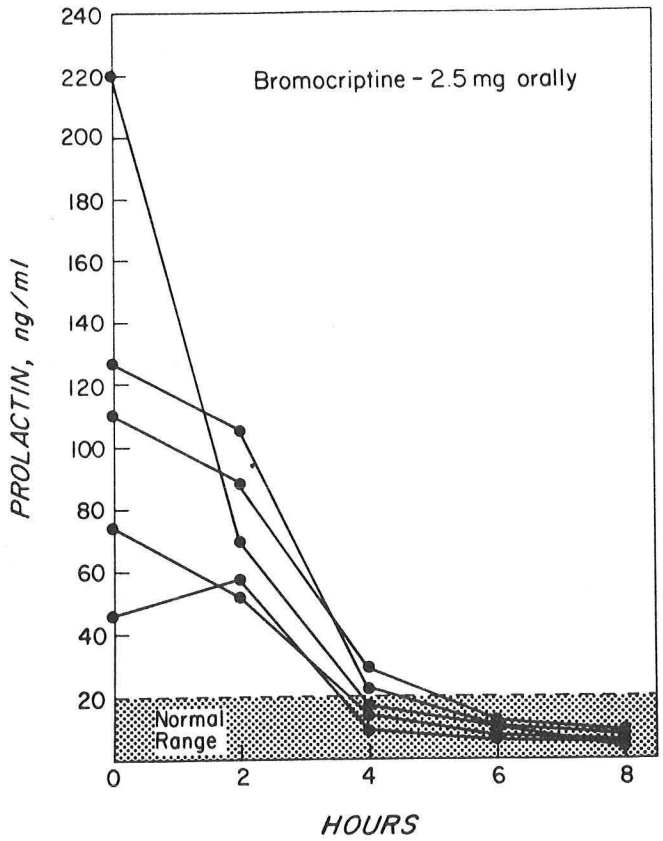
Treatment of Prolactin-Secreting Adenomas

The management of patients with PRL-secreting microadenomas is widely debated. The controversy relates in part to the specific indications for treatment, but it also pervades the issue of the optimal therapeutic modality for those patients with microadenomas in whom a definite indication for treatment exists.

In essence the controversy surrounding the issue of who to treat centers around women with microprolactinomas. Of these patients, the need to treat those with symptomatic spontaneous galactorrhea, infertility (if they wish to conceive), decreased libido, and symptoms related to atrophic genital changes seems clear. Similarly, the need to treat men with microprolactinomas is not a point of contention since they present with hypogonadal symptoms that resolve when the hyperprolactinemia is reversed. What is not yet clear however is the recommendation that should be made to hyperprolactinemic women with asymptomatic galactorrhea and/or amenorrhea who do not wish to conceive. The most compelling argument to treat every woman (or at least every premenopausal woman) with a PRL-secreting microadenoma is the preliminary evidence that these individuals are at risk of developing accelerated osteoporosis due to chronic hypoestrogenism (77). Long-term longitudinal studies that address this issue are presumably in progress. Others contend that the reason to treat every patient with a microadenoma is that the results of treatment (specifically, cure of hyperprolactinemia, cessation of galactorrhea, resumption of normal menses, and restoration of fertility) are significantly better in patients with microadenomas than in those with larger tumors (5, 9, 47, 48, 54, 55, 63, 87, 151-155). With the refinements that have been made in transsphenoidal microsurgery (156), this observation is indeed accurate (see below). However the implicit argument to treat on this basis is that all microadenomas eventually do enlarge. To refute this assumption, at least 1 longitudinal study of more than 40 untreated patients indicates that indeed most of these tumors, if they enlarge at all, do so only very slowly over many years of follow-up (128). This finding is supported by the high frequency of incidental microadenomas discovered at postmortem examination (68, 133, 134). Moreover, once a microadenoma has been identified, accurate monitoring of tumor growth by currently available high-resolution CT allows early detection of and prompt therapeutic intervention for those few adenomas that do begin to enlarge. Of utmost concern is that an asymptomatic woman with amenorrhea and a microprolactinoma not sustain undue morbidity from the therapeutic intervention. Considerations that may eventually coax a decision to treat such a patient are concerns for the potential risk of accelerated osteoporosis and for the practicality and expense of careful long-term medical follow-up if treatment is deferred.

All patients with macroadenomas, in particular those in whom there has been suprasellar or parasellar extension, should be treated since their tumors have already manifested the potential for further growth. The indications for treatment, in addition to those described for microadenomas, are the prevention of further tumor growth and the reversal of effects of compression of adjacent tissues by the tumor mass.

The primary modes of treatment consist of bromocriptine (2-bromo-alpha-ergocryptine mesylate) and transsphenoidal or transcranial hypophysectomy. Conventional radiation therapy is generally reserved as an adjunctive means of reducing the incidence of tumor recurrence following hypophysectomy in patients who have had incomplete tumor resection. Bromocriptine (Parlodel®) is a dopaminergic agonist originally developed to suppress lactation during the postpartum period. Its potential in suppressing lactation in nonpuerperal women was recognized soon after its introduction. A single dose of bromocriptine causes an acute fall in serum PRL levels within several hours of administration in all individuals (Fig. 23) (157). In most patients with hyperprolactinemia, including those with documented pituitary adenomas, the fall in PRL is into the normal range; however, some variability in response, unrelated to bromocriptine levels in



Change in serum prolactin values in patients with galactorrhea-amenorrhea syndrome after a single oral dose of 2.5 mg of bromocriptine.

Ref. 157

Fig. 23

blood, has been noted (158). With institution of bromocriptine therapy, galactorrhea ceases and menses return within several weeks in more than 90% of women with hyperprolactinemia (19, 72, 138, 139, 157, 159-164). The serum PRL returns to its baseline level and galactorrhea-amenorrhea returns soon after cessation of therapy (72, 160). In this country bromocriptine has been released for use only in those women with galactorrhea-amenorrhea in whom radiographic evaluation for a pituitary tumor is negative. It is further recommended that treatment not exceed a period of 6 months and that a barrier contraceptive method be utilized during the course of treatment. However, the efficacy of bromocriptine is dependent on its continued administration. Side effects from bromocriptine,

primarily nausea, vomiting, dizziness, and orthostatic hypotension, usually subside within a week or two (165). They are minimized by starting with a small bedtime dose (1.25 mg) and increasing slowly to the minimally effective dose that suppresses serum PRL to within the normal range (usually 5 to 7.5 mg per day in 2 to 3 divided doses). To further minimize side effects doses are taken with meals. Bromocriptine is quite expensive, a month's treatment at 5 mg per day costing approximately $40.

In European and other countries bromocriptine has been frequently used for the past 5 to 7 years to induce ovulation in patients with hyperprolactinemia, including those with microprolactinomas. Its success rate in this regard, including patients with documented tumors, approaches 90% to 95% (94, 145, 159, 164). Lower incidences of fertility (approximately 75%) are reported in other series (166). Most of the protocols described for ovulation induction with bromocriptine involve continuous administration of the drug until a positive pregnancy test is obtained. Mechanical contraception is advised until the first menses occur so that when contraception is discontinued, the patient will know when a menstrual period has been missed. This policy means that the medication is not stopped until a gestation of approximately 5 1/2 weeks has been reached (94). Exposure to bromocriptine during this early period of gestation may be eliminated by an intermittent treatment regimen, in which bromocriptine is administered only from the fifth day after the onset of menstruation until the second day after the rise of basal temperature (167). As described previously, complications of tumor growth in women with microprolactinomas who have been followed through bromocriptine-induced pregnancies have been negligible. Furthermore, rates of abortion and congenital malformations have been no higher than in other series of women with normoprolactinemic infertility who have had pharmacologic induction of ovulation (94). However, because of a clinical experience limited to the past several years, an effect of bromocriptine on postnatal behavioral development cannot be ruled out at this time. For this reason, as well as for persisting concern of significant tumor growth during pregnancy and of Food and Drug Administration guidelines regarding use of bromocriptine, most physicians in this country currently recommend that infertility (as well as symptomatic galactorrhea and hypoestrogenism) secondary to a PRL-secreting microadenoma be managed by transsphenoidal adenomectomy.

In addition to ameliorating effects of PRL hypersecretion, bromocriptine is also reported to have an antiproliferative effect on large prolactinomas. Radiographic evidence of a decrease in tumor size (168-175), normalization of visual fields (168, 170, 174-176), resolution of extraocular cranial nerve defects (169, 173) and headache (168, 169), and a persisting suppression of PRL secretion after bromocriptine withdrawal from long-term treatment (177) have been reported in patients with macroadenomas. This latter effect has not been demonstrated in patients with microadenomas or with macroadenomas and only moderately elevated PRL levels. Improvement in symptoms due to mass effects of the tumor is reported to begin within days to weeks of institution of bromocriptine, and improvement continues with prolonged treatment. The dose of bromocriptine utilized is generally larger (20 to 40 mg per day) than that used in the treatment of hyperprolactinemia due to microadenomas, but improvement is not infrequently seen with doses of 5 to 10 mg per day. Antiserotonin drugs such as cyproheptadine and methysergide have also been used in the management of hyperprolactinemia but with far less success (178-180). These drugs have dopaminergic activity which may be responsible for the PRL-lowering activity they do exhibit. A new dopaminergic agonist, lisuride hydrogen maleate, may be effective in lowering PRL levels (181).

The surgical management of pituitary tumors has been greatly enhanced by integrating use of the operating microscope, microsurgical techniques, and image-intensified radiofluoroscopy into the transsphenoidal as well as the transcranial approach to the pituitary. The choice of surgical approach depends on the size and location of the tumor. Microadenomas and tumors that extend into the sphenoid sinus are always approached transsphenoidally. Transsphenoidal microsurgery allows visual differentiation of small tumors within the gland and is associated with minimal brain trauma and a low morbidity and mortality (Table V) (54, 55, 151, 153). The incidence of postoperative deficits of pituitary hormones in patients with smaller tumors is also exceedingly low with this technique (182, 183). With

Table V Ref. 151

MORTALITY AND MORBIDITY FROM TRANSSPHENOIDAL SURGERY DURING THE 6-WEEK POSTOPERATIVE PERIOD

Mortality and Morbidity	Cases (%)
Mortality	0.4
Major Morbidity	
Early CSF Leak	4.4
Late CSF Leak	2.0
Extraocular Muscle Palsy	1.2
Pneumonia	1.6
Bacterial Meningitis	2.0
Increased Field Deficit (Transient)	2.8
Postoperative Hematoma	1.2
Mental Change	1.6
Hemiparesis (Transient)	0.4
False Aneurysm	0.4
Minor Morbidity	
Transient Partial ADH Insufficiency	3.6
Persistent Partial ADH Insufficiency	3.6
Persistent Total ADH Insufficiency	2.0
Epistaxis	2.8
Sinusitis	1.2
Aseptic Meningitis	1.2
Corneal Abrasion	0.4

microadenomas, the gland may have to be incised before the tumor is visualized (54, 55). After resection, even if there is a discrete cleavage plane between the tumor and normal pituitary, tumor may still be found within the apparently normal gland surrounding the adenoma. Therefore, following gross total excision of a microadenoma, an arc of microbiopsy specimens is taken from the tumor bed to study with rapid stains on frozen section (55, 184). When evidence of tumor is seen, another arc of tissue is excised; this process is continued until all tumor has been removed. Finally, the tumor bed is irrigated with absolute ethanol to destroy any

remaining tumor cells. Although 20% to 30% of normal gland may be removed with this procedure, postoperative hypopituitarism does not occur since only approximately 15% of the pituitary is required for normal function. The transsphenoidal approach is also utilized for large macroadenomas with suprasellar extension, as long as the suprasellar portion of the tumor communicates widely with the intrasellar portion. Most pituitary adenomas are soft and the suprasellar portion usually drops into the sella with suctioning of the tumor. If however the sella is small or the tumor is dumbbell-shaped (constricted by a tight diaphragma sella), transcranial surgery is necessary (54, 185). Extension of tumor anteriorly beneath the frontal lobe or laterally into the middle fossa also precludes a transsphenoidal approach. The goals of surgery for microadenomas and the smaller macroadenomas are different from those for large macroadenomas with suprasellar and parasellar extension. Selective total adenomectomy[1] is attempted for microadenomas and for smaller macroadenomas. For larger tumors with marked suprasellar extension, either selective subtotal tumor removal[1] (if the adenoma is not clearly defined from the gland) or nonselective subtotal removal[1] (if the normal gland is not identified) is performed (185).

The results of surgery in patients with PRL-secreting tumors depend on both the size of the adenoma as well as on the pre-operative PRL level. Normalization of serum PRL, cessation of galactorrhea, and restoration of menses occur in 70% to 80% of all women with microadenomas (47, 48, 55, 63, 87, 152-155, 186). PRL-secreting microadenomas in men are unusual, but a similar incidence of postoperative normalization of PRL would be anticipated. In patients with larger tumors the results of surgery are less successful, with only 40% to 50% attaining normal PRL levels postoperatively (47, 48, 55, 63, 83, 87, 152-155). If the tumor exhibits localized invasion of the sella, the incidence of normalization of PRL falls to 25% to 40% (48, 153). No patients with generalized sellar invasion attain normal PRL levels postoperatively (48, 153). A preoperative level of serum PRL greater than 200 ng/ml, regardless of tumor size, is also a predictor of a less favorable outcome following surgery (87, 151, 152, 154, 155). The surgical normalization of PRL levels in relation to preoperative PRL values and tumor size in 70 patients with prolactinomas is shown in Table VI (87). Another predictor of a less favorable surgical outcome in women with PRL-secreting adenomas, although not entirely independent of tumor size and PRL level, may be a history of onset of amenorrhea-galactorrhea unrelated to estrogen use or pregnancy (187). The overall rate of serum PRL normalization in men (17%) versus that in women (57%) is the result of a larger tumor size in the men (87). In those men who are cured by surgery (188-190), recovery of the hypothalamic-pituitary-gonadal axis requires several weeks following correction of the hyperprolactinemia (Fig. 24) (190). Symptoms of hypogonadism (i.e. decreased libido and impotence) in men with decreased gonadotroph mass due to tumor compression or surgical trauma may not resolve with testosterone treatment until the serum PRL is lowered further by bromocriptine (81, 191). On the other hand, some men regain normal potency and libido despite persistent post-operative hyperprolactinemia (87). In women the incidence of reappearance of menses following surgery correlates with the incidence of achieving a normal PRL level. However, many patients whose PRL falls only into the 30-to-75 ng/ml range have return of normal menses and may become pregnant (48, 153, 186). Return of ovulatory menses occurs within a month following

[1] Selective toal removal is performed when the normal pituitary has been well identified and biopsied and all pathological tissue is removed.

Selective subtotal removal is performed when the normal pituitary has been identified with a biopsy and remains, but there may be residual pathological tissue.

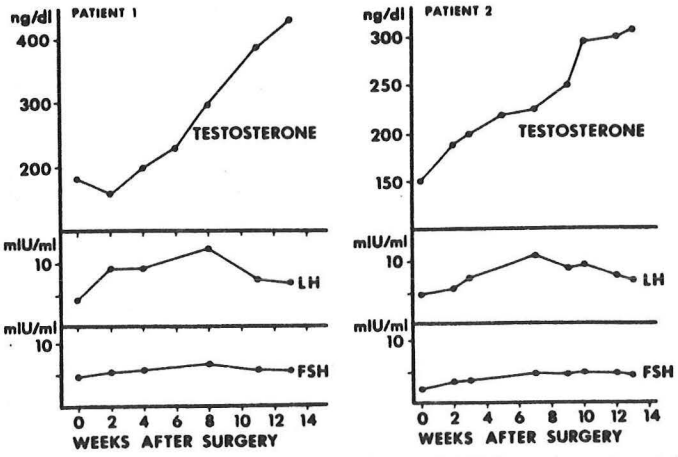
Nonselective subtotal removal consists of partial removal of sellar contents including normal and pathological tissue, with residual tissue (normal and pathological) remaining.

Table VI Ref. 87

SURGICAL NORMALIZATION OF PROLACTIN LEVELS IN RELATION TO PREOPERATIVE PROLACTIN VALUES AND TUMOR SIZE

	% Of Patients With Normal Postoperative Prolactin Levels In Individual Groups*		
	Preoperative Prolactin >200 ng/ml	Preoperative Prolactin ≤200 ng/ml	Total
Adenoma Diameter >10 mm	4% (27)	90% (10)	27% (37)
Adenoma Diameter ≤10 mm	55% (11)	86% (22)	73% (33)
Total	18% (38)	88% (32)	50% (70)

*Numbers in parentheses represent total number of patients in group.



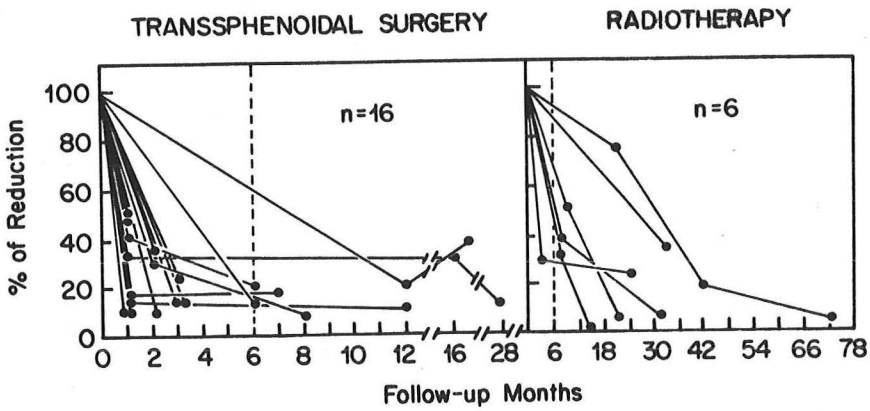
Ref. 190

Serial measurements of T, FSH, and LH in patients 1 and 2 over 13 weeks after surgery.

Fig. 24

successful tumor removal in most patients but may be delayed for as long as 18 months in a few women (63, 153).

Conventional supervoltage radiation therapy should be considered only as adjunctive therapy in the postoperative management of patients whose tumors have been incompletely resected and/or whose serum PRL levels remain elevated (192). The availability of a neurosurgical procedure that has a very low morbidity and mortality and that results in a rapid decline in serum PRL makes radiation therapy less desirable as a primary treatment modality for PRL-secreting adenomas. In Fig. 25 the slow rate of decline of serum PRL in 6 patients following radiation therapy is compared to the rapid decline observed in 16 patients following surgery



Ref. 4

Results of transsphenoidal surgery and radiotherapy. Reduction of serum prolactin levels after treatment is shown as a percentage of the pretreatment value. Note the faster decrease following transsphenoidal surgery.

Fig. 25

(4). The recommended dose is between 4000 and 5000 rads administered at the rate of 900 to 1000 rads per week (192). Complications, including hypopituitarism, are minimal with this regimen. Proton beam radiation has been advocated as a primary treatment modality for pituitary tumors (193), but it requires very expensive equipment limited to a few institutions, is associated with a long delay from onset of treatment until a beneficial lowering of serum PRL occurs, has a significant risk of hypopituitarism, and does not match the precision and completeness of tumor removal that is accomplished with transsphenoidal microsurgery.

A summary of the management of patients with prolactinomas is given in Table VII.

Table VII

MANAGEMENT OF PATIENTS WITH PROLACTIN-SECRETING ADENOMAS

Microadenomas	No Symptoms	Follow vs. Transsphenoidal surgery vs. Bromocriptine
	Symptoms of PRL Excess, Infertility	Transsphenoidal Surgery vs. Bromocriptine
		Postoperative Bromocriptine Or Radiation Therapy If PRL Remains Elevated.
Macroadenomas		Transsphenoidal Or Transcranial Surgery
		Postoperative Radiation Therapy If Tumor Not Completely Resected And/Or PRL Remains Elevated; ? Postoperative Bromocriptine

Post-Treatment Follow-Up

The serum PRL falls to some extent in all patients following surgical resection of PRL-secreting adenomas and is lowest at 1 week (48). The level may rise subsequently, but if it remains normal at 6 months postoperatively it is unlikely to rise unless there is recurrence of the tumor (48, 151). Persistent elevation of the PRL is indicative of residual tumor and of the need for adjunctive radiation therapy or bromocriptine. The long-term recurrence rate in patients with large prolactinomas who have had surgical resection followed by radiation therapy is not known. Patients with "chromophobe" adenomas resected or radiated more than 10 years ago will not have had pretreatment measurements of serum PRL. Estimates of the recurrence rate of prolactinomas over a long-term period must therefore be taken from series consisting of patients with both PRL and non-PRL secreting tumors. The recurrence rate in 2 series of patients followed for 5 to 15 years after transcranial resection and radiation of pituitary tumors demonstrating suprasellar extension (some of which were undoubtedly prolactinomas) was 20% to 25% (194, 195). In all cases the recurrence was detected by CT and none was apparent on plain films of the sella. Other modalities to evaluate for tumor recurrence are visual-field testing and follow-up serum PRL levels. Evaluation of visual fields in patients with no or only partial defects in the immediate postoperative period detects tumor recurrences only after a variable degree of suprasellar extension has developed. A serum PRL level greater than 200 ng/ml generally indicates residual or recurrent tumor, but a level of 100 ng/ml or less may indicate either tumor or damage (surgical or radiation-induced) to the hypothalamus and/or pituitary stalk. The latter is made less likely if there are no deficiencies of other pituitary trophic hormones. Thus the most sensitive method of detecting tumor recurrence is CT. Prolonged follow-up should incorporate CT approximately every 3 years, with yearly clinical endocrinologic evaluation including a serum PRL determination. If recurrence is detected, more frequent evaluation, including visual-field testing, is necessary. Reoperation (and perhaps bromocriptine) is necessary in patients who develop significant suprasellar extension with tumor recurrence.

Careful follow-up of women with prolactinomas who become pregnant is mandatory regardless of prior treatment. This is particularly critical in those patients with microprolactinomas in whom ovulation was induced by bromocriptine or in those few women with spontaneous pregnancy in whom recognition of a pituitary tumor is not made until some point during gestation (196). Patients are questioned carefully about headache and visual symptoms, and formal visual-field testing is performed at 1- to 2-month intervals beginning in the second trimester (94, 95, 136, 139). If symptoms and signs of progressive tumor growth develop intervention with either transsphenoidal surgery (143, 145, 147, 198, 199), bromocriptine (94, 142, 198), glucocorticoids (198, 200), or termination of pregnancy (140, 148) is necessary. Neurological symptoms regress spontaneously within several days following delivery (141, 146-148, 197). Although some believe that nursing is contraindicated (145), on theoretical grounds that suckling may cause further growth of the tumor, others maintain that lactation for the customary limited time is unlikely to cause further growth of a tumor that has already been stimulated by pregnancy. There are several reports of patients with tumors who have nursed without any difficulties (95).

Conclusions

Most patients with hyperprolactinemia unassociated with pregnancy, drug ingestion, renal failure, or hypothyroidism probably have PRL-secreting adenomas. Although the pathogenesis of these tumors is undoubtedly heterogeneous, many

appear to be the result of a primary pituitary defect in which there is a deficiency of dopamine localized to the area of the adenoma. The use of eponymic terms (Forbes-Albright, Chiari-Frommel, and Argonz-del Castillo) in referring to hyperprolactinemic disorders is of historic interest only (201-203). The high incidence of PRL-secreting adenomas in autopsy series of patients without previously recognized pituitary disease suggests that most of these tumors grow very slowly if at all. Because of the positive effect of estrogens in promoting growth of preexistent prolactinomas, every woman with a complaint of menstrual abnormality in whom estrogen therapy is contemplated should have a pretreatment PRL determination. Management of patients with prolactinomas is directed at controlling effects of both PRL hypersecretion and of mass effects of the tumor. Bromocriptine is very effective in reversing hyperprolactinemia, but until longer term studies have been completed, transsphenoidal microsurgery will continue to be the primary mode of therapy in most patients with these tumors.

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