CHAPTER 1

INTRODUCTION

Galactorrhea

Pathological galactorrhea is a condition of which the secretion of milk is inappropriate to the physiological status of the patient, in other words, the patient is not, or has not been recently pregnant (Basser and Edwards, 1972). A little milky secretion can often be expressed from the breast of multipara (Besser and Edwards, 1972); especially if associated with amenorrhea (Glass et al., 1975; Simpson and Plunket, 1979; Badawy et al., 1980; Duchen and McNeilly, 1980), or any lactation in males (Volpe et al., 1972; Besser et al., 1972; Kleinberg et al., 1977; Thorner and Besser, 1977), is a significance abnormality.

Normal babies often secrete small amounts of milk after delivery. This secretion is called "Witch's Milk" resluting from an elevated level of prolactin due to either a temporary secretion from the baby's own pituitary or due to the high level of prolactin present in the amniotic fluid (Besser and Edwards, 1972; Martin et al., 1977; Friesen et al., 1977).

The secretory condition of galactorrhea is found in 2 forms; Spontaneous secretion of which there is continuous milk flow without any external induction, and the type that needs manual expression or physical examination to instigate the milk letdown (Archer et al., 1974; Frantz et al., 1978; Thorner and Besser, 1978). Apparently the

most commonly found is the latter form. However, both are always accompanied by a similar outcome, infertility (Thorner and Besser, 1977; Shewchuk et al., 1980; Skrabanek et at., 1980).

Disorder usually found with galactorrhea is associated with the menstrual cycle (Robyn et al.; 1977; Thorner and Besser; 1977). Most commonly found is Amenorrhea - Galactorrhea Syndrome (Robyn et al.; 1973; Bohnet and Schneider; 1977; L' Hermite et al.; 1977; Strauch et al.; 1977). The classification describing the clinical symptomatology of this syndrome is classically identified as 3 clinical entities (Lloyd et al., 1975; Archer et al., 1977; Boyd et al., 1977; L'Hermite et al., 1977; Martin et al., 1977) :

1) The "Chiari - Frommel Syndrome"; the persistance of postpartum amenorrhea and galactorrhea for more than 1 year following delivery and without evidence of pituitary tumor (Mendel, 1946).

2) The "Ahumanda - del Castillo Syndrome"; the spontaneous onset of amenorrhea and galactorrhea without pituitary adenoma (Argonz and del Castillo, 1953).

3) The "Forbes - Albright Syndrome"; the syndrome which is comparable to the above but with roentgenologic evidence of pituitary adenom-a (Forbes et al., 1954).

However the symptoms occuring along with galactorrhea may not be exclusively limited to only amenstruation (Besser et al., 1972; Thorner et al., 1975; Thorner and besser, 1977; Evans et al., 1980) or even demonstrate regular menstrual cycle (Keye et al., 1977; Pepperell et al., 1977; Thorner and besser, 1977; Frantz, 1978; Skrabanek et al., 1980); while the abnormalities of the cycle can only be proven through further laboratory investigation.

Frantz and Kleinberg (1970) and Hwang et al. (1971) measured prolactin levels in a variety of subjects and found that many with galactorrhea were among those who had high concentration of circulation prolactin. It has subsequently been shown by numerous investigations that patients with amenorrhea/galactorrhea often have hyperprolactinemia (Edwards et al., 1971; Besser et al., 1972; Archer et al., 1974; Boyd et al., 1977; Frantz, 1978).

There appeared to be many theories explaining the incidence of galactorrhea with or without menstrual disorders and its relationship to hyperprolactinemic states. The galactorrhea observed in these patients is probably caused primarily by constant stimulation of the mammary glands by the high prolactin levels (Cuellar, 1980). The cessation of menstruation and ovulation in some cases is thought to occur because hyperprolactinemia either interferes with the secretion of the ganadotropin-releasing hormone (GnRH), thus preventing the ovulatory release of FSH and LH (Horrobin, 1973), or blocks the action of FSH and LH at the gonadal level (Thorner et al., 1974).

Hyperprolactinemia may occur in association with pituitary tumors, (Zarate et al., 1973a ; Ezrin et al., 1978; Wiebe, 1978; Simpson and Plunket, 1979). Other causes of hyperprolactinemia include hypothalamic disease (Thorner and Besser, 1978), disease or disruption of the hypophyseal/hypothalamus stalk (Turkington et al., 1971; Cryer and Kissane, 1979; Vaughan et al., 1980), primary hypothyroidism (Edwards et al., 1971) and the taking of certain drugs that act either by blocking dopamine receptors at the pituitary e.g. Phenothiazides (Friesen et al., 1977), Butyrophenones (Frantz, 1978), Benzamides (Cryer and Kissane, 1979), Metoclopramide (Thorner and Besser, 1978), Sulpiride (Faglia et al., 1977) and Primozide (Maleod and Lehmeyer,

1974), or by depleting the stores of dopamine e.g. Reserpine (Friesen et al., 1977), Methyldopa (Archer, 1977); or through nondopamine machanism at the pituitary level e.g. Estrogens (Raymond et al., 1978) and Thyrotropin Releasing Hormone (Bowers et al., 1971; Jacobs et al., 1971).

It has also been observed that patients who developed amenorrhea and galactorrhea after withdrawal of estrogen-progesterone oral contraceptives may suffer from hyperprolactinemia (Arrata and Haward, 1973; Steel et al., 1973; Thorner et al., 1974; Tyson et al., 1975). It is unclear whether the taking of these preparation is etiologically related to the development of hyperprolactinemic conditions. Jacobs and colleagues (1977) have suggested that it may be coincidental.

Despite the intensive investigation, among the hyperprolactinemic patients there still is a high percentage of idiopathic cases which etioloical factors remain obscure (Archer, 1977; Asfour et al., 1977; Boyd et al., 1977; Van Look et al., 1977).

Prolactin : Isolation and Structure

Prolactin was first discovered in 1928, as a lactogenic substance present in extracts of the pituitary gland of the cow (Stricker and Grueter, 1928). However, it was only since 1970 that this hormone has been definitely identified and measured in human blood (Frantz and Klienberg, 1970). The long delay in its recognition as a distinct hormone in humans, unlike in non-primates, was due to the similarity to human growth hormone which had strong intringsic lactogenic potency, thus, hindering detection of the small amount of prolactin present in human pituitary extracts (Sherwood, 1971; Pasteels et al., 1972 Horrobin,

1973; Frantz, 1978). Moreover, previous reports are most important because they challenged the prevailing view that primate's growth hormone and prolactin were one and the same molecule (Friesen et al., 1977).

In 1970, by means of a sensitive bioassay, prolactin was shown to present in human blood as a substance immunologically distinct from growth hormone and masurement was implemented in physiologic and various pathologic states (Frantz and Klienberg, 1970). Hwang et al. (1971) developed a radioimmunoassay for the human prolactin and measured it in plasma. Human prolactin was finally isolated and found to be a single chain polypeptide of 198 amino acid residues (Hwang et al., 1972) and have only 16 % identical with human growth hormone. (Shame and Parlow, 1977) as shown in figure 1.

Human prolactin is very similar to ovine prolactin in the amount of amino acid residues of 198 as a marked similarity of amino acid sequence, the 3 sulfide bridges within its structure and also having leucine as the NH_2 terminal residue (Friesen et al., 1977; Wenner et al., 1982). Apart from the structural resemblance, ovine and human prolactin also display identical immunalogical reactions (Guyda et al., 1971). Ovine prolactin cross reacts with that of human but has no such cross reactions with growth hormone, thus eliminate any interferance from the latter in RIA procedures (Guyda et al., 1971; L'Hermite et al., 1972; Horrobin, 1973).

As for monkeys, Guyda and Friesen had isolated monkey prolactin from pituitary extracts and separated from monkey growth hormone by using affinity chromatography technic in 1971. And for other animals, notably rats (Meites et al., 1961), mice (Cheever et al., 1969), cattle

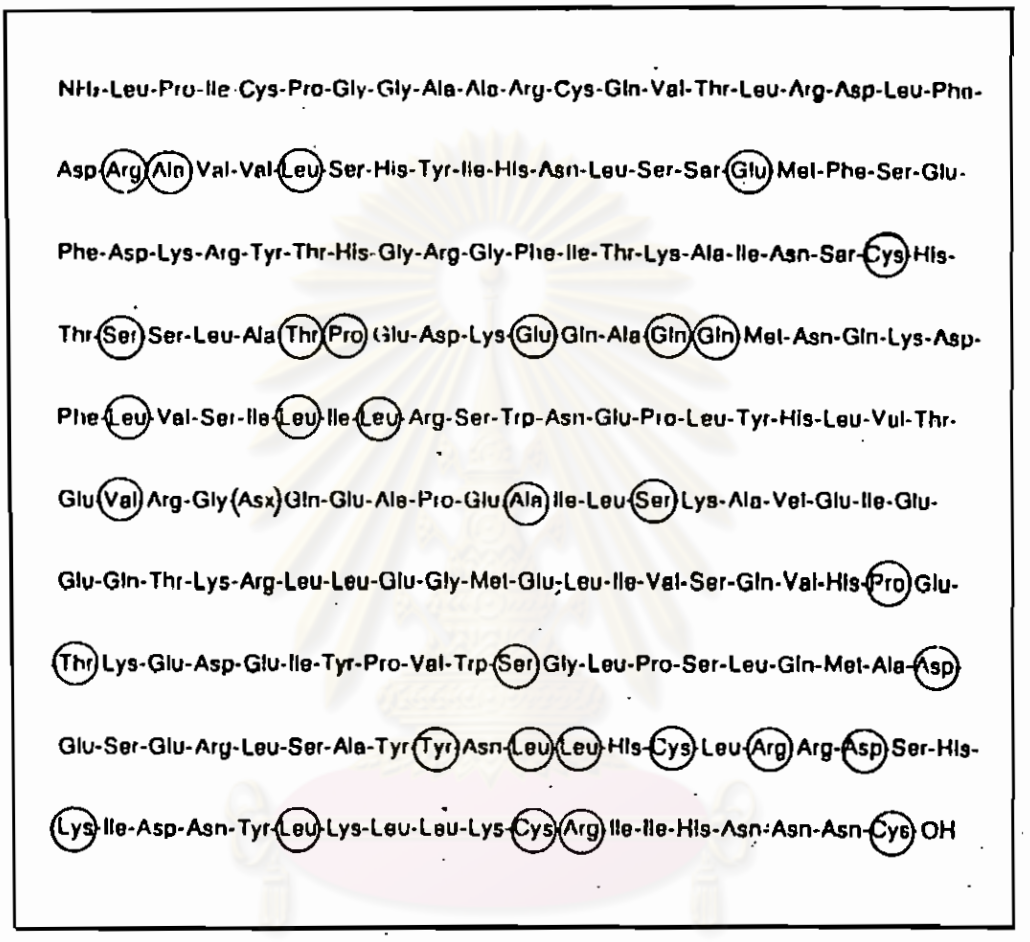


Fig. 1 Human Prolactin, a single chain polypeptide of 198 amino acid residues with 16 % identicle to human growth hormone (Shame and Parlow, 1977)

(Bryant and Greenwood, 1968), small amount of pure prolactin have also been obtained but usually in quantities necessary for developments of RIA rather than for the effects of exogenously administered hormone (Horrobin, 1973).

Regulation of Prolactin Synthesis and Release

The synthesis and release of prolactin from the adenohypophysis is tonically suppressed by a hypothalamic factor, termed "Prolactin Inhibiting Factor" or PIF (Turkington et al., 1971; Horrobin, 1973; Meites et al., 1972).

PIF considered to be a hypothalamic hormone, is secreted into the hypothalamic-pituitary portal venous system, from which it reaches the lactotroph cells of the anterior pituitary (Cueller, 1980). Dopamine and norepinephrine are thought to be the neurotransmitters which stimulate hypothalamic prolactin inhibiting factor secretion (Friesen et al., 1977), whereas serotonin is thought to antagonize prolactin suppression (Kamberi 1971; Lu and Meites, 1973; Kato et al.; 1974). However, considerable evidences showed that dopamine is a PIF in human (MacLeod and Lehmayer, 1974; Archer, 1977; Fuke et al., 1978; Nillius, 1978; Cryer, 1979; Kinch, 1980), in monkeys (Diefenbach et al., 1976; Neill et al., 1981) and in rats (Sharr and Clemen, 1974; Gibbs and Neill, 1978; Plotskey et al., 1978).

In addition to the prolactin inhibiting factor, there have been several experiments that suggest the existence of a "prolactin releasing factor" or PRF elaborated by the hypothalamus as well (Mishkinsky et al., 1968; Valverde et al., 1972; Schally et al., 1973). However, identification of a factor with this unique property has so far been unsuccessful (Horrobin, 1973; 1974; Martin and Bassy, 1980).

In several species, including rats, monkeys and human beings, the tripeptide : Pyroglutamyl-Histidyl-Prolineamide, or Thyrotropin Releasing Hormone (TRH), has been reported to be a potent stimulator of prolactin secretion (Bowers et al., 1971; Jacobs et al., 1971a; 1973; Horrobin, 1974; Stevens et al., 1977; Milmore, 1978; Quadri et al., 1979). TRH might function in this capacity since it also instigates prolactin release very efficiently. However, the physiological importance of TRH in the regulation of prolactin secretion as the Prolactin Releasing Factor is still equivocal (Jacobs et al., 1971; Horrobin, 1973; 1974; Archer, 1977, L'Hermite, 1977). Besides TRH, Estrogen is found to be a potent releaser of prolactin in rats (Raymond et al., 1978; Neil, 1980), while it has very little stimulatory effect on prolactin secretion in monkeys (Quadri et al., 1979; Frawley and Neill, 1980).

In addition to its major role on stimulation of milk secretion, prolactin is known as a stress hormone (Noel et al., 1972). Its concentrations may rise after emotional or physical stress (Grosvenor et al., 1965; Akikusa, 1971; Dunn et al., 1972; Frantz, 1978), and apparently, this hormone may feed-back on its own secretion at the hypotalamic level (Sherwood, 1971; Spies and Clegg, 1971; Sud et al., 1971; Martin et al., 1977).

Pattern of Prolactin Release

The circulating levels of prolactin fluctuate during certain peroid of life (Ehara et al., 1973; McNeilly and Chard, 1974; Robyn et al., 1977). At birth, the levels are very high which then decrease within the first week of life and remains at a low level during childhood (Guyda and Friesen, 1973; Aubert et al., 1974; Lee et al., 1974;

Winter et al., 1975). In men, this prepubertal concentration is maintained throughout life (Aubert et al., 1974; Lee et al., 1974; Ehara et al., 1975; Del Pozo et al.; 1977); but in women, prolactin secretion is increased in the presence of estrogen. Thus, resulting in a rise during puberty and pregnancy (Jacobs et al., 1972; Ehara et al., 1973; Guyda and Freisen, 1973; Aubert et al., 1974).

A circadian rhythm exists in serum prolactin concentration in human, which more irregular variations, are also noted during the 24-hour period. Serum prolactin shows a marked nyctohemoral rhythm with high levels during the night and low levels during the day (Nokin et al., 1972; Ehara et al., 1973; Sassin et al., 1973). This rhytum of hormone is sleep-entrained with irrespective of neither sex nor stage of the cycle (Parker et al., 1973, 1974; Sassin et al., 1973; Martin and Bassy, 1980).

Similar variations of circadian rhythm in prolactin release have been observed in the rats (Dunn et al., 1972), rhesus monkeys (Quadri and Spies, 1976) and cynomolgus monkeys (Siripim, 1982), but it is not known whether prolactin release as in these animals are also sleep related as in man because of the difference in sleep pattern of various species (Quadri and Spies, 1976). And similar to those found in man, neither sex nor stage of the cycle have any effect on this kind of rhythm in the monkeys (Quadri and Spies, 1976; Siripim, 1982).

As for the pattern of prolactin release during menstrual cycle, the relation to the hormonal change during the cycle in primates is still a matter of controversy. In rhesus monkey, Quadri and Spies (1976); Butly et al., (1975); and Milmore (1978) reported that there were no surge in serum prolactin during the prevulatory period or any

other stage of the menstrual cycle. This pattern is similar to those in cynomolgus monkeys observed by Varavudhi and co-workers (Varavudhi et al., 1982) or in chimpanzees (Reyes et al., 1975) and in women, which there is no evidence that the secretion of this hormone changes during the menstrual cycle (Ehara et al., 1973; Tyson and Friesen, 1973). A different pattern is observed in rodents and ungulates as sheep, cattle and goats (Bryant and Greenwood, 1968; Anderson et al., 1972; Meites et al., 1972) in which serum prolactin increased significantly on the day of proestrus and estrus.

Since several authors found no constant changes in serum concentration of prolactin during the menstrual cycle, and they therefore believed that, in physiological conditions, prolactin exerts no important role in the regulation of the menstrual cycle (Hwang et al., 1971; Ehara et al., 1973; Jaffe et al., 1973; Tyson and Friesen, 1973; Yuew et al., 1973; McNeilly and Chard, 1974; Epstein et al., 1975).

This conclusion that prolactin is not essential for normal gonadal function is further supported by many reports. For the patients whose prolaction was suppressed, no alterations were observed either of the length of the cycle or of the hormone secretions (del Pozo et al., 1975) and they usually ovulate and may become pregnant (Thorner et al., 1974: 1975). Nevertheless, prolactin also has a role in the control of normal corpus luteum function, but not maintenance, as described by McNatty et al. (1974). They have shown that, the production of progesterone by human granulosa cells in vitro requires low concentration of prolactin. The suppression of serum prolactin to below normal levels may cause defective progesterone synthesis, but does not alter the plasma levles of LH, FSH and E_2-17B (Schulz et al.,

1978). Morever, this role of prolactin on corpus luteum function can be supported by data demonstrating the presence of specific prolactin receptors in human ovary (Saito and Saxena, 1975).

In monkeys, Quadri and Spies (1976) and Varavudhi et al., (1982) showed that prolactin had no function in controlling corpus luteum formation and maintenenance, while the data of Epinosa-Campos and his colleagues (1975) suggested a possible luteotropic role of this hormone in rhesus monkeys as well as in rats (Dohler and Wattke, 1974; Archer, 1977; Martin et al., 1977).

Hyperprolactinemia

Hyperprolactinemia is the condition of which there is excessive amount of prolactin in the circulation (Martin et al., 1977). There are two types of hyperprolactinemia; which is Physiological type that occurs during lactation, and the latter one, the Pathological type, such as pituitary tumor (Besser and Edwards, 1972; Yuen et al., 1973; Martin et al., 1977; Nillius; 1978).

In condition of hyperprolactinemia, either physiological or pathological stage, the excessive amount of circulating prolactin is known to inhibit ovarian function, which causes amenorrhea (Hwang et al., 1971; Seppala et al., 1975; Delvoye et al., 1977; Tyson, 1977), oligomenorrhea (Reyes et al., 1977), irregular menstruation (Thorner et al., 1974), regular menstruation but with shortened luteal phase (L'Hermite et al., 1975; Muhlenstedt et al., 1978), regular menstruation but with decreased progesterone levles due to corpus luteum insuffiency (Seppala et al., 1976), with incomplete ovulation or even anovulation (Strauch et al., 1977). Whatever the disorder, the result

of infertility can be found among those patients as well as it is found during lactation in normal women (Hwang et al., 1971; Thorner et al., 1974; L'Hermite et al., 1975; Seppala et al., 1976; Reyes et al., 1977; Strauch et al., 1977; Tyson, 1977).

The inhibitory effect of excessive levels of prolactin shown to exert its effect at 3 specific sites; which are the hypothalamus, the pituitary gland and the ovary (Archer, 1977; Kenn et al., 1977; Frantz, 1978). As for the action at the hypothalamic level, prolactin was found to increase the dopamine turnover in the median eminence neurons, which resulted in less GnRH secretion (Hokfelt and Fuke, 1972). This was confirmed by many investigators who also reported the action of elevated prolactin on dopamine turnover that could directly interfere with LH or FSH secretion by blocking the release of GnRH (Sawyer et al., 1974; Grandison et al., 1977; Van Look et al., 1977; Quigley et al., 1979; Tresgurres et al., 1981). Other supportive evidence for a hypothalamic etiology is the lack of possitive feedback effect from exogenous estrogen, as well as failure of change in serum gonadotropin levels during and after the administration of clomiphene citrate (Gambrell et al., 1971; Glass et al., 1975; Bohnet et al., 1976; Robyn et al., 1976; Seki et al., 1976; Franks et al., 1977; Reyes et al., 1977; Van Look et al., 1977; London et al., 1977).

At the pituitary level, excessive prolactin concentrations could act by desensitizing the gonodotropes to GnRH, thus leading to impaired gonadotropin secretion (Winter and Loriaux, 1978). However, this possibility is rendered less likely by the finding of most investigators that ganadotropin responsiveness to exogenous GnRH is usually normal in woman with hyperprolactinemia and in ovariectomized hyperprolactinemic animals (Mortimer et al., 1973; Thorner et al.,

1974; Wentz et al., 1975; Grandison et al., 1977).

At the ovary level, high prolactin levels have been found to induce refractoriness of the ovary to gonadotropins (Reyes et al., 1972; Tyson et al., 1972; Zarate et al., 1972; Thorner et al., 1974; Rolland et al., 1975a), to depress estrogen secretion (Reyes et al., 1972; Tyson et al., 1972; Bonnar et al., 1975; Frank and Jacobs, 1977), to decrease the production of progesterone (McNatty et al., 1974) or even induces luteal insufficiency (L'Hermite et al., 1975; Seppala et al., 1976).

Besides ovarian inhibition effect, high prolactin levels can also effect directly towards the mammary gland, for it is found that many of hyperprolactinemic patients usually show the clinical signs of galactorrhea (Frantz and Klienberg, 1970; Forsyth et al., 1971; Hwang et al., 1971; Besser and Edwards, 1972; Thorner et al., 1974; Frantz, 1978; Thorner and Besser, 1978; Kinch, 1980).

Increasing attention has been paid to the important role plays by hyperprolactin in several cases related to female infertility. Despite the study in both physiological hyperprolactinemia in normal lactating women and pathological hyperprolactinemia in patients, many investigators also induce the hyperprolactin secretion in experimental animals and even in human subjects by several methods as the models for studies. They were including the use of chemical substances to induce hyperprolactinemia in human (Delvoye et al., 1973, 1977; Boyer et al., 1974; Jewelewicz et al., 1974; Zarate, 1974; Bohnet et al., 1975; L'Hermite et al., 1975; Faglia et al., 1976; Robyn et al., 1976; Seppala et al., 1976), the rhesus monkey (Milmore, 1978), the baboon (Stevens et al., 1977) and the rat (McLeod and Robyn, 1976; Faglia et al., 1977; Vasquez et al., 1980). Hyperprolactinemia was also found

to be induced by surgical methods in the human (Turkington et al., 1971), the rhesus monkey (Diefenbach et al., 1976; Frawley and Neill, 1980; Voughan et al., 1980; Neill, 1981), and the rat (Lu et al., 1971; Welsh et al., 1971; Grandison et al., 1977; McNeilly et al., 1978; Winter and Loriaux, 1978; Transquerres et al., 1981).

Galactorrhea, Hyperprolactinemia and Their Treatment

In case of the excessive prolactin secretion due to the pituitary tumor, this can be monitored down to normal level by surgical method (Turkington, 1971; Friesen et al., 1972; Faglia et al., 1977; Franks and Jacobs, 1977; L'Hermite et al., 1977; Reyes et al., 1977; Cryer and Kissane, 1979), by radiotheraphy (Child et al., 1975; Franks et al., 1975; Thorner et al., 1975; Faglia et al., 1977; Reyes et al., 1977; Werder et al., 1978) or by chemical treatments (Thorner et al., 1975; Faglia et al., 1977; Franks and Jacobs, 1977; Keye et al., 1977; Klienberg et al., 1977; LiHermite et al., 1977; Thorner and Besser, 1977; Mornex et al., 1978; Cuellar, 1980). In addition, the chemical treatments have also widely used in other cases of hyperprolactin secretion. (Besser et al., 1972; Thorner et al., 1974; Bohnet et al., 1976).

PIF or dopamine and the hypothalamic extract were direct substances which have been used to lower the level of prolactin secretion from pituitary gland, both in man and experimental animals as monkeys and rats (Amenomori and Meites, 1970; Chen et al., 1970; Ben-David et al., 1971; Kamberi et al., 1971; Klienberg et al., 1971; Watson et al., 1971; Arimura et al., 1972; Crossignani et al., 1977; Spies et al., 1980; Neill et al., 1981). However, due to the hypothalamic extract complex functions, the short duration and side

effects of dopamine and its capability to converse into other physiological substances, these two substances were rejected to the therapeutic usage (Schally, 1973; Hokfelt, 1978; Thorner et al., 1980).

Other therapeutic agents such as estrogen, clomiphenecitrate, L-Dopa, hMG and hCG were also used for treatment of hyperprolactinemia, galatorrhea and the restoration of gonadal functions but these treatments have yielded only mixed and temporary improvement (Yuen et al., 1973; Bohnet and Schneider; 1977; Faglia et al., 1977; Reyes et al., 1977).

Recent studies have indicated that an ergot alkaloid peptide, Bromcryptine or 2-Bromo-α-ergocryptine (CB-154) may be an effective agent in decreasing serum prolactin levels, inhibiting lactation and reinitiating meanstruation (Lutterback et al., 1971; Besser et al., 1972; del Pozo et al., 1972; Thorner et al., 1974; Bohnet et al., 1976; Thorner and Besser, 1978). Bromocryptine is a long-acting orally dopamine agonist and lowers prolactin levels to normal both in puerperal women for suppression of post-partum lactation and in patients with hyperprolactinemia (Besser et al., 1972; Vargar et al., 1972; Thorner et al., 1974; Klienberg et al., 1977; Rolland and Schellekens, 1978; Thorner and Besser, 1978; Bergh et al., 1978). Bromocryptine can act as a function analogue of the endogenous dopamine (Hokfelt, 1978; Kinch, 1980; Thorner et al., 1980). The fall of prolactin level is associated with the return of normal gonadal function and cessation of any galactorrhea (Lutterbeck et al., 1971; Besser et al., 1972; del Pozo et al., 1974; Klienberg et al., 1977; Thorner et al., 1977).

As in human, bromocryptine is capable to inhibit prolactin secretion in monkeys (Weiss et al., 1973; Epinosa-Campos et al., 1975; Schulz et al., 1978) and rats (Brooks and Welsh, 1974; Flukiger and

Kovacs, 1974; Lloyd et al., 1975).

L-Dopa

The administration of a prolactin inhibiting agent, namely L-DOPA or Levodopa, has been reported to inhibit prolactin secretion and used as the therapy in amenorrhea-galactorrhea syndrome (Lu and Meites, 1971; Meites et al., 1972; Turkington, 1972; Zarate et al., 1973a; Ayalon et al., 1974). Levodopa is a sequence of amino acids (d-OH-Phenylalanine) which after initial decarboxylation will turn into dopamine (Hokfelt, 1978). This drug acts both via the hypothalamus and directly on the pituitary lactotrophs in inhibiting prolactin secretion, as infered from experiments in rats (Macleod and Lehmayer, 1974) and in monkeys (Diefenbach et al., 1976). The constant infusion of L-dopa in normal individuals suppresses serum prolactin levels, however, upon discontinuation of infusion, there is a prompt rebound of prolactin above the initial basal values (LeBlanc et al., 1976).

Although L-dopa can reduce the elevated levels of prolactin, the therapeutic effect is of short duration, and there are attendant side effects most notably nausea and vomitting (Boyd and Reichlin, 1975; LeBlanc and Yen, 1976). Other side effects also include psychologic disturbances and rebound effects, which all result in patients becoming refractory to it (Tyson et al., 1975a; Frantz et al., 1978; Zarate et al., 1978). Apart from this, its short half-life making it necessary for very frequent administrations has deemed this drug unsuitable for therapeutic modality (Frantz et al., 1978).

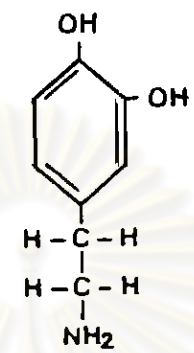
Bromocryptine

Bromocryptine is a semisynthetic brominate ergot alkaloid with a molecular weight of 750.72 and has the chemical name 2-Bromo-∝ Ergocryptine Mesylate (del Pozo et al., 1979) as shown in figure 2. This drug is a dopamine agonist; for in vivo and in vitro studies point to a high affinity and high intrinsic activity of bromocryptine on the dopaminergic receptors on lactotrophes (Calabro and MacLeod, 1978; Cronon et al., 1978). It is rapidly and fairly completely absorbed from the gastrointestinal tract in man which reaches the peak plasma levels in 2 to 3 hours after administration; and small traces persist for up to 24 hours (Mehta and Tolis; 1979; Thorner et al., 1980).

Another asset of this drug is its non-accumulative properties (Thorner et al., 1980). The major route of elimination of bromocryptine is biliary (Mehta and Tolis, 1979). Furthermore, the serum levels of bromocryptine measured in 7 patients after 3 and 6 months of continuous therapy did not differ (Thorner et al., 1980). Therefore, it appears that the prolactin lowering effect of both acutly and chronically administered bromocryptine arises from the pharmacological properties of unchanged drug and not from circulating metabolites (Thorner et al., 1980).

Bromocryptine has two sites of action, at the hypothalamus which results in an increase in hypothalamic content of dopamine and a direct inhibitory effect of the pituitary lactotrophs (Lloyd et al., 1975; Frantz, 1978; Fuxe et al., 1978; del Pozo et al., 1979; Thorner et al., 1980). The rapid and profound lowering of prolactin; inhibiting prolactin and reinitiating menstruation by bromocryptine has been well established (Lutterbeck et al., 1971; Besser and Edwards, 1972; del Pozo et al., 1972; Thorner et al., 1974; Klienberg et al., 1977;

DOPAMINE



BROMOCRIPTINE

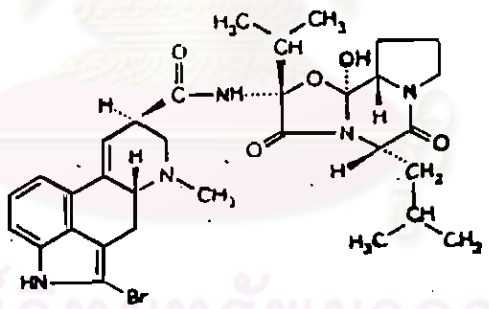


Fig. 2 Structural formula of Dopamine and Bromocryptine

Thorner et al. 1980). Bromocryptine has been reported to posses a long-acting properties than dopamine and L-dopa (Boyd and Keichlin, 1975; Leblanc and Yen, 1976; Archer, 1977; Frantz, 1978; Thorner et al., 1980) but fewer side effects and is apparently free of the uterotonic and vasoconstrictor effects caused by some older ergot compounds (Frantz, 1978). However, there also appeared to be some side effects related to bromocryptine, which includes mild nausea, occasional emesis and mild dizziness during the first 2 - 3 days of treatment. But these symptoms were relieved when this drug was ingested with meals (Thorner et al., 1974; Lloyd et al., 1975; Tyson et al., 1975; Cuellar, 1980).

Therefore, bromocryptine is widely used as an effective drug for treatment of hyperprolactinemia,galactorrhea, menstrual disordeds and infertility (Besser et al., 1972; Bohnet et al., 1976; Rolland and Schellekens, 1978; Thorner and Besser; 1978; Kinch, 1980). The high ovulation and pregnancy rates observed in a study by Bergh et al. (1978) were much better than those usually obtained with clomiphene or hCG therapy. These results were in good agreement with those obtained by other investigators (Yuen et al., 1973; Thorner et al., 1975; Bohnet and Schneider, 1977; Franks et al., 1977; Friesen and Tolis, 1977; Kinch, 1980). However, in many cases of hyperprolactinemic patients, the drug is also effective in restoring gonadol function and fertility while their prolactin levels may remain elevated (Thorner et al., 1980).

Rational

In human, galactorrhea is always accompanied by the outcome of infertility (Thorner and Besser, 1977; Shewchuk et al., 1980; Skrabanek et al., 1980). Frantz and Kleinberg (1970) and Hwang et al.

(1971) had also measured prolactin levels in a variety of subjects and found that many with galactorrhea were among those who had high concentration of circulating prolactin, this has also subsequently been shown by numerous investigators in their galactorrhea patients studied (Edwards et al., 1971; Besser et al., 1972; Archer et al., 1974; Boyd et al., 1977; Frantz, 1978).

Evidences showed that galactorrhea seems to be the clinical hallmark of hyperprolactinemia, and in condition of hyperprolactinemia, this excessive amount of circulating prolactin is known to inhibit ovarian function which causes the result of infertility (Hwang et al., 1971; Thorner et al., 1974; L'Hermite et al., 1975; Seppala et al., 1976; Reyes et al 1977; Strauch et al., 1977).

In monkeys, the report of natural occurances of galactorrhea seems to be less, except for one case of galactorrhea monkey in a colony at the Biology Department, Faculty of Science; Chulalongkorn University (Varavudhi and Yodyingyuad, 1980) and the other one in the report of Shculz et al. (1978) that refer to Bruggemann's study (un-published data) in the successful improvement of fertility in a hyperprolactinemia monkey. However, these were merely two cases and were not embarked upon to study in details. Moreover, there are reports of hyperprolactinemia in monkeys, but it is such a kind of conditioning induction by means of drugs or certain chemicals in order to use them as modalities in any investigations or studies. This can be examplified in a study by Aso et al. (1982) who used sulpiride to induce hyperprolactinemia in Baboons (Papio cynocephalus), thus, using this specie as a model comparative to human beings for determination of hormonal changes during the condition.

Research Aim

In our monkey colony, the displaying of galactorrhea in 5 females certainly proves to be an extraordinary and interesting phenomenon. This intrique rises from the fact that the galactorrhea condition in these monkeys were natural occurances happening on their own accord. Our interests in the incidence of galactorrhea, which is also a significant clinical symptom of human reproductive disorders, is an event to be study in detail. The clinical history and also carefully observations are the first, and then lead to our study which concerns hormonal investigation in galactorrhea and therapeutic measures, using bromocryptine as the drug of choice in case of hyperprolactin in these galactorrhea monkeys, identical to those best actually used in human (Lutterback et al., 1971; Besser et al., 1972; del Pozo et al., 1972; Thorner et al., 1974; Rachman et al., 1982).