CHAPTER 4

DISCUSSION

In the study, according to the menstrual disorder, five galactorrhea monkeys have displayed two types of menstruation : regular and irregular cycles. The first three, monkey # 74, monkey # 24 and monkey # 29, were in regular cycle group, while the remaining two, monkey # 11 and monkey # 58, were the irregular ones. All of them were under suspection on infertility. Evidences showed that galactorrhea in these monkeys were accompanied with hyperprolactinemia, as prolactin in each individuals showed the average levels of about three times higher than the normal levels in control grop. (Figure 8 and 9) This was in agreement with many other investigators reporting in human (Frantz and Klienberg, 1970; Hwang et al., 1971; Besser et al., 1972; Archer et al., 1974; Thorner and Besser, 1977).

For monkey # 74 in the regular cycle group, she was approximately 10 years old and had a good menstrual record in range of 30 - 33 days length. She respectively delivered normal babies in 1980 and 1981. Since then, she had failed on pregnancy. Galactorrhea persisted for at least three months before the study began, as detected by manual impression. The milk secretion in this monkey was noticing of greater amount than other galactorrhea monkeys. Her hormonal pattern, as shown in graph 2, Figure 1, showed high prolactin levels while the other reproductive hormones as LH, E_2 and progesterone were in the same manner as in normal monkeys as shown in graph 1, figure 1. It is

of interest that preovulatory surge of LH, eventhough occuring but with lower level (84 ng/ml) compared to 286 ng/ml of normal cycling group. This low LH surge may due to the missing day of actual peak because of discontinued blood sampling, or due to the inhibition of positive feedback of E_2 on LH secretion by high prolactin levels as was found in sulpiride induced hyperprolactinemia in woman (Robyn, 1977). Other supportive evidences on the lower or absence of LH peak in hyperprolactinemic women has been obtained by many investigators as reported by Glass et al., 1975; Faglia et al., 1977 and L'Hermite et al., 1977. However, the machanism of this was still unknown.

The similar pattern as in monkey # 74 was found in monkey # 29. As shown in graph 3, figure 1, monkey # 29 showed the high prolactin levels and also low LH peak. E_2 peak and progesterone elevation in luteal phase were in normal patterns. LH peak was only 66 ng/ml while the normal was 286 ng/ml. This monkey was one in the regular cycle group with the range of cycle length was 28 - 31 days. Like monkey # 74, she was over 15 years old and had her last baby in 1975. After that time, no pregnancy occured and galactorrhea can be found for three months before study by hard pressing of breasts, but in small amount.

Monkey # 24 showed regular cycle of 24 days. She was fat, inert and tame and was over 12 years of age. She was the only one who found to have no pregnancy before. Her milk secretion was present with very small amount.

She had high prolactin levels (357 - 780 mU/l), low LH peak (91 ng/ml.) and no mid-cycle E_2 peak. (figure 8, graph 4). The similar pattern of hormonal profile were reported by many authors (Delvoye et al., 1973; Jewelwicz et al., 1974; L'Hermite et al., 1977; Robyn et al., 1977; Tyson et al., 1977). The progesterone levels reached the peak of 14.8 nmol/ml and lasted only 9 days which may cause the luteal function insufficiency (Seppala et al., 1976). This phenomenon was in agreement with those found in hyperprolactinemic patients with luteal phase length of 8 - 11 days and low progesterone levels (Muhlenstedt et al., 1978). Moreover, diminished progesterone production in vitro by granulosa cells of human antral follicles exposed to higher concentrations of prolactin reported by McNatty et al. (1974) also supported this contention. Our result and these previous reports suggest that excess prolactin may act directly on the ovaries by interfering with several aspects of follicle maturation. The absence of E_2 peak and the inconspicuous of sexual skin in monkey # 24 also suggested the impairment of follicular development. This similarity was seen in the hyperprolactinemic baboon induced by sulpiride (Aso et al., 1982). Thus, with respect to their observations, all these authors postulated the direct effect of prolactin on the ovary. However, the real machanism was still unknown.

The interesting one in monkey # 24 was her menstrual disorder. On the study, she was found to have luteal insufficiency as described. After that, her menstrual pattern was changed to the kind of anovulatory cycle with E_2 and progesterone were in very low levels. As on day 22 in the cycle before bromocryptine treatment,

E_2 was in low levels and no elevated progesterone can be seen. (graph 3, Figure 3). Her menstruation was occured on day 28. This can be explained that the hypothalamic-pituitary-ovarian function may change due to the duration of hyperprolactinemia (Aso et al., 1982). Thus, impaired luteal function might cause anovulatory cycle and finally cause amenorrhea if the duration of hyperprolactinemia was still prolonged (Seppala et al., 1976).

For the irregular cycle group , the remaining two, monkey # 11 and monkey # 58, had shown the similar hormonal patterns of anovulation through 100 days of amenorrhea. Prolactin were found in high levels (graph 1 - 2, figure 2). No LH peak, E_2 peak and progesterone elevation were occured but basal E_2 and progesterone were the same as in normal range of control cycle in follicular phase. These anovulatory patterns of galactorrhea-amenorrhea conditions were widely seen in most hyperprolactinemic patients (Hwang et al., 1971; Thorner et al., 1974; Glass et al., 1975; L'Hermite et al., 1975; Robyn et al., 1977; Tyson et al., 1977; Rachman et al., 1982). All these investigators also pointed out the hypothalamic-pituitary-ovarian axis dysfunction, but the machanism, as stated above, cannot be clearly explained.

It is of interest that monkey # 11, monkey # 29 and monkey # 24 were aged of 12 - 15 years. Besides this, their durations of non-pregnancy were long, as more than 9 years in monkey # 11 and monkey # 29, and never pregnancy in monkey # 24. Therefore the old ages and the long durations of non-pregnancy may be the interesting problem of infertility to be concerned. Differences can be seen in the other two, monkey # 74 and monkey # 58, with younger age of

approximaldy 10 years old and the shorter durations of non-pregnancy on 2 - 3 years.

Bromocryptine Treatment

From the study, bromocryptine was administered at the dose of 2.5 mg/day, as the minimum effective doses using in human (Thorner et al., 1974; Kliemberg et al., 1977; L'Hermite et al., 1977). It has been found that during the period of 30 days of bromocryptine treatment, prolactin were returned to the normal levels in all five galactorrhea monkeys. (Graph 1 - 5, figure 9). This effect did not depend on the day of menstrual cycle since bromocryptine were given in any day of the cycle in each monkey. Bromocryptine may exert direct effect on prolactin secretion in the monkey in the same manner as in human. Since this drug is the dopamine agonist (Besser et al., 1972; Thorner et al., 1974; Klienberg et al., 1977; Del Pozo et al., 1979), it mimics dopamine action by binding to dopaminergic receptors on lactotroph cells resulting in suppression of prolactin secretion (Hokfelt, 1978; Kinch, 1980; Thorner et al., 1980). Besides this, bromocryptine has been also reported to increase hypothalamic dopamine content (Lloyd et al., 1975; Frantz, 1978; Fuxe et al., 1978).

It is of interest that serum prolactin increased upto the high levels again after bromocryptine withdrawal. It seems that the bromocryptine rate of clearance is quite rapid (Metha and Tolis, 1979; Thorner et al., 1980). It might need long time treatment since 11 % of hyperprolactinemic patients can have prolactin returned to normal levels with no signs of recurrences after drug

withdrawal, after 1 year of bromocryptine treatment (Moriondo et al., 1985).

During 30 days of bromocryptine treatment, galactorrhea were reduced and then disappeared within 15 days of drug treatment. The only one, monkey # 74, had no cessation of this abnormal milk secretion but only in reduced amount throughout the drug period, even her prolactin had returned to normal range. These phenomena were in agreement with those reported in many patients. (Thorner and Besser, 1977; Klienberg et al., 1977; L'Hermite et al., 1977). However, after bromocryptine withdrawal, galactorrhea were recurred in all monkeys within one or two days. The recurrences of galactorrhea after stopping the drug treatment may due to the prolactin level which increased upto the high levels again (Leblanc et al., 1976).

Bromocryptine treatment were continued for 3 months in 4 monkeys (monkey # 74, monkey # 29, monkey # 11 and monkey # 58). Inspite of non-pregnancy occured, after mating with fertile male on every mid-cycle periods during treatment, it has been found that all animals seemed to improve their mating behaviour with high receptivities. The high successful rate on getting pregnancy in hyperprolactinemic patients using bromocryptine has been reported (Besser et al., 1972; Thorner et al., 1975; Bohnet et al., 1976; Franks et al., 1977; L'Hermite et al., 1977; Kinch, 1980; Rachman et al., 1982). The unsuccessful in getting pregnancy in these monkeys may due to the short period of treatment. The certain cause of infertility besides hyperprolactinemia in these monkeys will need to be further investigated.

Conclusion

It could be concluded from the study that

1. Galactorrhea may occured spontaneously in the monkey. The galactorrhea were accompanied by hyperprolactinemia which suppressed preovulatory LH. surge, leading to menstrual disorder and infertility.

2. Bromocryptine can suppressed prolactin secretion in all hyperprolactinemic monkeys, but had no effect on other reproductive hromones as LH, E_2 and progesterone.

3. Withdrawal of bromocryptine after the first 30 days of treatment caused prompt recurrent of high serum prolactin levels associated with galactorrhea.

4. Three months of bromocryptine treatment at the dose of 2.5 mg/day seemed to be unable to improve fertility in aged monkeys.