CHAPTER IV

RESULTS

1. Basal levels of thyroid hormones, TSH, PRL, E_2 and P during D10 and D23 of the immediate pretreatment cycle and D3 of treatment cycle

1.1 E_2 and P

Greater E_2 levels during late follicular phase (D10) was exhibited (143.6 pg/ml) and differed significantly from those during early follicular phase (D3) and luteal phase (D23) showing 72.5 and 47.7 pg/ml, respectively (table 1). Peripheral serum P levels were always high (6.24 ng/ml) on D23 but very low on D3 and D10 of cycle (0.25 and 0.45 ng/ml).

1.2 T3, T4, fT4, TSH, PRL and TBG

As shown in table 1, the mean value of these hormones at various phases of the cycle did not differ significantly from each other. Mean serum levels of T3, T4, fT4, TSH, TBG and PRL on D3 of treatment cycles were 144.5 $\pm$ 39.9 ng/dl, 7.25 $\pm$ 1.41 ug/dl, 1.37 $\pm$ 0.25 ng/dl, 2.97 $\pm$ 1.72 mIU/L, 11.72 $\pm$ 1.43 ug/ml and 285.64 $\pm$ 242.22 mIU/L, respectively. The levels on D10 and D23 of cycle prior to initiation of treatment were as followed : 155.63 $\pm$ 27.79 and 148.30 $\pm$ 42.12 ng/dl for T3; 5.10 $\pm$ 0.68 and

Table 1. Serum hormone levels during major phases of menstrual cycle

Day of Cycle / Cycle Range (d)	E2 (pg/ml) (x ± SD)	P (ng/ml) (x ± SD)	T4 (ug/dl) (x ± SD)	T3 (ng/dl) (x ± SD)	fT4 (ng/dl) (x ± SD)	TSH (mIU/L) (x ± SD)	TBG (ug/ml) (x ± SD)	PRL (mIU/L) (x ± SD)
D10 (26-35d)	143.61* ±42.02	0.45 ±0.20	5.10 ±0.68	155.63 ± 27.79	1.32 ±0.27	1.93 ±0.84	10.90 ±1.60	368.21 ±217.57
D23 (26-35d)	72.45 ±11.87	6.24** ±4.97	6.83 ±1.40	148.32 ± 42.12	1.28 ±0.29	1.88 ±0.85	12.10 ± 2.00	390.87 ±249.67
D3 (24-34d)	47.70 ±26.96	0.25 ±0.12	7.25 ±1.41	144.49 ±39.28	1.37 ±0.25	2.97 ±1.72	11.72 ±1.43	285.64 ±242.2

Abbreviation : a, Do of treatment; *, P< 0.05 ; **, P< 0.01

6.03 ± 1.48 ug/dl for T4; 1.32 ± 0.27 and 1.28 ± 0.29 ng/dl for fT4; 1.93 ± 0.84 and 1.88 ± 0.85 mIU/l for TSH, 368.51 ± 217.57 and 390.67 ± 249.67 mIU/L for PRL; 10.90 ± 1.60 and 12.10 ± 2.0 ug/ml for TBG, respectively.

Normal menstrual cycle (24-35) was exhibited during the pretreatment cycle. Pulse rates ranged between 140-180/min. All monkeys were active . These observed clinical pictures as well as normal levels of these hormones were defined as the euthyroid state.

2. Study the effects of MMI on serum levels of thyroid hormones and TSH.

The summary data of MMI-induced hypothyroidism were shown in table 2. Results made it possible to classify degree of MMI induced hypothyroidism into 3 levels as follows:

2.1 Severe hypothyroidism

In this state, fT4 concentrations reduced to range between 0.03 - 0.45 ng/dl corresponding with lower T3 (<80 ng/dl) and T4 (<2 ug/dl) respectively.Conversely, the TSH levels increased prominently (>35 mIU/L). The animals showed typical symptoms of hypothyroidism including dry and scaling face skin, both edematous eye lid (fig 15), obvious galactorrhea from both nipples (fig 16), irregular bleeding cycles interspersed with amenorrhea, lethargy and anorexia. Pulse rates lessened

Table 2. The summarized serum fT4 (ng/dl), TSH (mIU/L) levels obtained in MMI-induced hypothyroidism monkeys.

no.	Basal values	Induction time (day)	Severe state (day)	Compensatory period (day)	Mild state (day)	Recovery period (day)
63	fT4 1.53 TSH 6.65	140	0.3-0.45 >35 (84)	-	0.6-0.9 6-19 (147)	pregnancy (158)
78	fT4 1.53 TSH 1.83	105	0.03-0.45 >35 (56)	-	0.8-1.04 6-10 (168)	1.49-2.13 2-2.97 (119)
25	fT4 0.90 TSH 1.83	70	0.06-0.35 >35 (126)	0.5-1.10	0.6-0.8 6-12 (95)	1-1.20 1-2.5 (105)
87	fT4 1.27 TSH 2.17	91	0.1-0.45 >35 (63)	-	0.8-1.10 5-12 (231)	1.2-1.50 1-2.10 (112)
77	fT4 1.48 TSH 3.30	77	0.05-0.30 >35 (140)	-	0.7-1.10 8-14 (189)	1.2-1.45 3-6.21 (116)
101	fT4 1.48 TSH 2.99	105	0.03-0.40 >35 (126,56)	0.5-1.10 (84)	0.95-1.10 4-6 (80)	1.20-1.45 1-3.5 (105)
33	fT4 1.47 TSH 2.01	28	0.03-0.08 >35 (70)	0.1-1.10 (77)	0.45-0.60 4-6 (98)	0.7-1.28 1-2.78 (101)
Range	fT4 0.9-1.53 TSH 1.83-6.65	70-140	0.03-0.45 >35 (63-140)	0.5-1.10 (-,84)	0.6-1.10 4-19 (80-231)	1-2.13 1-6.21 (105-119)

Abbreviation : *, exclude no. 33.

Fig 15. Both edematous eye lids in severe hypothyroidism monkey as indicated by arrow.

Fig 16. Galactorrhea in severe hypothyroidism monkey as indicated by arrow.

to 110-132/min.

2.2 Mild hypothyroidism

It was noticed that the compensatory period was exhibited after reducing the daily dose of MMI during severe hypothyroidism which varied in time. Monkeys no. 77 ,87, 63, and no. 78 dit not show definite compensatory phenomena. Approximate range of serum fT4 levels during compensatory period was between 0.50 - 1.10 ng/dl while the TSH levels were declined. Following the compensatory period, the levels of fT4 of six out of seven monkeys readjusted to maintain existently ranging 0.45 - 1.1 ng/dl. However, the fT4 levels of monkey no.33 ranged between 0.45-0.60 ng/dl. During this period, the levels of both T3 and T4 were slightly increased and ranged between 110-260 ng/dl and 2.00-6.20 ug/dl, respectively. Additionally,the TSH levels were fluctuated ranging 4-19 mIU/L. All monkeys showed the resumption of bleeding cycle, more activities, and appetite. Edematous eye lids were remained. Galactorrhea was exhibited and did not obviously seen with squeezing. The pulse rates were ranged between 136-168/min. This period was classified as the state of mild hypothyroidism.

2.3 MMI-withdrawal (recovery) period

In this period, the fT4 concentration was over 1.20 ng/dl after MMI-withdrawal in six monkeys. Only in monkey no. 33, the fT4 concentrations ranged 0.70 - 1.28

ng/dl during this period. The levels of both T3 and T4 elevated ranging 110-270 ng/dl and 4.80-12.40 ug/dl, respectively. Serum TSH levels further dropped below 7.0 mIU/L (1.00-6.20 mIU/L) after complete withdrawal of MMI. The time-response of MMI-induced hypothyroidism varied in each monkey (table 2). All monkeys showed the resumption of bleeding cycles and more activities.. Disappearance of galactorrhea and edematous eye lids was exhibited. The pulse rates ranged 148-172/min.

Apart from using fT4 as being the first criteria to classify the state of hypothyroidism, the TSH , T3 and T4 were another criteria confirming and considering with fT4. Patterns of fT4 levels during MMI treatment were differed among each monkey which characterized into 2 types. The first type showed rapid response to MMI 10 mg/day treatment exhibiting sudden decline in fT4 levels. The second type showed gradual decline in fT4 levels after several weeks of marked fluctuations. Significant reduction of fT4 levels in this type lasted for 70 - 140 days.

2.4 Rapid response of fT4 concentrations to MMI treatment

Only monkey no. 33 showed rapid response to MMI treatment. The immediate pre-treatment values of fT4, T4, T3 and TSH were 1.47 ng/dl; 8.64 ug/dl; 191.54 ng/dl and 2.01 mIU/L, respectively. After daily administration of

10 mg MMI for one week, fT4 levels suddenly declined to 0.74 ng/dl and then oscillated for 5-6 weeks prior to establishment onset of severe hypothyroidism (fig 17). Very low levels of fT4 (< 0.2 ng/dl) was evidenced and accompanied by a concomittent rise of TSH exceeding 46 mIU/L. In this state, both T3 and T4 levels were also reduced to the values lower than 60 ng/dl and 1.5 ug/dl respectively. Reduction of MMI from 10 mg/day to 5 mg/day was capable of maintaining state of severe hypothyroidism with lowest fT4 concentration (< 0.1 ng/dl) in this animal. Further reduction of MMI to 2.5 mg/day showd prompt relieve of the severe hypothyroidism state with compensatory phenomenon of high fT4 increment within 4-5 weeks but the monkey need to readjust for 14-15 weeks to the state of mild hypothyroidism. The striking rise in fT4 levels during rebound period were followed by sudden decrease in TSH levels and remained in the values near pre-treatment levels for several weeks with tendency to moderate rise (20-25 mIU/L) during late compensatory period. Both T3 and T4 levels also exhibited compensatory phenomena. The fT4 levels during mild hypothyroidism were oscillated within the narrow range of 0.45 - 0.60 ng/dl for 98 days. During 98 days of mild hypothyroidism period, the levels of TSH reduced and maintained within the range of 2-6 mIU/L while both T4 and T3 increased and fluctuated within the range of 1.70 - 3.40 ug/dl and 160-280 ng/dl, respectively. Withdrawal of MMI on the

first day of resumed menstruation caused fT4 levels to rise rapidly and oscillated within the range of 0.70 - 1.28 ng/dl whereas the TSH levels further dropped to normal levels of 1.60 - 3.0 mIU/L. It was noted that the lower thyroid hormone levels (0.33 ng/dl for fT4, 107.68 ng/dl for T3 and 3.53 ug/dl for T4) were appeared prior to an increase in TSH levels during early severe hypothyroidism. Moreover, relative changes in thyroid hormone levels were greater than those in TSH levels as represented in late severe hypothyroidism.

2.5 Slow response of fT4 concentrations to MMI treatment.

Six out of seven monkeys (no. 25, no. 78, no. 77, no. 87, no. 101 and no. 63) exhibited slow response of fT4 to MMI treatment as represented in fig 18-23. These monkeys required 70-140 days of 10 mg/day MMI treatment before serum fT4 levels dropped to the values below 0.45 ng/dl of severe hypothyroidism state. The strong fluctuations of fT4, T3 and T4 were revealed and ranged between 0.75 - 3.40 ng/dl, 95-310 ng/dl and 4.7 - 12 ng/dl, respectively during an earlier phase of treatment. Compensatory increase in TSH levels (> 35 mIU/L) were evidenced whereas both T3 and T4 levels reduced to 10-103 ng/dl and 0.5 - 2.0 ug/dl. It was noticed that lower thyroid hormone levels were appeared prior to an increase in TSH levels during early severe hypothyroidism. Additionally, the thyroid hormone levels elevated slightly

while the serum TSH remained in moderate high levels as evidenced during late severe hypothyroidism. Duration of severe hypothyroidism was in the range of 56-140 days. It should be noted that the sufficient times required for relieve the lowest fT4 concentrations in the typical state of severe hypothyroidsm reaching the compensatory period were 14-98 days. Only one monkey (no. 101), showed two periods of severe hypothyroidism for 126 and 56 days, respectively (fig 22).

In monkeys (no. 77, 87,63 and no. 78), the compensatory phenomena could not detected on the basis of weekly measurements but the other four animals showed definite compensatory period having fT4 concentrations ranging 0.5 - 1.1 ng/dl and time being (21-84 days). Prolonged compensatory period, 84 days, of animal no. 101, showed fT4 range of 0.60 - 1.10 ng/dl. During this period, TSH levels declined prominently and readjusted the levels to be normal. Both T3 and T4 levels were increased coincidentally with the fT4 levels. During mild hypothyroidism, fT4 concentrations readjusted within the range of 0.60 - 1.10 ng/dl. Slight increase in TSH levels were observed ranging 4-19 mIU/L during this period. Meanwhile, the levels of both T3 and T4 oscillated and ranged between 110-260 ng/dl and 2.0 - 6.20 ug/dl, respectively. Prolonged period of mild hypothyroidisn in monkey no. 87 lasted for 231 days. Otherwise, the fT4 levels during a shorter period for 80 days in no. 101

tended to be reached the pretreatment values (fig 22). It was noted that the plateau level of fT4 in monkey no. 77 during early period of mild hypothyroidism was followed by the elevated fT4 levels reaching the pretreatment value during late period. After complete MMI withdrawal, most animals showed prompt increase in fT4 levels ranging 1.00 - 2.13 ng/dl with profound decrease in TSH levels to the normal value ranging 1-6.21 mIU/L. T4 and T3 levels fluctuated before returning to the normal range of pretreatment values.

In summary, four states of MMI-induced hypothyroidism obtained from both the clinical observation and the experimental data were described and classified in all 7 monkeys as followed :

1. Severe hypothyroidism

During this period, serum levels of fT4 showed below 0.45 ng/dl except the monkey no. 33 having 0.03 - 0.08 ng/dl whereas the TSH levels accentuated continuously over 35 mIU/L. Serum levels of both T3 and T4 were less than 80 ng/dl and 2 ug/dl,respectively. Among 7 studied monkeys, only one monkey (no. 101) had two periods of severe hypothyroidism occurring with different induced time. During the typical severe hypothyroidism, most animals showed the clinical pictures of lethargy, anorexia, galactorrhea, irregular bleeding interspersed with amenorrhea, edematous eye lids and dry skin.

2. Compensatory period.

This compensatory periods were evidenced in various response time (table 2). Four out of seven monkeys (no. 77 ,87,63 and 78) unable to detect compensatory period from the immediate recovery period after severe hypothyroidism. Since the short transitional period, the clinical observations were evidenced and overlapped with some observations during mild hypothyroidism.

3. Mild hypothyroidsim

From the data, the criteria which defined this state was 0.60 - 1.10 ng/dl for fT4 levels excluding no. 33 exhibited the low ranging of 0.45 - 0.60 ng/dl. Most animals during mild hypothyroidsm showed moderate levels of TSH (4-19 mIU/L) and T4 (2.00-6.20 ug/dl). However, the serum levels of T3 ranged within the pretreatment values (110-260 ng/dl). During this period, all animals showed resumption of bleeding cycle, and more activities.

4. Complete MMI-withdrawal (recovery) period :

During 100-120 days of MMI withdrawal, the levels of T3, T4, and fT4 increased to reach the pretreatment values while the TSH levels declined to 1-6 mIU/L. Monkey no. 33 showed relatively low levels of fT4 and ranged between 0.70 - 1.28 ng/dl. All animals were mated with the fertiled male monkeys during the mid cycle of each

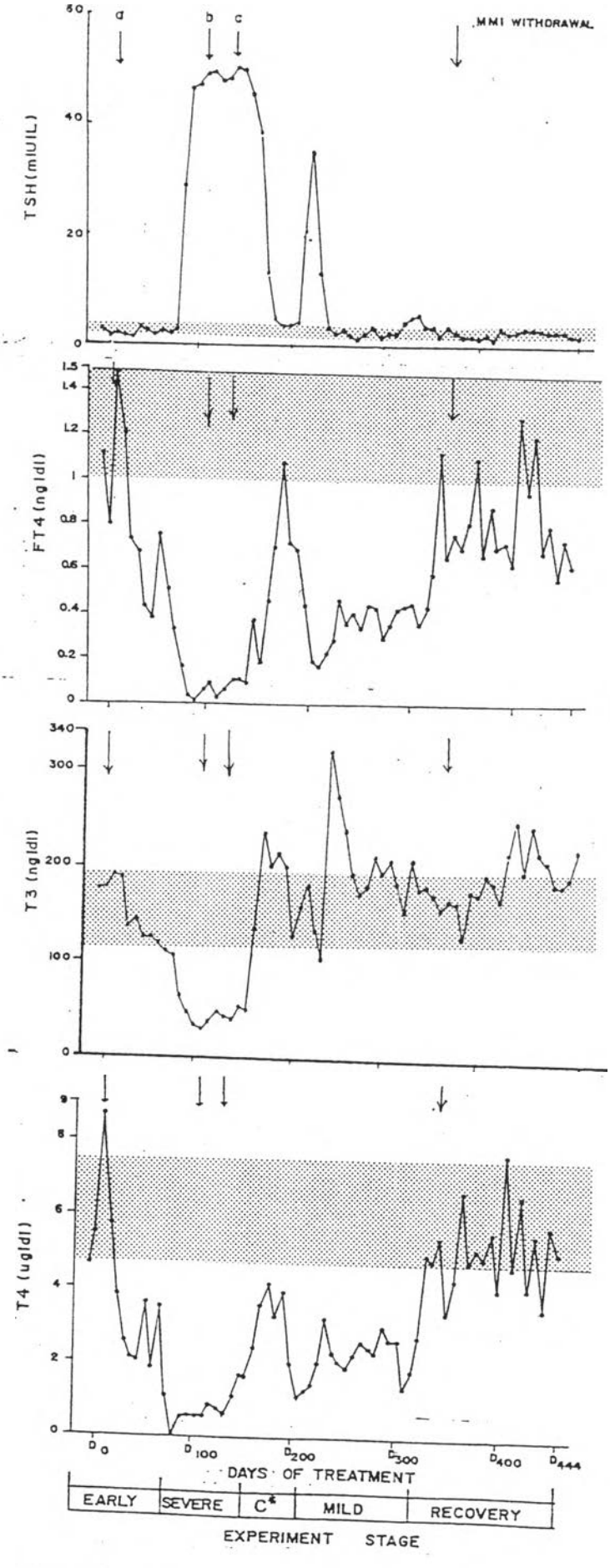

Fig 17. MMI-induced hypothyroidism with changing the levels of fT4, T4, T3 and TSH in monkey no. 33.

Abbreviation : a, MMI 10 mg/day ; ▒ pretreatment value ($\bar{X}\pm SD$)
b, MMI 5 mg/day ; C*, compensatory period
c, MMI 2.5 mg/day

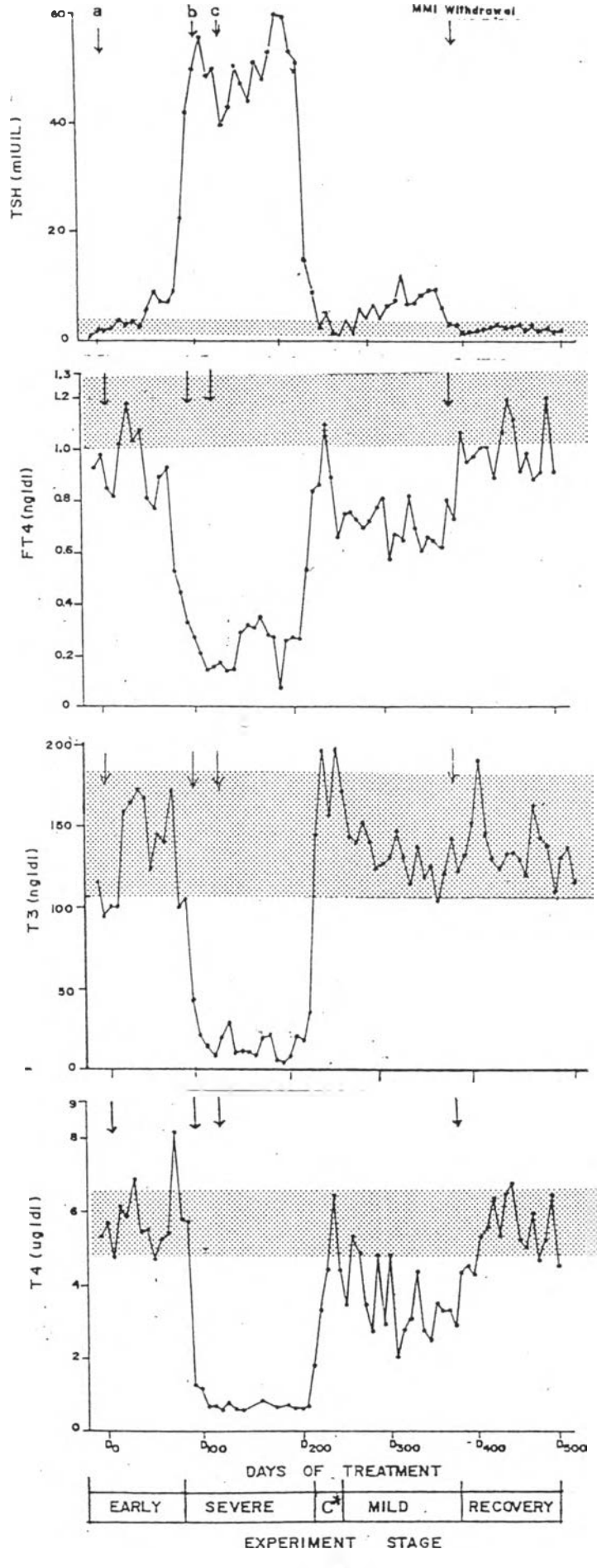

Fig 18. MMI-induced hypothyroidism with changing the levels of fT4, T4, T3 and TSH in monkey no. 25.

Abbreviation : a, MMI 10 mg/day ; ▒ ; pretreatment value ($\bar{X}\pm SD$)
b, MMI 5 mg/day ; C*, compensatory period
c, MMI 2.5 mg/day

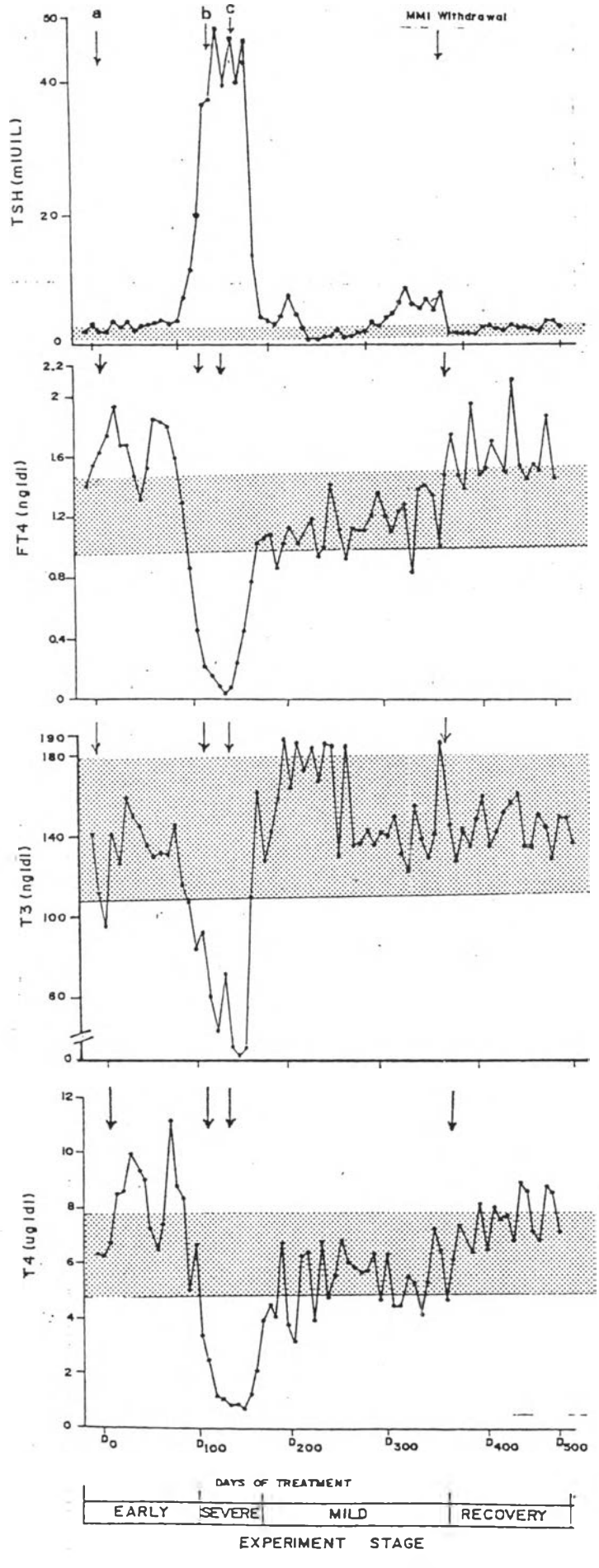

Fig 19. MMI-induced hypothyroidism with changing the levels of fT4, T4, T3 and TSH in monkey no. 78.

Abbreviation : a, MMI 10 mg/day ; pretreatment value ($\bar{X}\pm SD$)
b, MMI 5 mg/day
c, MMI 2.5 mg/day

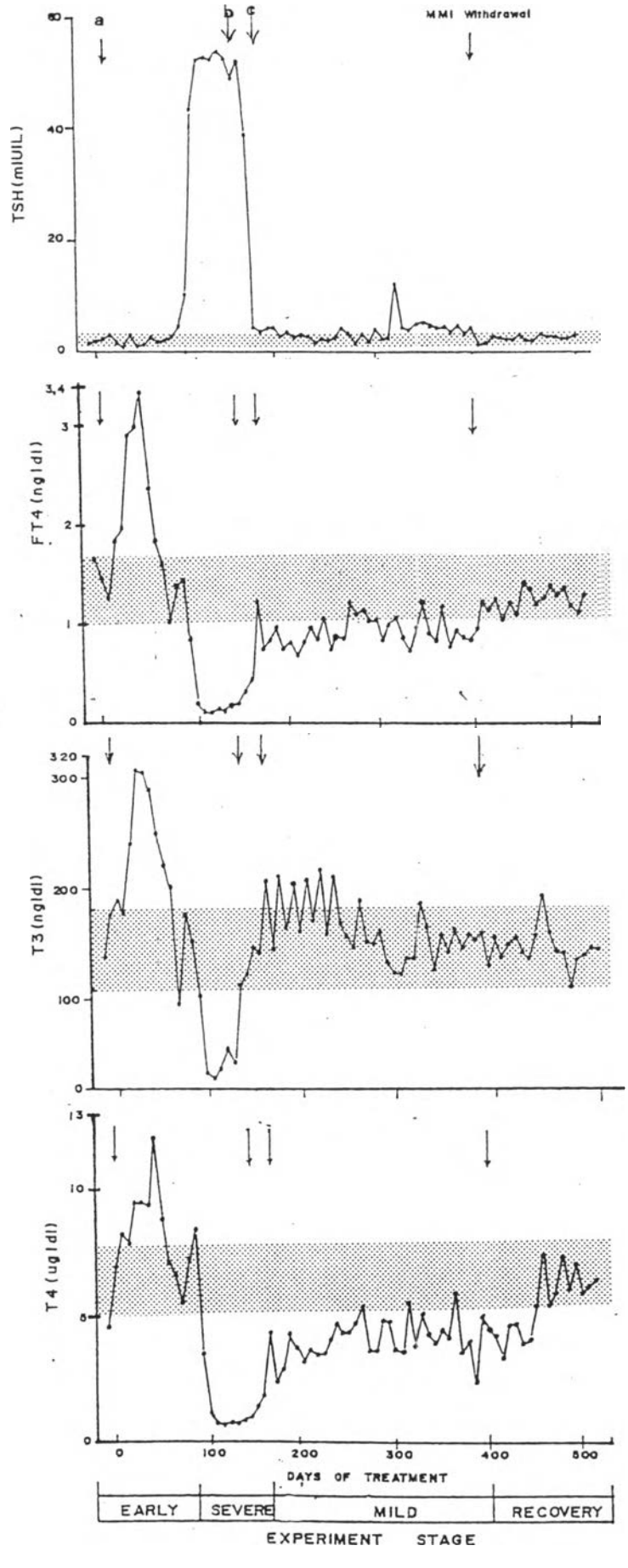

Fig 20. MMI-induced hypothyroidism with changing the levels of fT4, T4, T3 and TSH in monkey no. 87.

Abbreviation : a, MMI 10 mg/day ; pretreatment value ($\bar{X}\pm SD$)
b, MMI 5 mg/day
c, MMI 2.5 mg/day

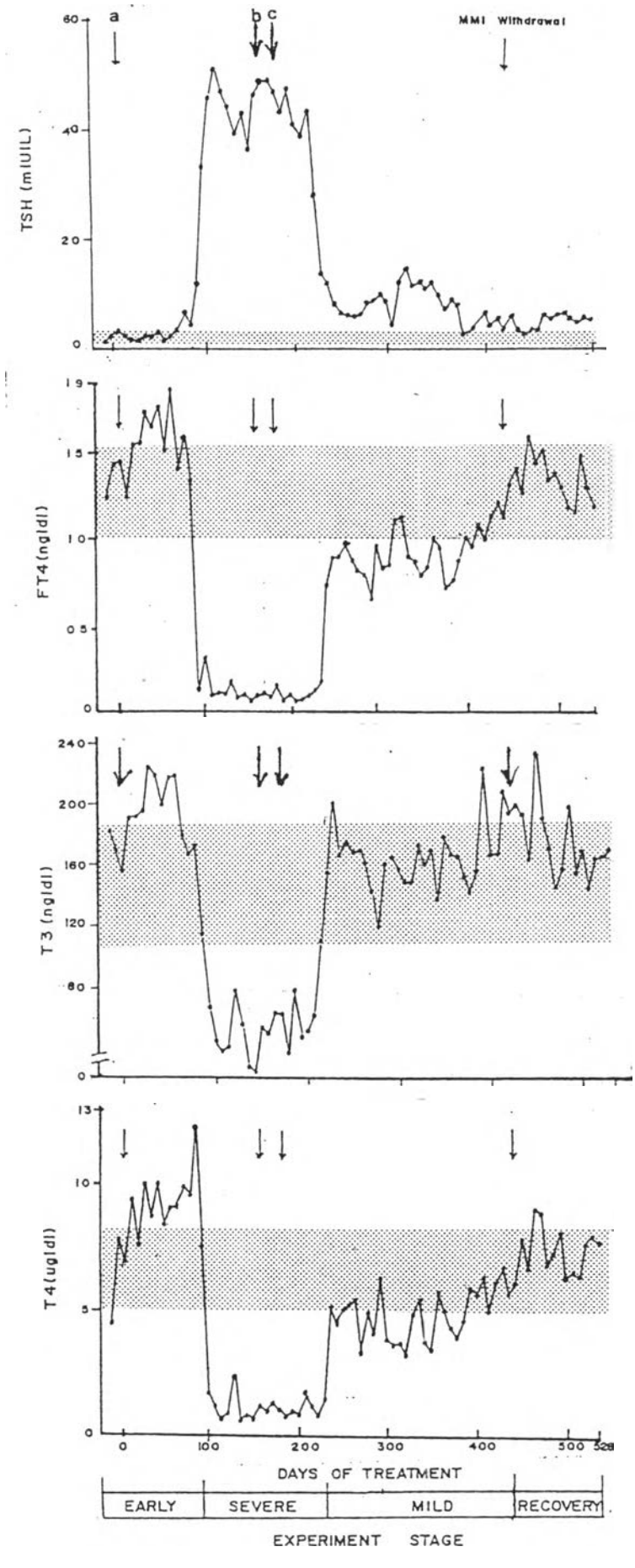

Fig 21. MMI-induced hypothyroidism with changing the levels of fT4, T4, T3 and TSH in monkey no. 77

Abbreviation : a, MMI 10 mg/day ; ▒ pretreatment value ($\bar{X}\pm SD$)
b, MMI 5 mg/day
c, MMI 2.5 mg/day

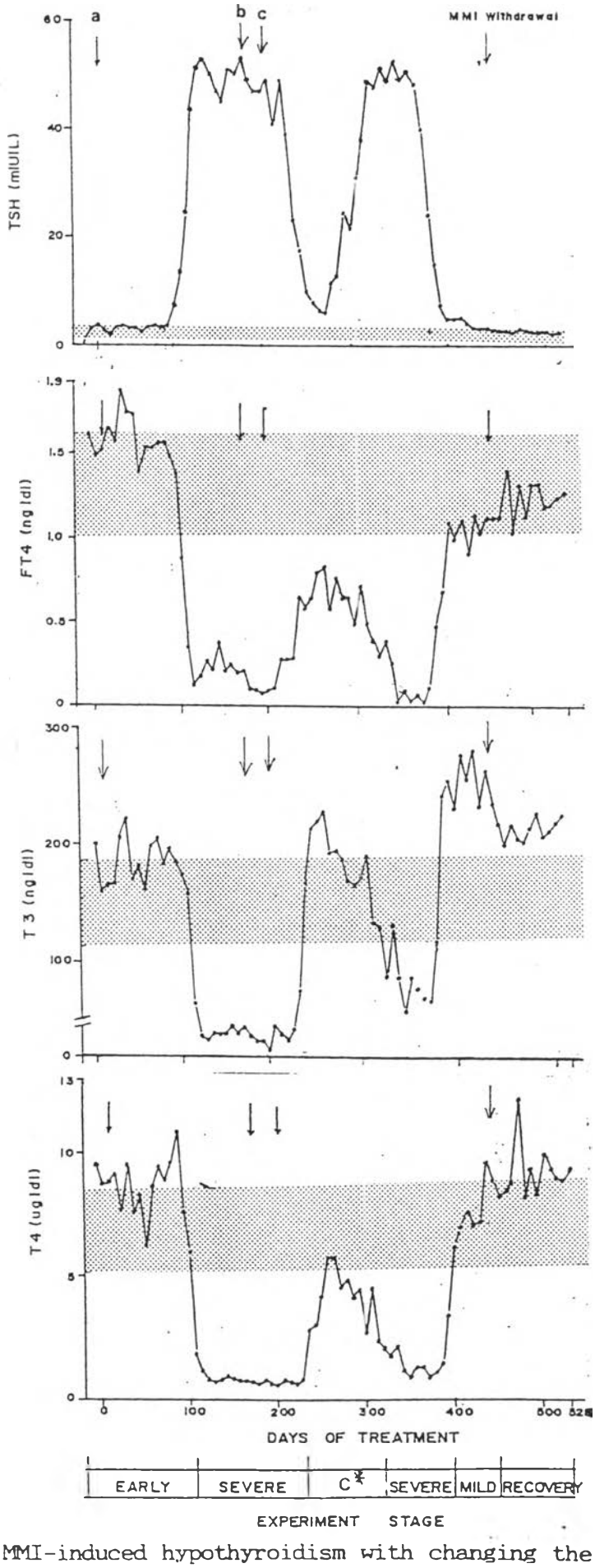

Fig 22. MMI-induced hypothyroidism with changing the levels of fT4, T4, T3 and TSH in monkey no. 101.

Abbreviation : a, MMI 10 mg/day ; ▒ pretreatment value ($\bar{X}\pm SD$)
b, MMI 5 mg/day ; C*, compensatory period
c, MMI 2.5 mg/day

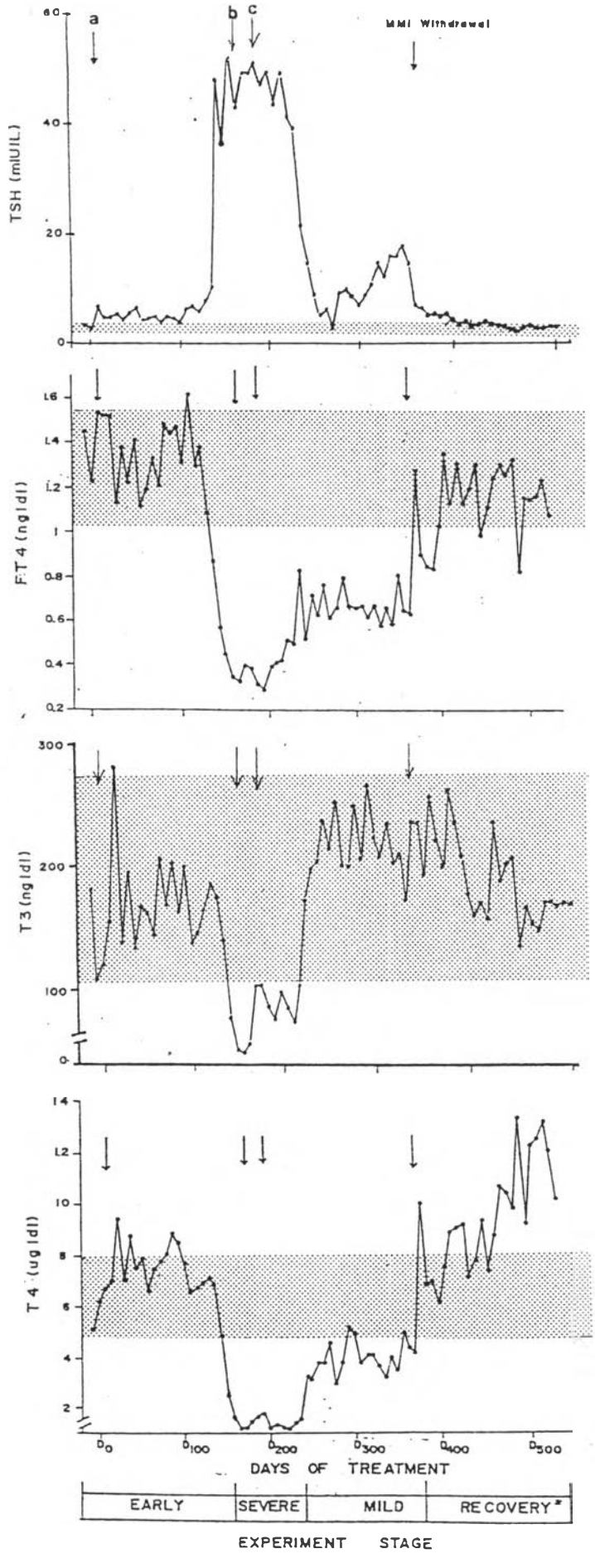

Fig 23. MMI-induced hypothyroidism with changing the levels of fT4, T4. T3 and TSH in monkey no. 63.

Abbreviation : a, MMI 10 mg/day ; ▒ pretreatment value ($\bar{X}\pm SD$)
b, MMI 5 mg/day
c, MMI 2.5 mg/day

cycle. Total twenty mating times of post treatment were exhibited in all seven monkeys. Only one successful mating of monkey no.63 was accomplished. In the clinical pictures of this recovery period, all monkeys showed euthyroidism.

3. Patterns of TSH and PRL secretion during MMI-induced hypothyroidism and drug withdrawal: Hyperprolactinemia complication during MMI treatment

Results in table 3, showed the relationship between TSH and PRL during severe and mild hypothyroidism in each monkey. During severe hypothyroidism, the serum levels of TSH and PRL in monkey no. 87 and 33 showed significant correlation ($r = 0.73$, $P < 0.05$; and $r = 0.69$, $P < 0.05$). Direct correlations of these hormones in other monkeys were also revealed but not reached the significant levels. It should be noticed that TSH and PRL levels correlated indirectly and not significantly during mild hypothyroidism.

Monkey no. 33

Serum PRL levels in this monkey showed a progressive increase corresponding with higher levels of TSH during severe hypothyroidism (fig 24). Good and significant correlation between TSH and PRL were exhibited ($r = 0.69$, $P < 0.05$). Gradual reduction of PRL levels were also coincided with reduced TSH levels in early compensatory period (fig 24). During the compensatory period, PRL ranged between 380-500 mIU/L and then dropped

suddenly to 220-250 mIU/L for 3 weeks. The serum TSH levels failed to increase during early compensatory period but rose prominently in late rebound period (fig 24) An increase in TSH peak in a short time (21 days) did not affected the levels of PRL during late compensatory period. During mild hypothyroidism, serum PRL levels increase again with more oscillation than previous levels during the compensatory period while the TSH levels diminished suddenly to the range of 2-6 mIU/L. The correlation between TSH and PRL in this period was -0.45 and not significant. After MMI withdrawal, the TSH levels promptly readjusted to the normal range of 2-4 mIU/L. Similarly, the PRL levels oscillated and readjusted to the normal pre-treatment values.

Monkey no. 25

Both PRL and TSH levels increased simultaneously from 300 to 3700 mIU/L and 2 to 60 mIU/L, respectively during severe hypothyroidism (fig 25). Direct correlation between TSH and PRL was 0.44. Similar declined patterns of both TSH and PRL levels in late severe hypothyroidism period were evidenced. TSH levels declined from 8 to 2 mIU/L, however, the PRL levels rapidly increased from 500 to 1500 mIU/L during the compensatory period. During mild hypothyroidism, TSH levels were oscillated within the range 2-12 mIU/L and showed indirect correlation with PRL ($r = -0.42$). The levels of PRL promptly oscillated to be

high (250-1400 mIU/L) during the recovery period whereas the TSH levels readjusted to the normal range of 2-4 mIU/L (fig 25).

Monkey no. 78

Early MMI treatment resulted oscillation of serum PRL levels but consistent low levels of TSH (fig 26) During severe hypothyroidism, sudden increment of serum TSH levels were exhibited and corresponded with higher PRL levels. In late period of severe hypothyroidism, both PRL and TSH levels were reduced coincidentally. Direct correlation ($r = 0.15$) between TSH and PRL levels were presented during this period (table 3). During mild hypothyroidism, PRL levels fluctuated ranging 100-600 mIU/L while the levels of TSH dropped and remained 1-8 mIU/L. Reverse relationship between PRL and TSH levels during this period was showed ($r = -0.36$). After MMI withdrawal, TSH levels declined consistently to the normal pre-treatment levels while the PRL levels were highly oscillated but trended to be low approaching normal pre-treatment values later.

Monkey no. 87

The basal values of TSH and PRL were 2.17 and 818.20 mIU/L, respectively. The serum PRL levels oscillated strongly after 10 mg/day MMI treatment (fig 27). The response to MMI treatment occurred several weeks prior to TSH increment. It was noted that greater PRL

levels were showed before the TSH levels trended to be high (3-10 mIU/L). Good correlation between TSH and PRL was evidenced ($r = 0.73$, $P < 0.05$) (table 3) during severe hypothyroidism. It was noteworthy that the PRL levels dropped prominently at first during early mild hypothyroidism and then increased continuously in late mild hypothyroidism. Lower TSH levels were exhibited during the early mild hypothyroidism but tended to be high and showed sporadic increment during late mild hypothyroidism. Correlation between TSH and PRL was evidenced ($r = -0.33$) during this period (table 3). During MMI withdrawal, the PRL levels tended toward low whereas serum TSH levels readjusted to be normal as the pre-treatment value.

Monkey no. 77

As presented in fig 28, the peripheral serum PRL levels increased strikingly corresponding with higher TSH levels during severe hypothyroidism. The correlation coefficient of both hormones was 0.39 and did not achieve significant level. In late severe hypothyroidism period, TSH levels reduced sharply concomitantly with profound decrease in PRL levels. During mild hypothyroidism, TSH levels fluctuated within the range of 4-15 mIU/L and tended to be in the normal range in later (fig 28). Serum PRL levels oscillated strongly ranging between 100-600 mIU/L. Negative correlation between TSH and PRL was

showed (r = -0.09) during this period. During MMI withdrawal period, the levels of TSH ranged 3-7 mIU/L whereas PRL levels were more fluctuated ranging 80-450 mIU/L.

Monkey no. 101

Fluctuations of PRL levels exhibited several weeks prior to abrupt increment of TSH levels during early MMI treatment period as shown in fig 29. During both periods of severe hypothyroidism, serum levels of TSH and PRL increased concomitantly and were showed positive correlation (r = 0.37). Moreover, the TSH levels declined following by PRL levels during the compensatory period. Subsequently, only TSH levels reduced gradually during mild hypothyroidism period while the PRL levels still oscillated. Negative correlation of both hormone was -0.08. During the recoveery period, the levels of TSH lowered consistently and reached the normal value but serum PRL levels still more fluctuated ranging 100-400 mIU/L.

Monkey no. 63

Strong fluctuations of serum PRL levels (200-1000 mIU/L) were exhibited and in accorded with slight increase in TSH levels (3.5 - 10 mIU/L) during the early treatment of MMI as represented in fig 30. Moreover, the similar increased patterns of both hormones were exhibited during severe hypothyroidism with direct but not significant

correlation (r = 0.22) (table 3). Negative correlation of both hormones was showed (r = -0.18) during mild hypothyroidism. After MMI withdrawal on the first menstrual bleeding cycle, the monkey was mated with a fertile male and had successful pregnancy with 158 day gestation. During pregnancy, the levels of TSH gradually decreased and readjusted within normal range (3-6 mIU/L), on the other hand, the serum PRL levels extremely increased until term.

3.1 The relationship between TSH and PRL levels during each state of hypothyroidism in 7 monkeys

The correlations between TSH and PRL levels during each state of hypothyroidism in all 7 monkeys were summarized in table 4. During severe hypothyroidism, the concentration of TSH and PRL were correlated and reached significant level ($r = 0.30$, $P < 0.01$). It was evidenced that higher TSH levels were corresponded with greater PRL levels. Otherwise, negative and significant correlation between TSH and PRL was -0.21 ($P < 0.05$) during mild hypothyroidism. Also, the correlation of both hormones was -0.15 and not reached significance during MMI-withdrawal period.

In conclusion, only one monkey (no. 87) had greater PRL levels serveral weeks prior to the expected increase in TSH levels generally seen with of severe hypothyroidism. Most monkeys also exhibited galactorrhea

throughout period of treatment. Similar patterns of increase in TSH corresponding with higher PRL levels were found in all monkeys during severe hypothyroidism. But moderate levels of TSH (4-19 mIU/L) were exhibited whereas the PRL fluctuated and tended toward high during mild hypothyroidism. Furtheremore, TSH levels tended to be lowered (2-6 mIU/L) after MMI withdrawal within at least one week, while the PRL levels still more fluctuated at the same time.

4. Study the effect of various different states of MMI-induced hypothyriodism on serum profiles of E_2 and P.

The effects of various different states of hypothyroidism on serum profiles of E_2 and P were divided into 2 parts of treatment as following:

1. Early treatment phase:

The patterns of both E_2 and P were studied weekly after administration of MMI 10 mg/day following the dose of 5 mg/day and 2.5 mg/day for maintenance the severe hypothyroidism and reaching the mild hypothyriodism thereafter. Weekly patterns of E_2 and P were studied prior to and during period of severe hypothyriodism.

2. Late treatment phase:

The patterns of E_2 and P were studied on D5,D8,D9,D10,D11,D12,D13,D14,D16,D18,D21,D25,D29, and D34

Table **3** . The relationship between TSH and PRL in the state of severe and mild hypothyroidism in each monkey.

No.	Severe hypothyroidism TSH vs PRL	Mild hypothyroidism TSH vs PRL
# 87	0.73* (n=9)	-0.33 (n=32)
#77	0.39 (n=19)	-0.09 (n=21)
#25	0.44 (n=18)	-0.42 (n=17)
#78	0.15 (n=8)	-0.36 (n=24)
#33	0.69* (n=10)	-0.45 (n=13)
#63	0.22 (n=12)	-0.18 (n=17)
#101	0.37 (n=27)	-0.08 (n=7)

Abbreviation: *, $p<0.05$

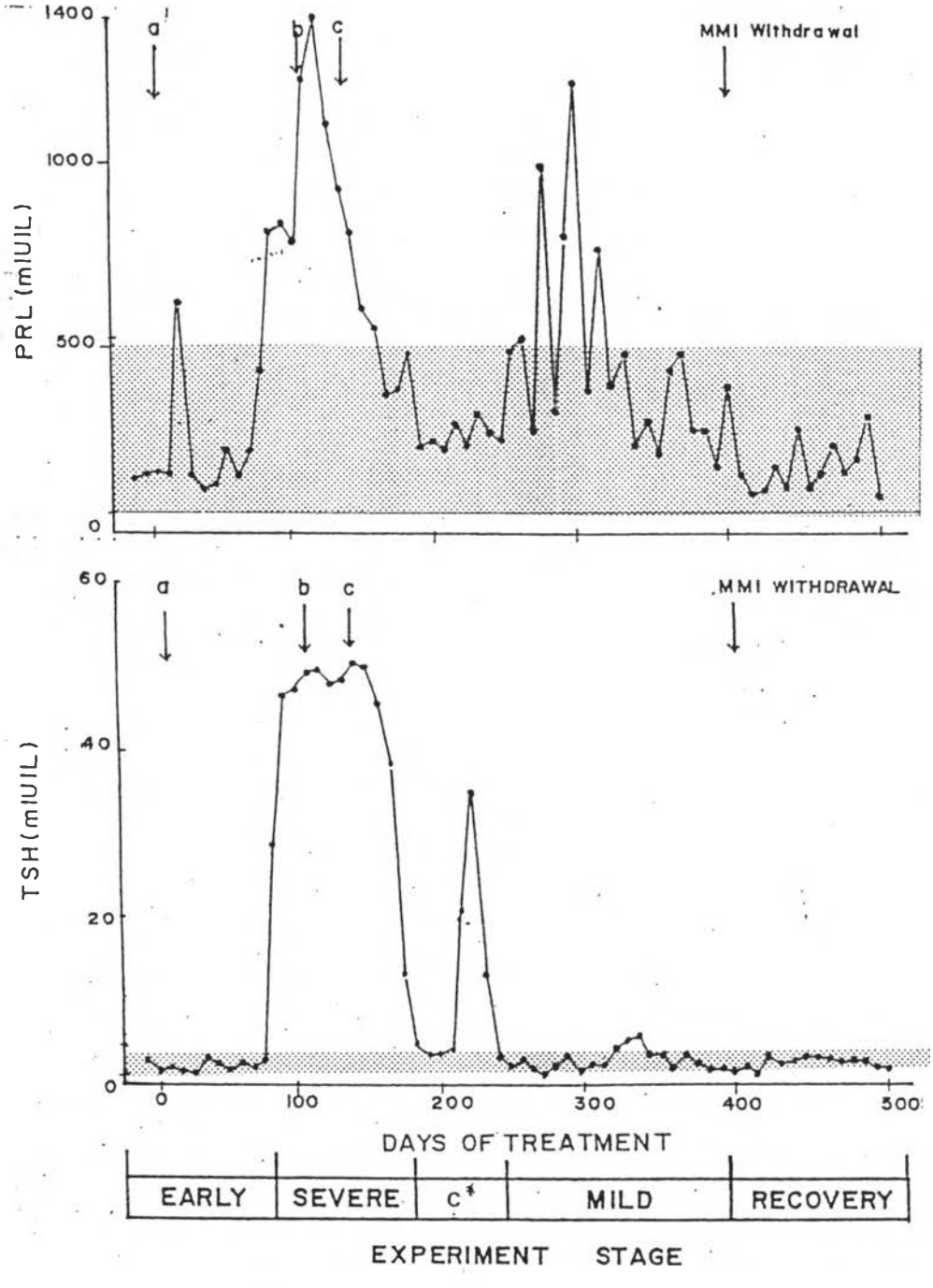

Fig 24. The profiles of serum TSH and PRL during each state of MMI-induced hypothyroidism in monkey no.33.

Abbreviation : a, MMI 10 mg/day ; ▒ pretreatment value ($\bar{X}\pm SD$)
b, MMI 5 mg/day ; C*, compensatory period
c, MMI 2.5 mg/day

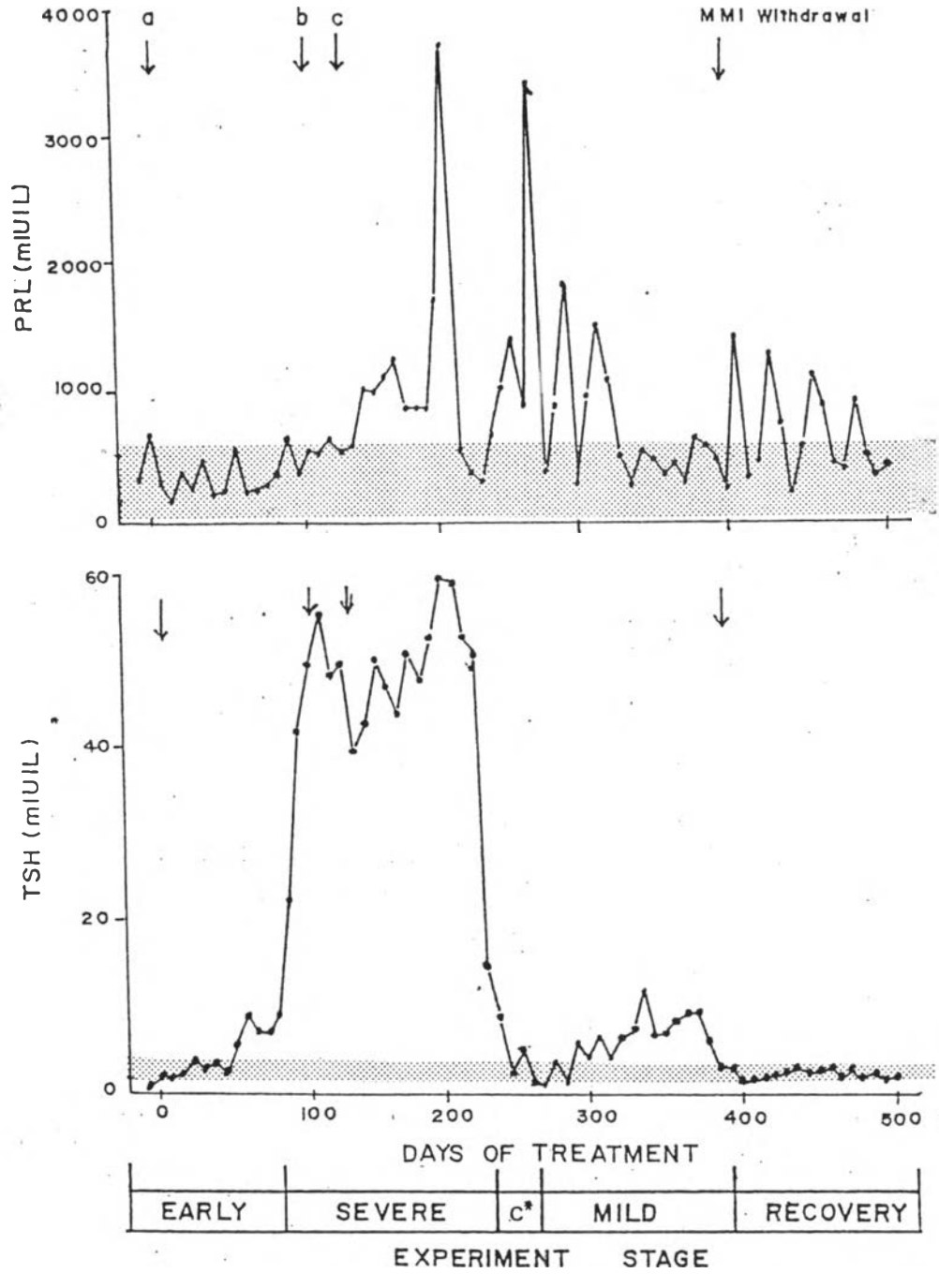

Fig 25. The profiles of serum TSH and PRL during each state of MMI-induced hypothyroidism in monkey no.25.

Abbreviation : a, MMI 10 mg/day ; pretreatment value ($\bar{X}\pm SD$)
b, MMI 5 mg/day ; C*, compensatory period
c, MMI 2.5 mg/day

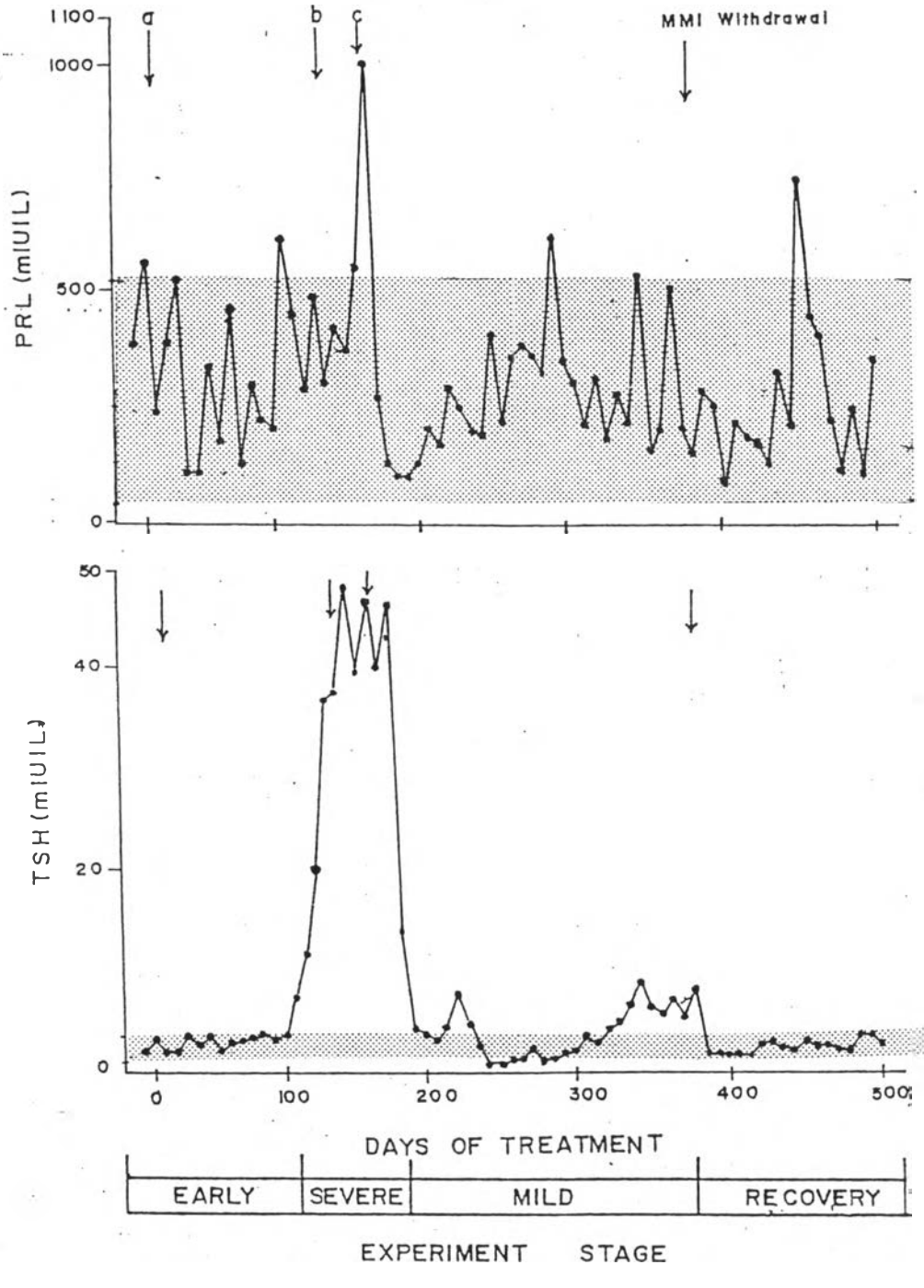

Fig 26. The profiles of serum TSH and PRL during each state of MMI-induced hypothroidism in monkey no.78.

Abbreviation : a, MMI 10 mg/day ; ▒ pretreatment value ($\bar{X}\pm SD$)
b, MMI 5 mg/day
c, MMI 2.5 mg/day

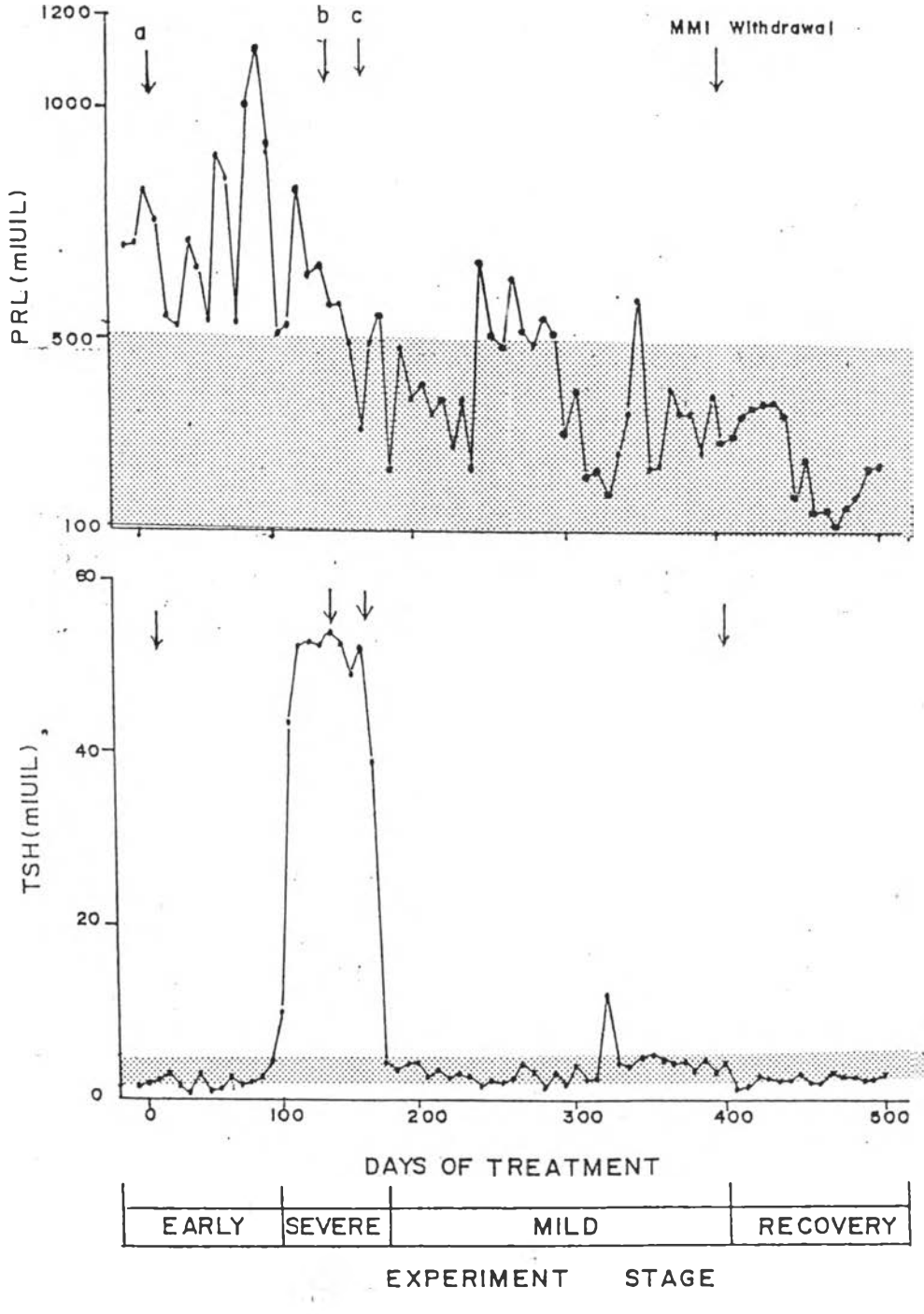

Fig 27. The profiles of serum TSH amd PRL during each state of MMI-induced hypothyroidism in monkey no. 87.

Abbreviation : a, MMI 10 mg/day ; pretreatment value ($\bar{X}\pm SD$)
b, MMI 5 mg/day
c, MMI 2.5 mg/day

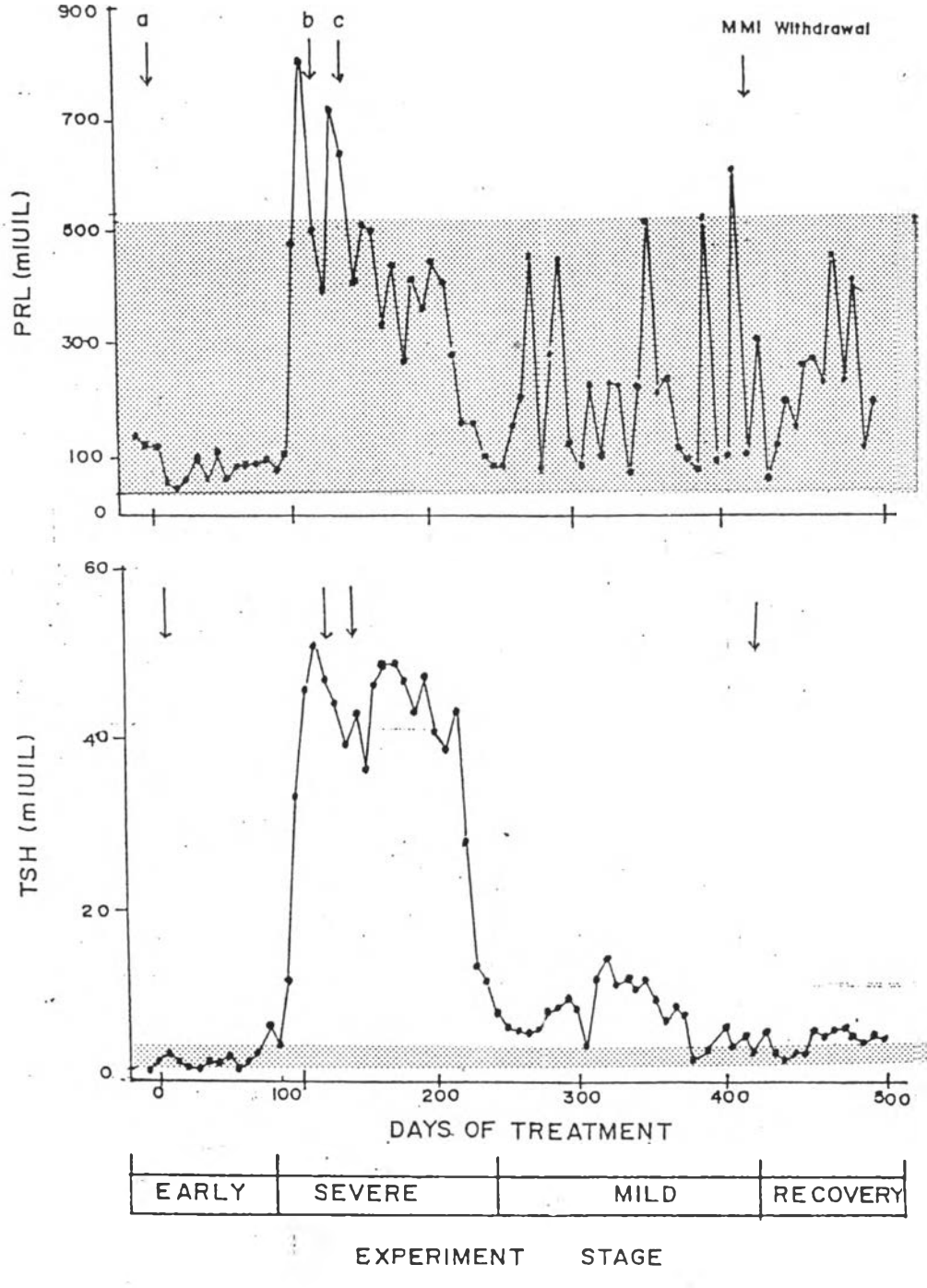

Fig 28. The profiles of serum TSH and PRL during each state of MMI-induced hypothyroidism in monkey no. 77.

Abbreviation : a, MMI 10 mg/day ; pretreatment value ($\bar{X}\pm SD$)
b, MMI 5 mg/day
c, MMI 2.5 mg/day

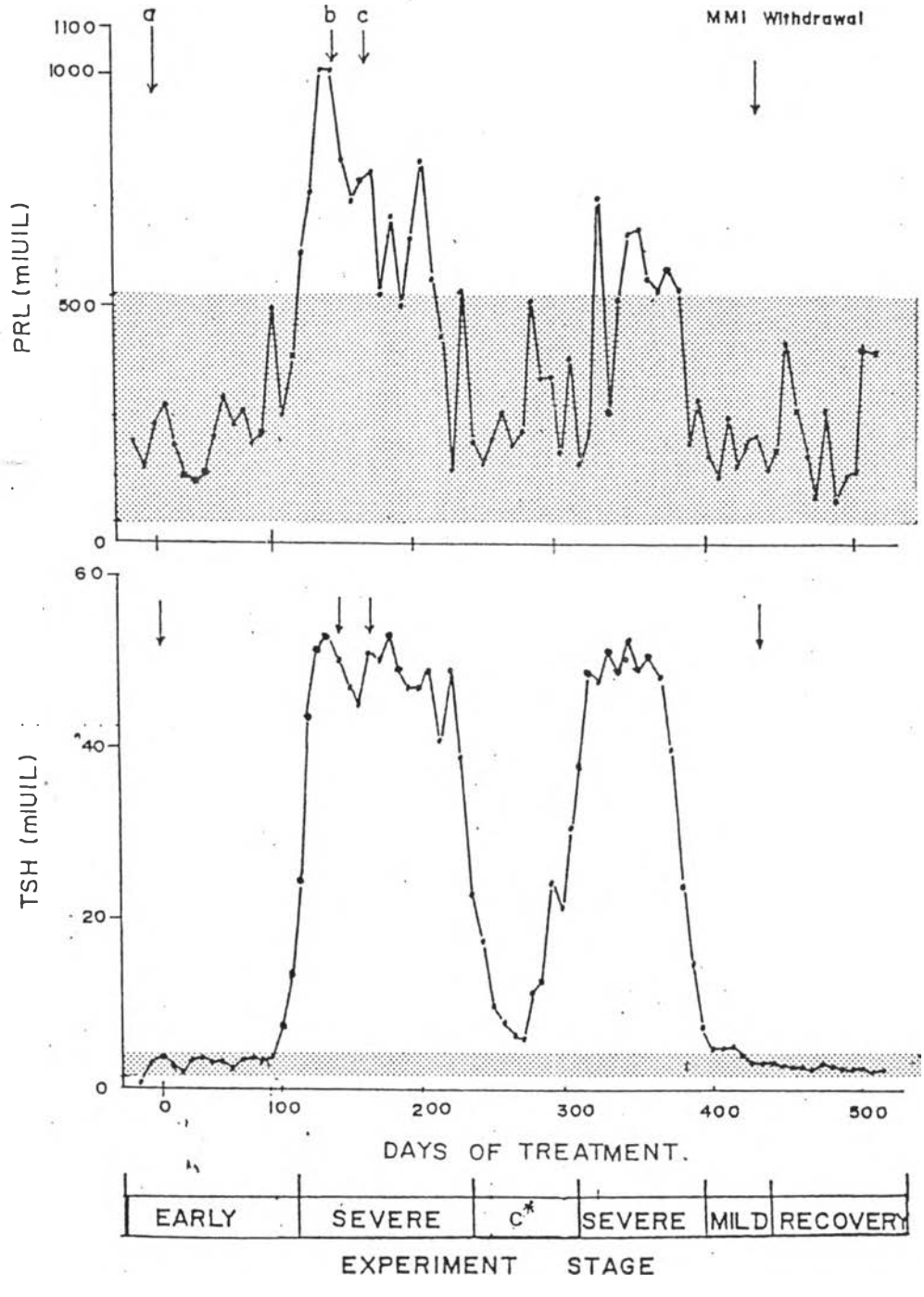

Fig 29. The profiles of serum TSH and PRL during each state of MMI-induced hypothyroidism in monkey no.101.

Abbreviation : a, MMI 10 mg/day ; pretreatment value ($\bar{X}\pm SD$)
b, MMI 5 mg/day ; C*, compensatory period
c, MMI 2.5 mg/day

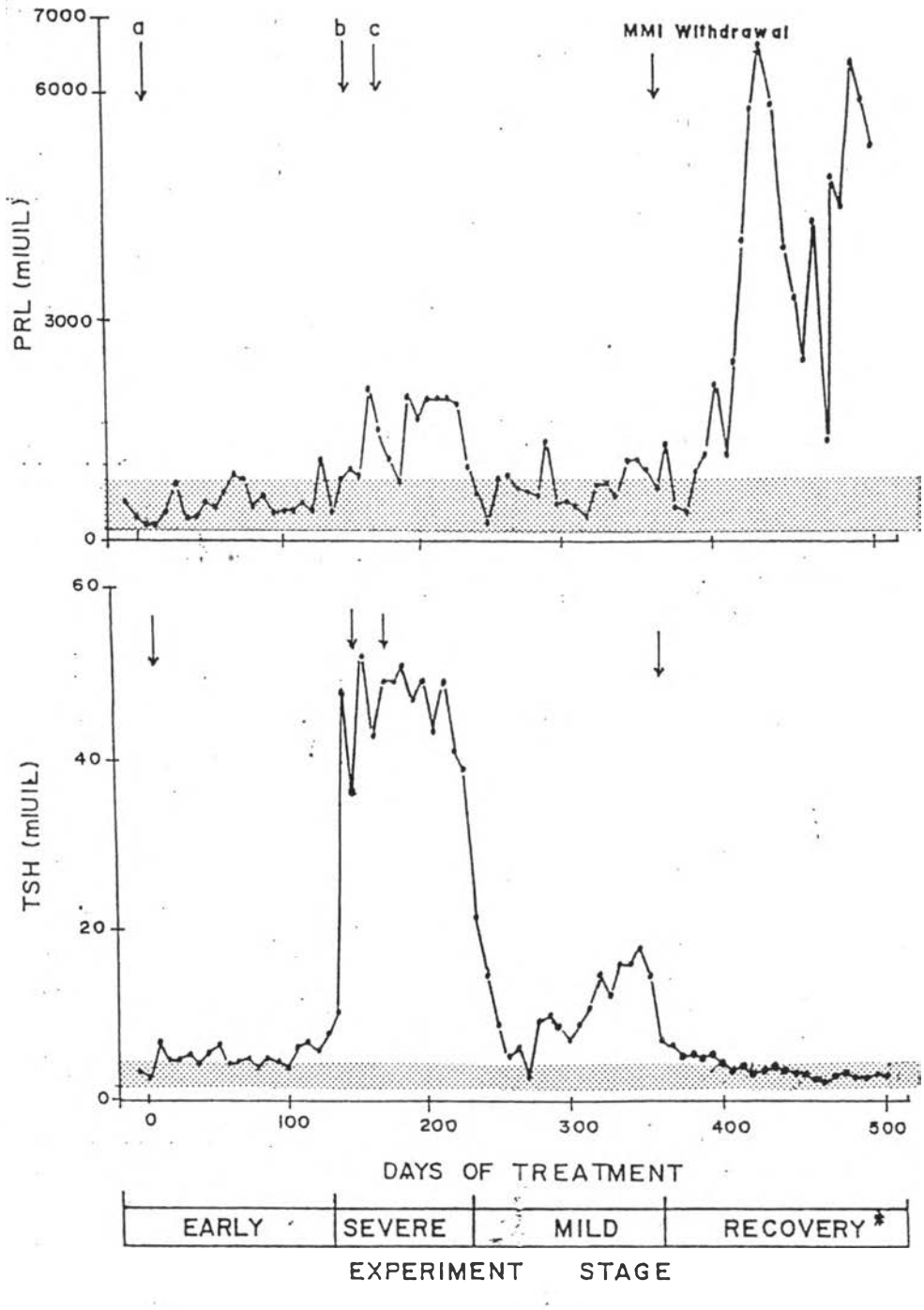

Fig 30. The profiles of serum TSH and PRL during each state of MMI-induced hypothyroidism in monkey no. 63.

Abbreviation : a, MMI 10 mg/day ; ▒ pretreatment value ($\bar{X}\pm SD$)
b, MMI 5 mg/day
c, MMI 2.5 mg/day

Table 4. The relationships between TSH and PRL in each state of hypothyroidism in seven monkeys.

State of hypothyroidism	TSH vs PRL
Severe state (n=102)	0.30^{**}
Mild state (n=130)	-0.21^{*}
Recovery state (n=92)	-0.15 NS

Abbreviation: *, $p<0.05$; **, $p< 0.01$; NS, Non-significant.

of cycle during this late treatment phase including the compensatory period, mild hypothyroidism and MMI-withdrawal states. All data were summarized in table 5.

Monkey no.33:

During early treatment of MMI, the fT4 concentrations decreased gradually for one week treatment showing rapid response while higher level of P (1.2 ng/ml) was detected on D17 after the E_2 level of 92.3 pg/ml on D10 of the 24 day cycle (fig.33). Small fluctuations of E_2 (67.50-83.20 pg/ml) were exhibited and not followed by greater P levels during the 20 day cycle.During the long cycle of 59 days in the severe hypothyroidism state, both E_2 and P levels were lessened thereafter. While the fT4 concentrations were readjusted, the levels, the serum levels of E_2 increased to be 186.90 pg/ml and followed by higher level of P(12.60 ng/ml on D34) of the 40 day cycle after the 15 day short bleeding. During the 28 day cycle, E_2 peaked to be 200.30 pg/ml on D11 and accompanied by 5.53 ng/ml of P level on D16 of cycle whereas the fT4 levels gradually reduced and readjusted to reach the state of mild hypothyriodism. Four irregular bleeding cycles containing 28, 29, 34 and 54 days were also recorded during mild hypothyroidism and showing the peaks of E_2 ranging 167.33-303.42 pg/ml corresponding with peaks of P (3.05-14.98 ng/ml) in the follicular and luteal phases of cycles,respectively. During MMI withdrawal state, four

bleeding cycles of 23,46,28, and 34 days were observed. Serum E_2 peaks were determined as 207.50, 70.00, 216.50, and 155.80 pg/ml on D5,D11,D10, and D10 of the 23,46,28, and 34 day cycles, respectively. Meanwhile, four peaks of serum P were 7.90, 2.34, 2.70 and 2.13 ng/ml on D17,D22,D16, and D29 of these cycles.

As presented in fig.32, the composition patterns of circulating levels of LH, E_2, and P in only the 34 day cycle during mild hypothyroidism in this monkey were showed and focused on the example of detecting ovulation. It was observed that the highest level of LH was 398.20 ng/ml on D18 which evidenced one day after E_2 peak (207.60 pg/ml) . After mid cycle, the progesterone levels followed a monophasic pattern reaching maximal (14.98 ng/ml) value on D29 of cycle whereas the levels of E_2 were low in late mid cycle and lower during luteal phase of the cycle.

Monkey no. 25:

The monkey had several short bleeding cycles during early treatment period (fig.33). Small rise in P level (1.70 ng/ml)and undetected E_2 greater than 100 pg/ml were found in the first 27 day cycle. Similar levels of E_2 were detected in the second 20 day cycle but P levels were smaller than those in the first cycle. Further reduction of P and E_2 levels were found in the third 14 day cycle. However, the animal readjusted obtaining higher levels of both E_2 (>140.00 pg/ml) and P (>2.00 ng/ml) in

the fourth 36 day cycle. Although, serum fT4 levels ranged 0.21-0.53 ng/dl. These were followed by prolonged 150 day bleeding cycle during severe hypothyroidism state. Peaks of E_2 and P were detected and synchronized each other during the latter part of the cycle (118.30 pg/ml on D227 and 4.50 ng/ml on D241 of treatment, respectively). This incidence was associated with compensatory of fT4 after prolonged severe hypothyroidism state. During mild hypothyroidism and MMI-withdrawal states, the monkey readjusted obtaining very precise onset of menstrual bleeding cycles (27-31 days) with definite peaks of E_2 synchronizing with high P levels during the luteal phase Peak levels of E_2 during mild hypothyroidism and MMI-withdrawal states ranged from 314.10-345.30 pg/ml and 327.10-480.80 pg/ml respectively. Also, the P peaks were 4.50-8.84 ng/ml and 2.26-8.33 ng/ml during mild hypothyroidism and MMI-withdrawal states. Meanwhile, fT4 levels were found to increase reaching the normal value within 1-2 weeks of complete MMI withdrawal.

Monkey no. 78:

As shown in fig. 34, two menstrual bleeding cycles (34 and 45 days) with detected greater P (9.22 and 19.20 ng/ml) peaks in luteal phase were exhibited. Althouh, the higher E_2 levels during the expected follicular phase were 94.16 and 128.06 ng/ml in 34 and 45 day cycles, respectively. The ovulation with higher E_2 and P levels in follicular and luteal phases was not determined during

severe hypothyroidism. During mild hypothyroidism, it was noted that the E_2 levels rose together with increase in fT4 levels and showed to be 117.80 pg/ml. Further increase in serum E_2 (138.60 pg/ml) and P (5.60 ng/ml) was determined during late 158 day cycle. During mild hypothyroidism state, E_2 peaks of the 35,35,22, and 29 day cycles were 171.80, 333.40, 259.30 and 285.51 pg/ml, respectively corresponding with greater P levels (14.24, 7.40, 3.88 and 10.72 ng/ml) in luteal phases. Moreover, serum E_2 peaks ranging 135.74-259.04 pg/ml following by higher P serum ranging 6.90-11.55 ng/ml in follicular and luteal phases of the 28,35,28, and 29 day cycles during MMI withdrawal period.

Monkey no. 87

An early treatment, three bleeding cycles consisting of 24,78 and 40 days were exhibited (fig. 35). Only the 24 day cycle, greater P level (1.20 ng/ml) was detected eventhough E_2 level was 73.70 pg/ml in expected the luteal and follicular phases. Thereafter, it was noted that serum levels of P were lowered until D168 of treatment. During the 78 and 40 day cycles, serum E_2 levels fluctuated (30.00-64.40 pg/ml) with lower P levels and corresponded with wide range of fT4 (0.1-3.2 ng/ml). During severe hypothyroidism, the lowest serum levels of E_2 and P were evidenced. Four irregular bleeding cycles consisting of 45,97,30, and 34 day cycles during mild

hypothyroidism as well as one bleeding cycle during MMI-withdrawal periods were also observed. High peak of E_2 (284.58 pg/ml on D29) which followed by greater P level (1.90 ng/ml) were determined during the 45 day cycle while the fT4 concentrations ranged between 0.80-1.30 ng/dl. Interesting, prolonged bleeding cycle with 97 days was found and exhibited the oscillation of E_2 (30-90 pg/ml) and lower P which the fT4 levels ranged 0.80-1.10 ng/dl. But further greater E_2 peaks (167.30 pg/ml on D14 and 188.13 pg/ml on D18) of the 30 and 34 day cycles were recorded with synchronized peaks of P (2.07 ng/ml on D20 and 1.89 ng/ml on D25) in the luteal phase. Thereafter, attempting increase in serum levels of E_2 was revealed as 110.72, 95.90, and 131.80 pg/ml on D8,D10, and D18 whereas the accompanied levels of P were detected only 0.80-0.90 ng/ml on D19 and D21 of prolonged 108 day cycle. In this transitional period, MMI was withdrawn and then both levels of E_2 and P were also lowered than those in the previous cycle; eventhough; the fT4 concentrations increased again to achieve the new plateau level. Peak of E_2 (153.71 pg/ml on D92 of the 108 day cycle) was exhibited with unsufficiented greater P values. During the last 45 day cycle, the E_2 peak was showed to be 106.07 pg/ml on D14 ;269.20 pg/ml on D29 and 258.84 pg/ml on D30 These were compatibled consequently with greater P level (1.99 ng/ml) on D37 of cycle.

Monkey no.77:

As shown in fig.36, three bleeding cycles of 29,36, and 38 days were revealed with increase in greater P levels (2.00,2.44, and 7.20 ng/ml on D22,D23, and D29, respectively) in expected luteal phase during early treatment with MMI 10 mg/day. The E_2 levels were ranged from 70-120 pg/ml on D9,D16 and D17 of each consecutive cycle. During severe hypothyroidism, profound reduction of both E_2 and P levels were showed. During the early period of mild hypothyroidism, it was noted that the raised E_2 levels (100.00 pg/ml) and then accompanied by higher levels of P 5.20-5.94 ng/ml within 14 day was exhibited. Precised normal menstraul bleedings ranging 30-33 day cycles of five consecutive bleedings containing 31,31,33,32, and 30 days were observed. Peaks of E_2 were ranged between 131.00-481.13 pg/ml and followed by greater P levels ranging 2.00-25.24 ng/ml of these bleeding cycles during mild hypothyroidism. Furthermore, E_2 levels peaked ranging 147.00-446.80 pg /ml with synchronized luteal greater P levels ranging 7.20-8.11 ng/ml were determined during MMI withdrawal period.

Monkey no. 101:

During early treatment, three detecting greater P levels of 1.86,6.02 and 3.41 ng/ml in the expected luteal phases of the 34,58 and 32 day cycle were exhibited and in accored with E_2 levels (120.00,189.50 and 157.20 pg/ml,

respectively) in the expected follicular phases (fig. 37). Lower levels of both E_2 and P were observed during severe hypothyroidism. But E_2 levels of 134.30-364.31 pg /ml following by luteal greater P levels ranging 2.72-11.60 ng/ml during prolonged compensatory period containing the 34,28,31 day cycle were detected. Further decrease in both E_2 and P levels during second severe hypothyroidism were also revealed and similar to the first severe hypothyriodism state fashion. Irregular bleeding during this period was also showed with lower E_2 and P levels. The spontaneous increase in fT4 (1.10-1.20 ng/ml) for 80 days was showed following the greater E_2 (160.54 pg/ml) and P(5.81 ng/ml) on D9 and D23 of the 26 day cycle,respectively. During post MMI treatment period, E_2 peaks were ranged between 235.99-334.20 pg/ml and followed by P peaks ranging 5.20-19.10 ng/ml of the 29,33 and 26 day cycles.

Monkey no. 63:

As represented in fig. 38, only one the 26 day bleeding cycle with E_2 and P peaks (229.80 pg/ml on D10 and 3.30 ng/ml on D17) of cycle was evidenced. Thereafter, the levels of E_2 were more fluctuated but the P levels still lowered during early treatment with MMI 10 mg/day. However, the fT4 concentrations at this time were fluctuated and ranged 1.20-1.50 ng/dl. During severe hypothyroidism, both lower E_2 and P levels were appeared.

Subsequently, the concentrations of E_2 were increased (120.00 pg/ml) and then followed by greater P level (18.20 ng/ml) within 7 days after increased E_2 during the compensatory period. During mild hypothyroidism, normal bleeding cycles consiting of 27,26 and 28 days were presented showing E_2 peaks ranging 282.50-391.20 pg/ml on D11-D12 of cycles. Peripheral serum P peaked showing 9.30,10.60 and 11.84 ng/ml on D18,D21 and D21 of these cycles. After MMI withdrawal, the animal became pregnancy after sucessful mating with fertile male monkey on D11-D14 of cycle showing higher E_2 level (253.70 pg/ml). Serum levels of E_2 and P during pregnancy were represented and described in detail in the further section of pregnancy.

Conclusion

1. During early treatment, two characteristic patterns of decrease in fT4 levels were exhibited: firstly, the rapid response to MMI suppression and secondly, the slow response to MMI suppression. These characteristic patterns of responsive fT4 influenced upon the profile of E_2 and P.

1.1. The rapid response.

During the rapid response of fT4 to MMI suppression in monkey no. 33, both E_2 and P levels tended toward low in accorded with lower fT4 concentrations. The lowest E_2 levels were showed whereas P levels were fluctuated markedly during severe hypothyroidism state.

1.2. The slow response

Since the slow response of fT4 to MMI suppression as evidenced in the monkey no. 25,78,77,87,101, and 63, both E_2 and P levels were exhibited their higher concentrations indicating ovulation and detected in the expected follicular and luteal phases of cycles. It was interesting that two types of profiled E_2 and P patterns were also found in this slow response period of fT4 to MMI suppression. Firstly, the complete suppression of P levels with still fluctuated E_2 levels (ie. monkey no. 63 and 87). Secondly, an ovulation having both determined greater E_2 and P peaks in the follicular and luteal phases of cycles (monkey no.25,77 and 101). At this time,the gradually striking decrease in fT4 levels were evidenced.

2. Amenorrhea associated with prolonged cycle were always found during severe hypothyroidism.

3. During the compensatory period recovering from severe hypothyroidism, gradual increase in fT4 always accompanied by attempting rise in E_2 levels firstly and followed by greater P levels.

4. An ovulation was always detected during both in the mild hypothyroidism and in MMI-withdrawal states.

1. TBG profile patterns during MMI-induced hypothyroidism and MMI-withdrawal peroid.

Table 5. Showing duration and menstrual cycle period of each experimental monkey in pretreatment, during treatment and post-treatment of MMI-induced hypothyroidism

Monkey No. / Cycle	Bleeding cycle length (days)													
	Pre-treatment		treatment									Post-treatment			
	1	2	1	2	3	4	5	6	7	8	9	1	2	3	4
# 33	35(10)	31(6)	24(7)	* 20(5)	* 59(5)	* 15(5)	40(6)	28(5)	29(5)	34(4)	54(4)	23(5)	46(3)	28(5)	34(3)
# 25	27(6)	27(3)	27(2)	* 20(3)	* 14(2)	* 36(4)	b 150(3)	29(4)	30(3)	29(3)	30(3)	28(4)	27(3)	31(3)	28(3)
# 78	28(4)	27(5)	34(3)	45(3)	b 158(7)	35(4)	35(4)	22(3)	29(4)	-	-	28(5)	35(3)	28(3)	29(4)
# 87	33(7)	26(5)	25(4)	24(4)	* 78(10)	* 40(3)	45(4)	b 97(4)	30(3)	34(6)	a 108(4)	45(4)	-	-	-
# 77	35(3)	35(4)	29(4)	36(3)	38(4)	b 164(4)	31(3)	31(3)	33(4)	32(4)	30(4)	37(2)	36(3)	36(4)	-
# 101	34(4)	35(2)	34(3)	58(4)	32(4)	b 148(5)	34(1)	28(3)	31(3)	53(3)	-	29(3)	33(3)	26(3)	-
# 63	27(5)	28(4)	26(5)	b 248(4)	27(3)	26(3)	28(4)	-	-	-	-	Pregnancy			

Abbreviations : ( ) , duration of bleeding ; b , prolonged cycle
* , anovulatory cycle
a , transitional period between treatment and post-treatment period

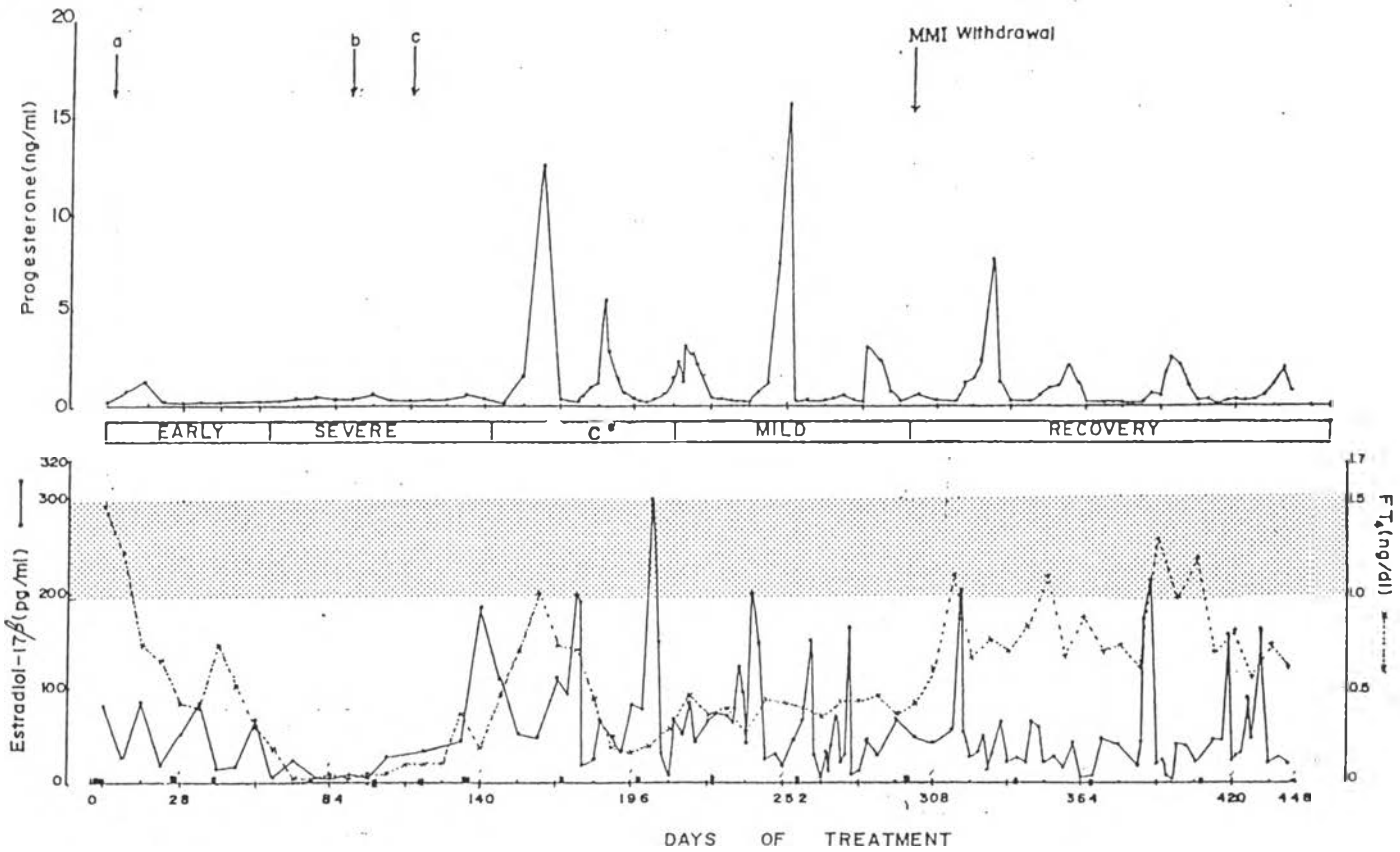

Fig 31. The profiles of serum E_2, P and fT4 during early MMI treatment, late MMI treatment and after MMI withdrawal in monkey no. 33.

Abbreviation : a, MMI 10 mg/day ; b, MMI 5 mg/day ; c, MMI 2.5 mg/day

fT4 pretreatment value (X±SD)

menstrual bleeding

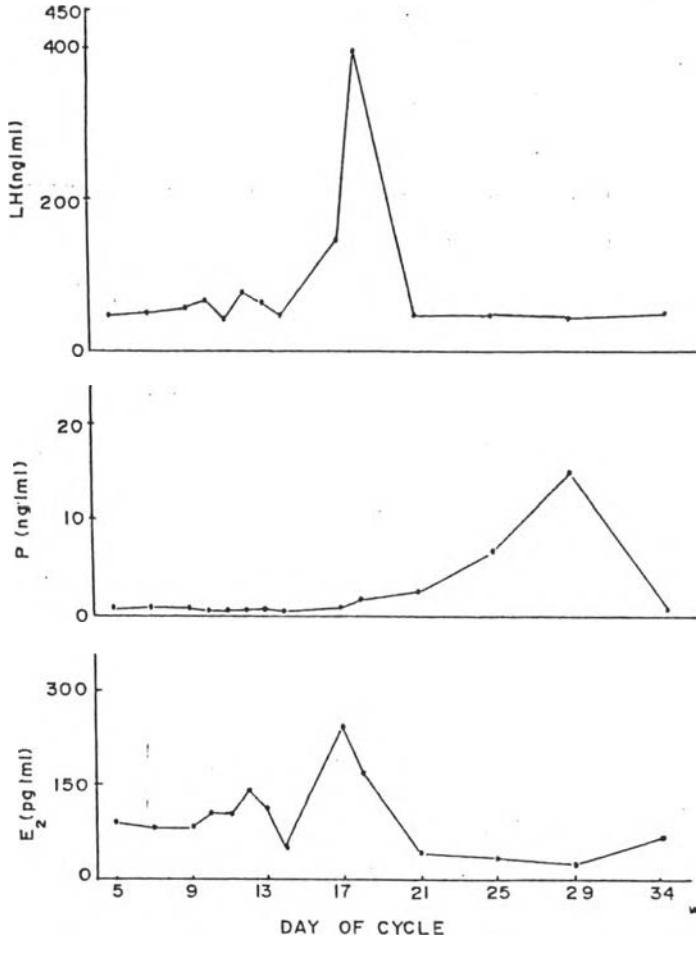

Fig 32. Composition pattern of circulating levels of serum LH, E_2 , P in the 34 day cycle of mild hypothyroidism state in monkey no. 33.

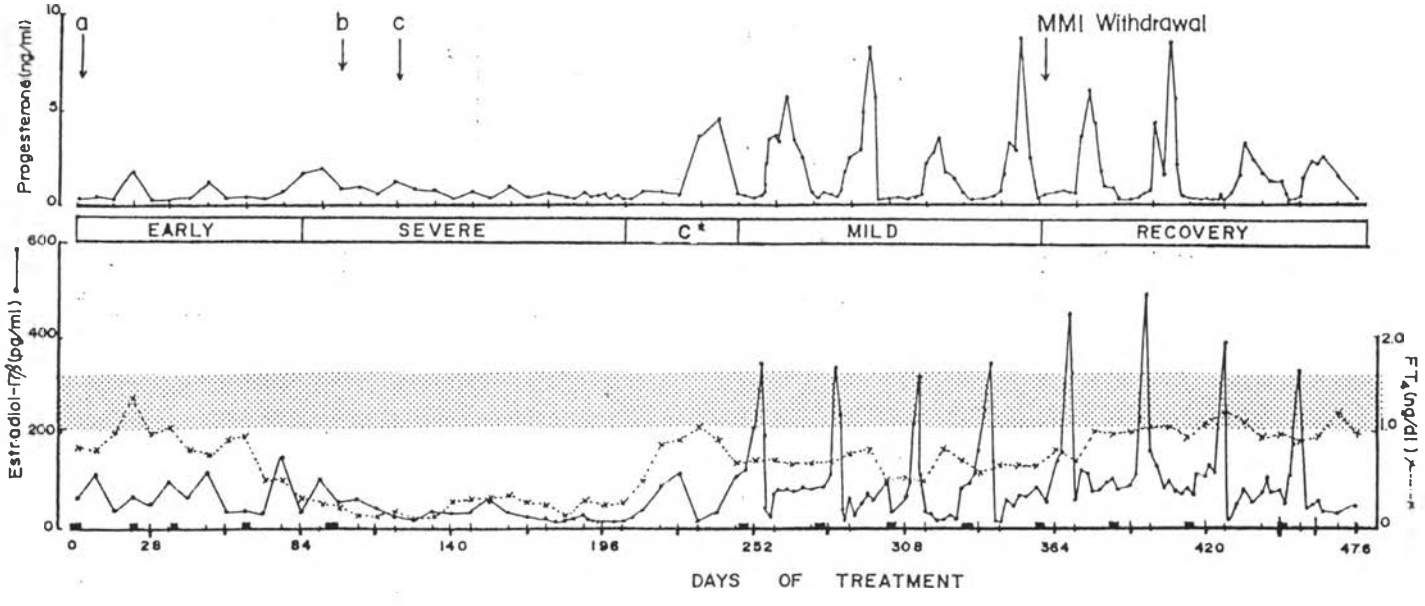

Fig 33. The profiles of serum E_2, P and fT4 during early MMI treatment, late MMI treatment and after MMI withdrawal in monkey no. 25.

Abbreviation : a, MMI 10 mg/day ; ▒ fT4 pretreatment value (X±SD)
b, MMI 5 mg/day ; ■ menstrual bleeding
c, MMI 2.5 mg/day

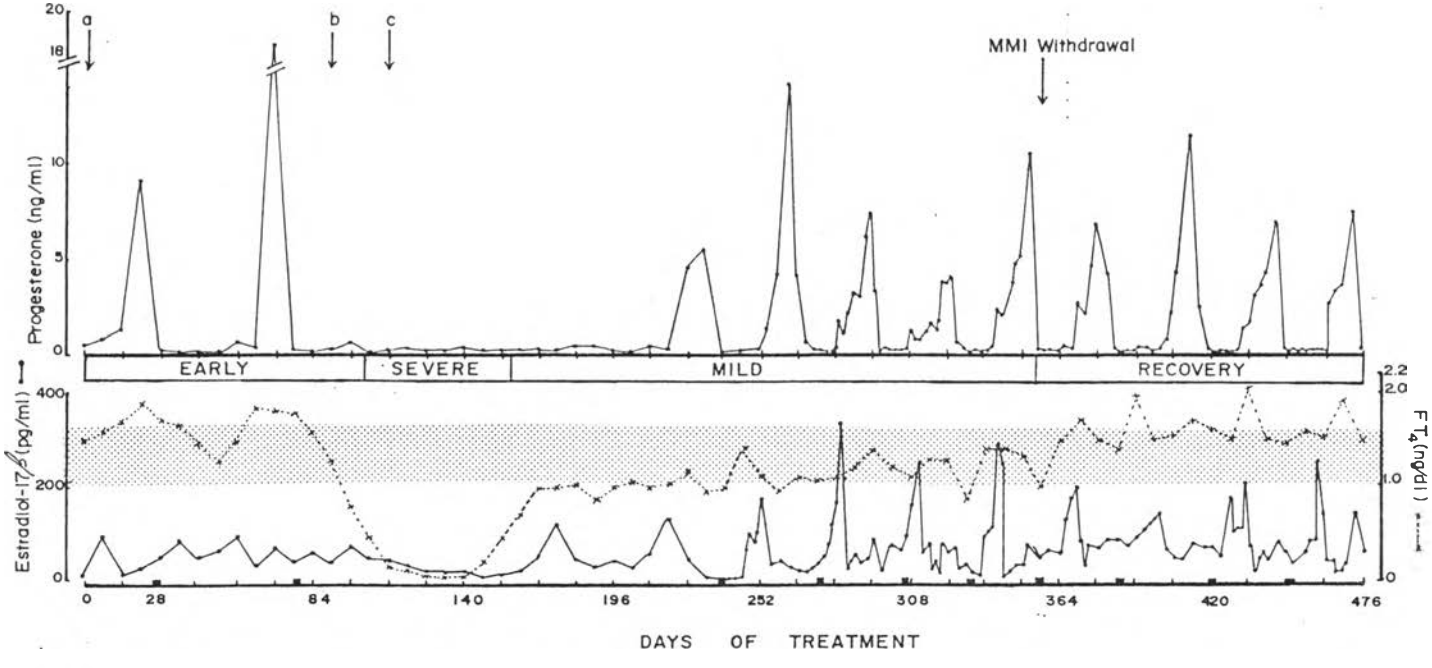

Fig 34. The profiles of serum E_2, P and fT4 during early MMI treatment, late MMI treatment and after MMI withdrawal in monkey no. 78

Abbreviation : a, MMI 10 mg/day ; b, MMI 5 mg/day ; c, MMI 2.5 mg/day

fT4 pretreatment value ($\bar{X}$+SD)

menstrual bleeding

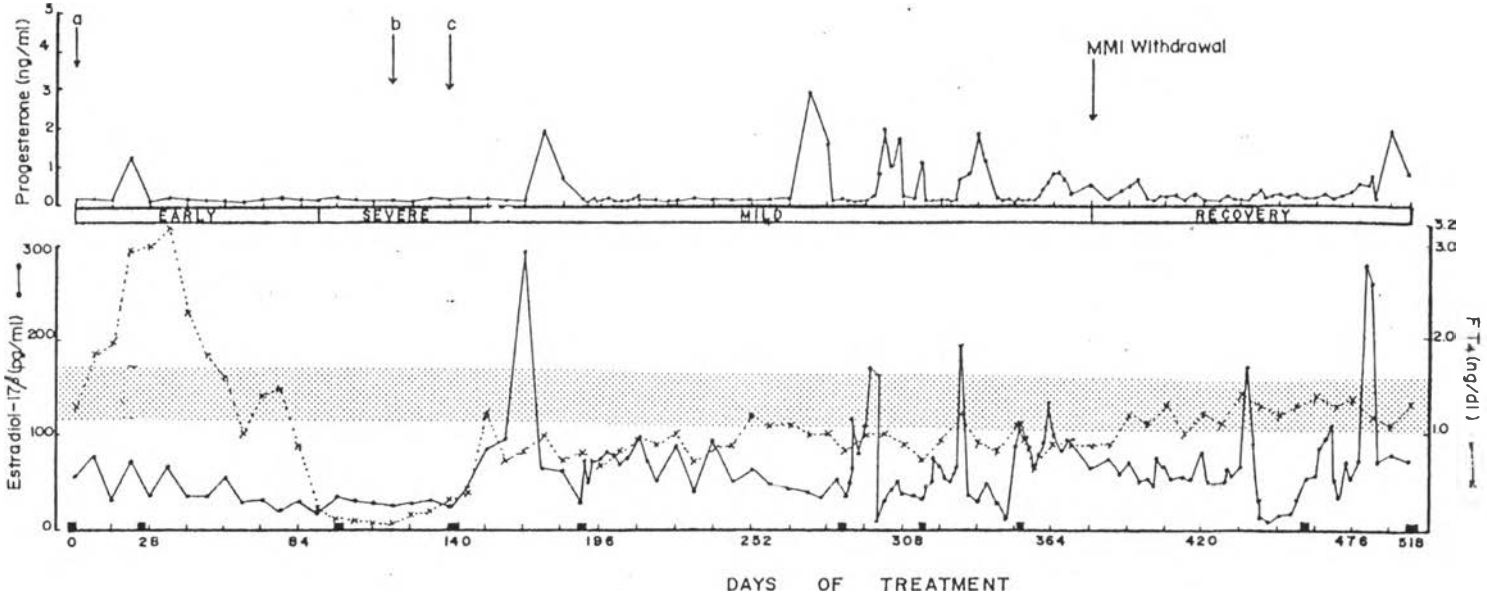

Fig 35. The profiles of serum E_2, P and fT4 during early MMI treatment, late MMI treatment and after MMI withdrawal in monkey no. 87.

Abbreviation : a, MMI 10 mg/day ;
b, MMI 5 mg/day ;
c, MMI 2.5 mg/day

fT4 pretreatment value (X±SD)
menstrual bleeding

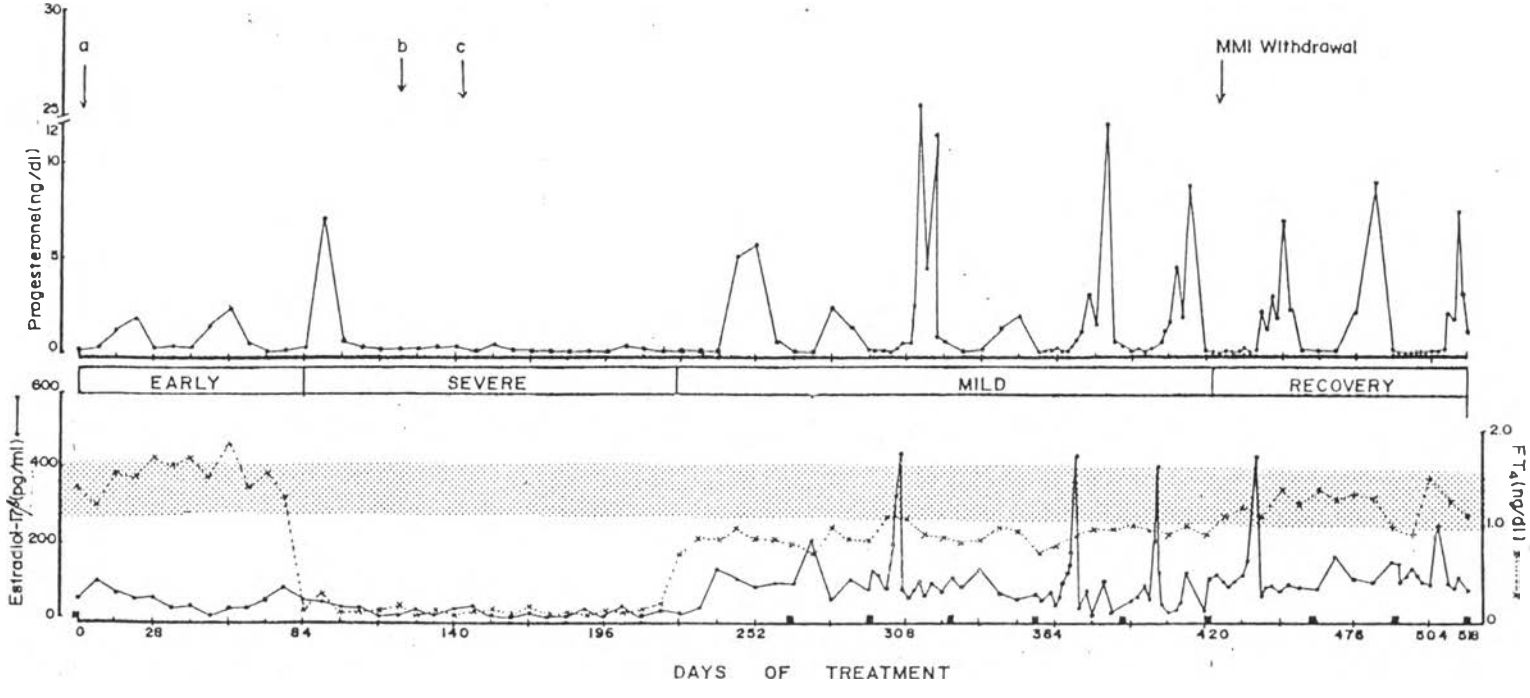

Fig 36. The profiles of serum E_2, P and fT4 during early MMI treatment, late MMI treatment and after MMI withdrawal in monkey no. 77

Abbreviation : a, MMI 10 mg/day ; b, MMI 5 mg/day ; c, MMI 2.5 mg/day

fT4 pretreatment value (X±SD)

menstrual bleeding

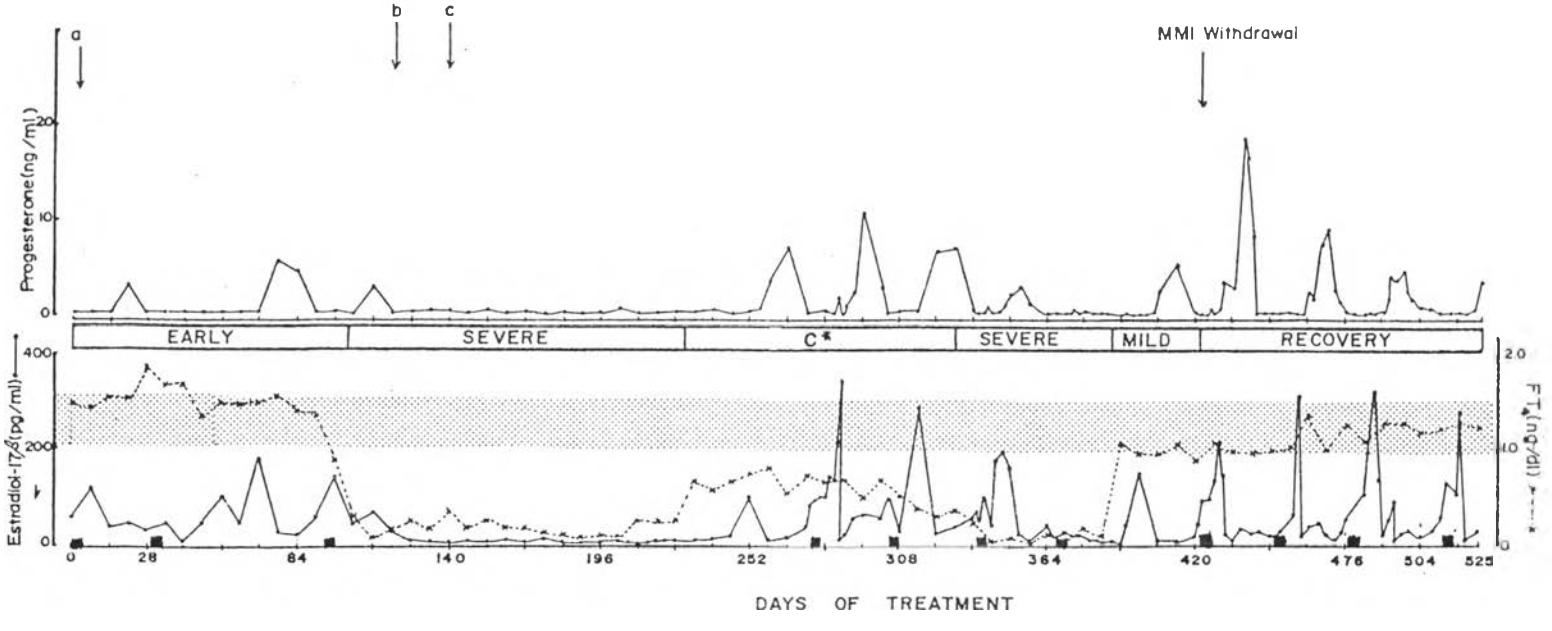

Fig 37. The profiles of serum E_2, P and fT4 during early MMI treatment, late MMI treatment and after MMI withdrawal in monkey no. 101

Abbreviation : a, MMI 10 mg/day ; ▒ fT4 pretreatment value (X±SD)
b, MMI 5 mg/day ; ■ menstrual bleeding
c, MMI 2.5 mg/day

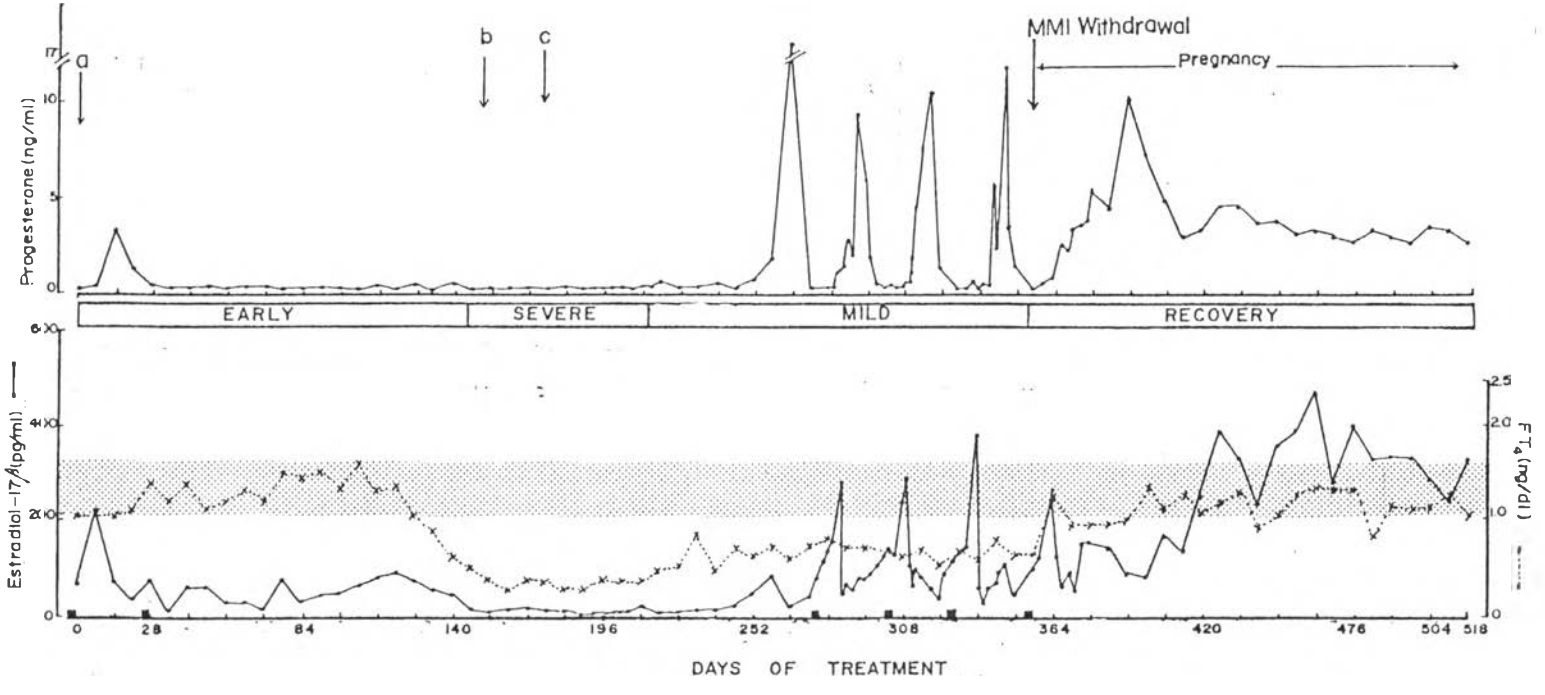

Fig 38. The profiles of serum E_2, P and fT4 during early MMI treatment, late MMI treatment and after MMI withdrawal in monkey no. 63

Abbreviation : a, MMI 10 mg/day ;
b, MMI 5 mg/day ;
c, MMI 2.5 mg/day

fT4 pretreatment value (X±SD)
menstrual bleeding

In order to study the changes in profile patterns of TBG during the three different states of hypothyroidism relevant to alteration of thyroid hormones concentration in blood, the TBG levels were observed during these states. The patterns of TBG levels were evidenced into two type responses during severe hypothyroidism. Firstly,an unchanged trend and secondly, an increased trend of TBG levels.

5.1 An unchanged trend of TBG profile during severe hypothyroidism.

During the early MMI treatment, it was noted that the serum TBG levels were markedly fluctuated which in accored with the thyroid hormone trended toward high in five animals (no. 63, 33, 25, 78, and 87) as presented in fig 39-43. However, the TBG levels did not alter significantly but ranged within the pretreatment values (9.40-13.00 ug/ml). during severe hypothyroidism. Furthermore, these levels remained unchanges during mild and recovery periods. In monkey no. 63, complete MMI withdrawal on the first day of menstruation caused great fluctuation of T4 and fT4 levels during the first week of post treatment while TBG remained unchange. The animal showed normal fertility as capable of mating with a fertile male on D11 of cycle and had successful pregnancy of 158 day gastation. Striking increase in both TBG and T4 was observed throughout the entire peroid of pregnancy.

But the fT4 levels strongly fluctuated and within the normal range.

5.2 An increased trend of TBG profile during severe hypothyroidism.

Monkey no. 77 and no. 101.

During early severe hypothyroidism of monky no. 77 , serum levels of TBG continuously increased, following by lowered TBG levels in late state of severe hypothyroidism. These were corresponded with slight increase in both T4 and fT4 levels (fig 44). Contrasted to no.77 in the early treatment, distinctive phase of TBG patterns of no.101 was showed (fig. 45). As both fT4 and T4 levels fluctuated to be high, the TBG subsequently reduced. But both fT4 and T4 levels reduced and rose again in second phrase, the TBG levels increased concurrently with them. During first and second severe hypothyroidism periods, it was noted that profound increase in TBG levels was evidenced.

In summary, two out of seven monkeys (no. 77 and 101) showed an increased trends of TBG profiles during severe hypothyroidism. An unchanged profiles of TBG in five monkeys were observed too.

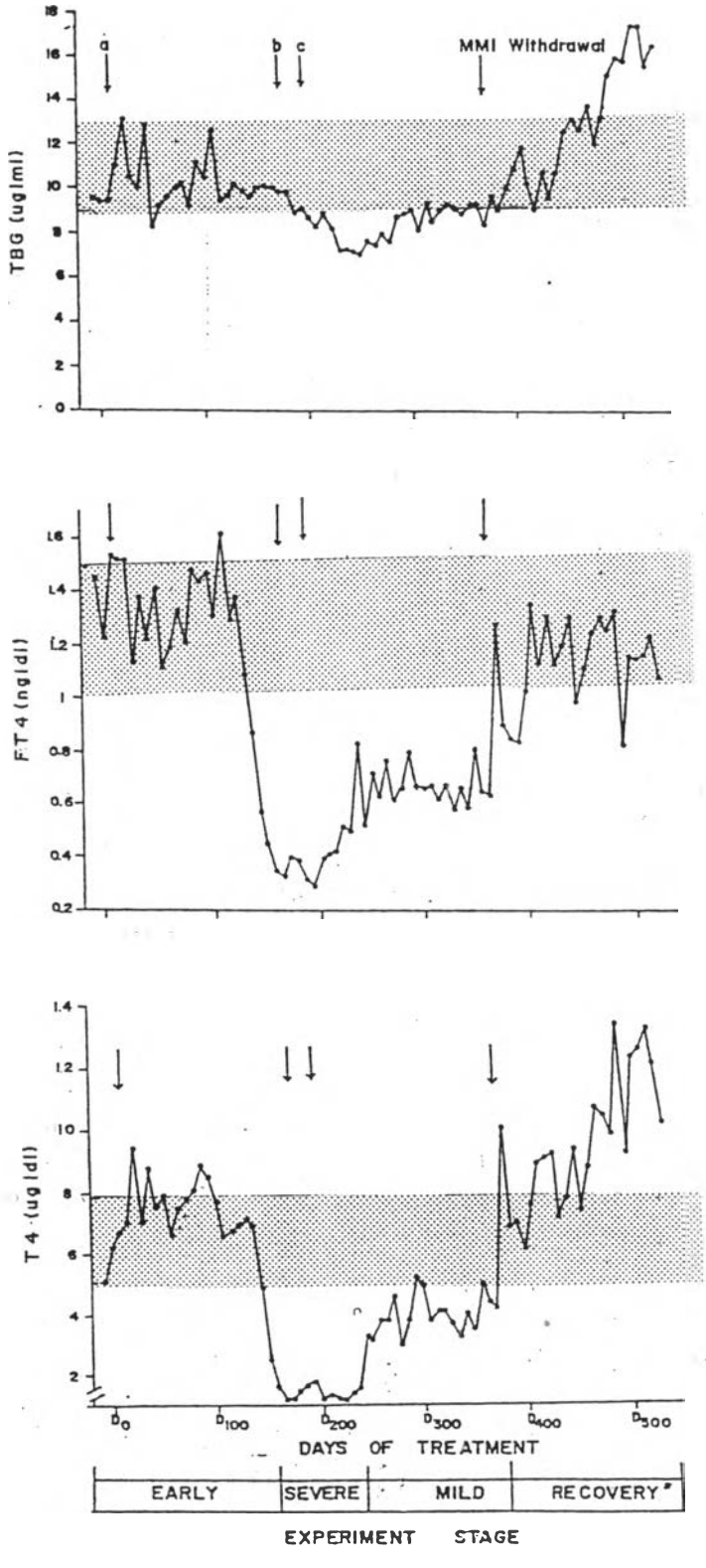

Fig 39. The serum TBG, fT4 and T4 profiles during hypothyroidism in monkey no. 63.

Abbreviation : a, MMI 10 mg/day ; ▒ pretreatment value ($\bar{X}\pm SD$)
b, MMI 5 mg/day
c, MMI 2.5 mg/day

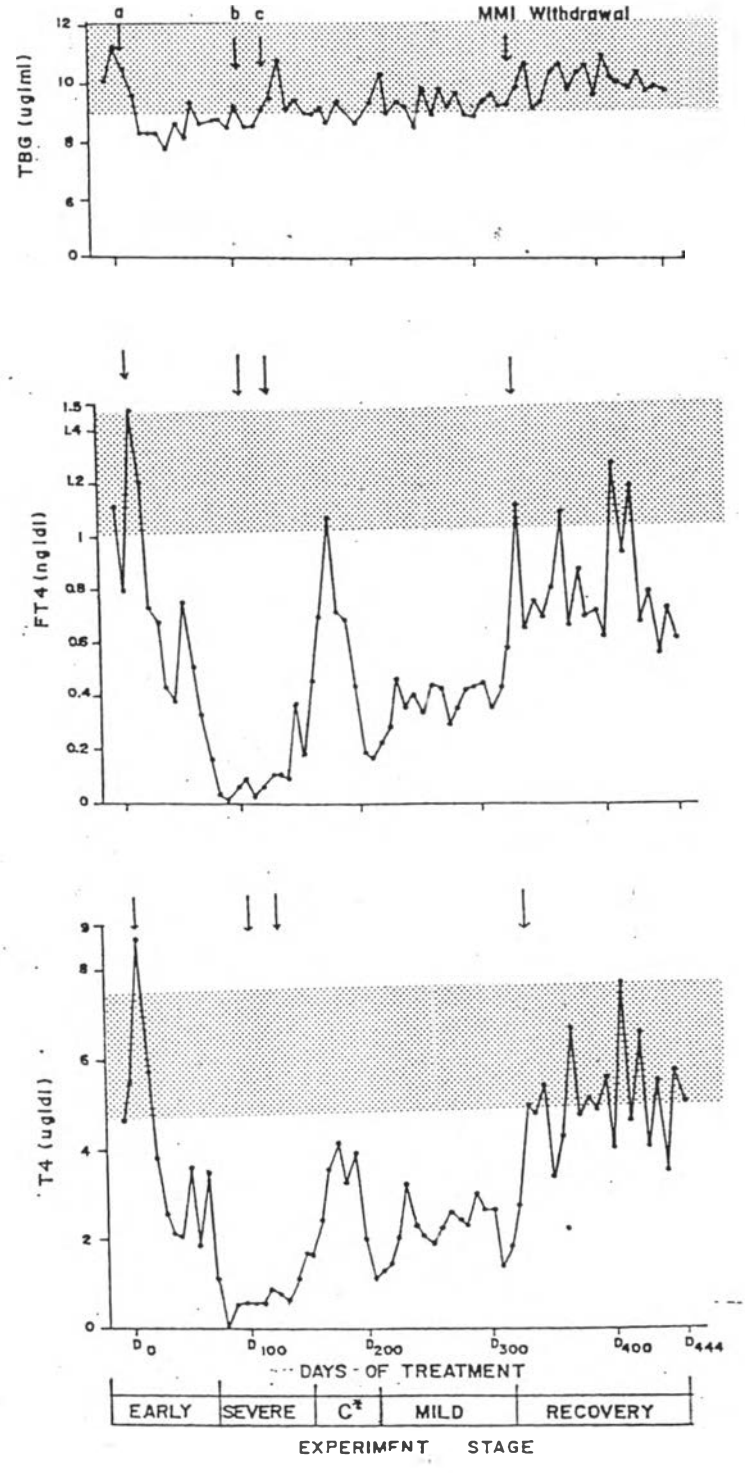

Fig 40. The serun TBG, fT4 and T4 profiles during hypothyroidism in monkey no. 33.

Abbreviation : a, MMI 10 mg/day ; pretreatment value ($\bar{X}$±SD)
b, MMI 5 mg/day ; C*, compensatory period
c, MMI 2.5 mg/day

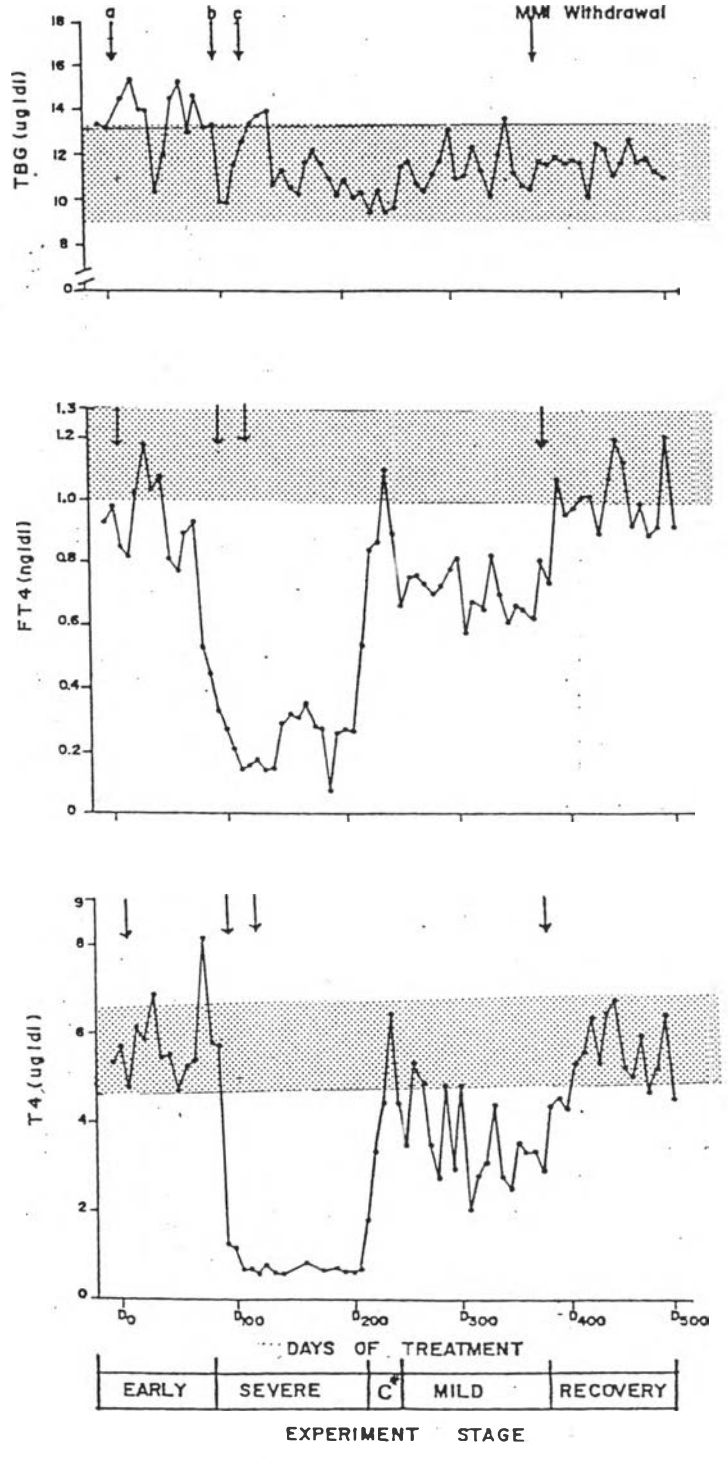

Fig 41. The serum TBG, fT4 and T4 profiles during hypothyroidism in monkey no. 25.

Abbreviation : a, MMI 10 mg/day ; ▨ pretreatment value ($\bar{X}\pm SD$)
b, MMI 5 mg/day ; C*, compensatory period
c, MMI 2.5 mg/day

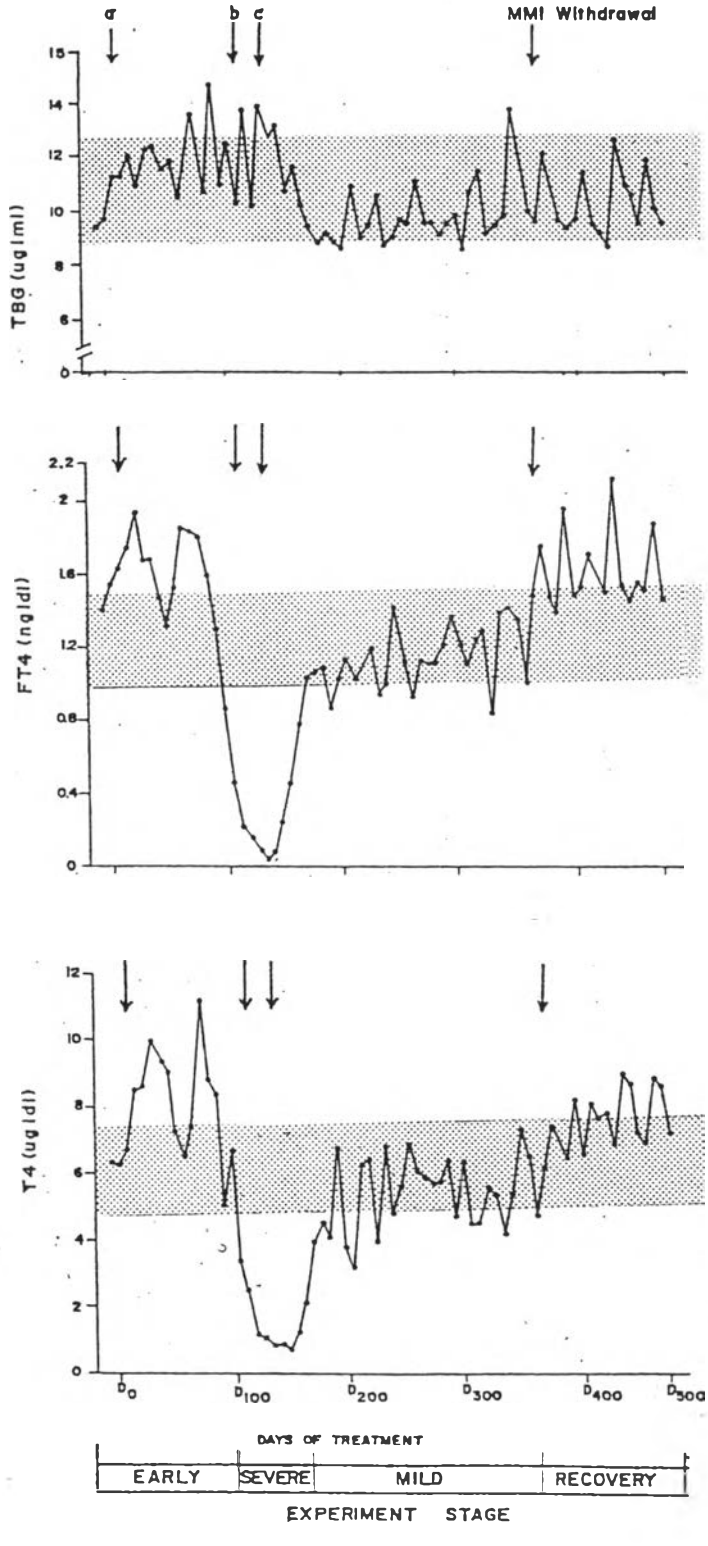

Fig 42. The serum TBG, fT4 and T4 profiles during hypothyroidism in monkey no. 78.

Abbreviation : a, MMI 10 mg/day ; ▒ pretreatment value ($\bar{X}\pm SD$)
b, MMI 5 mg/day
c, MMI 2.5 mg/day

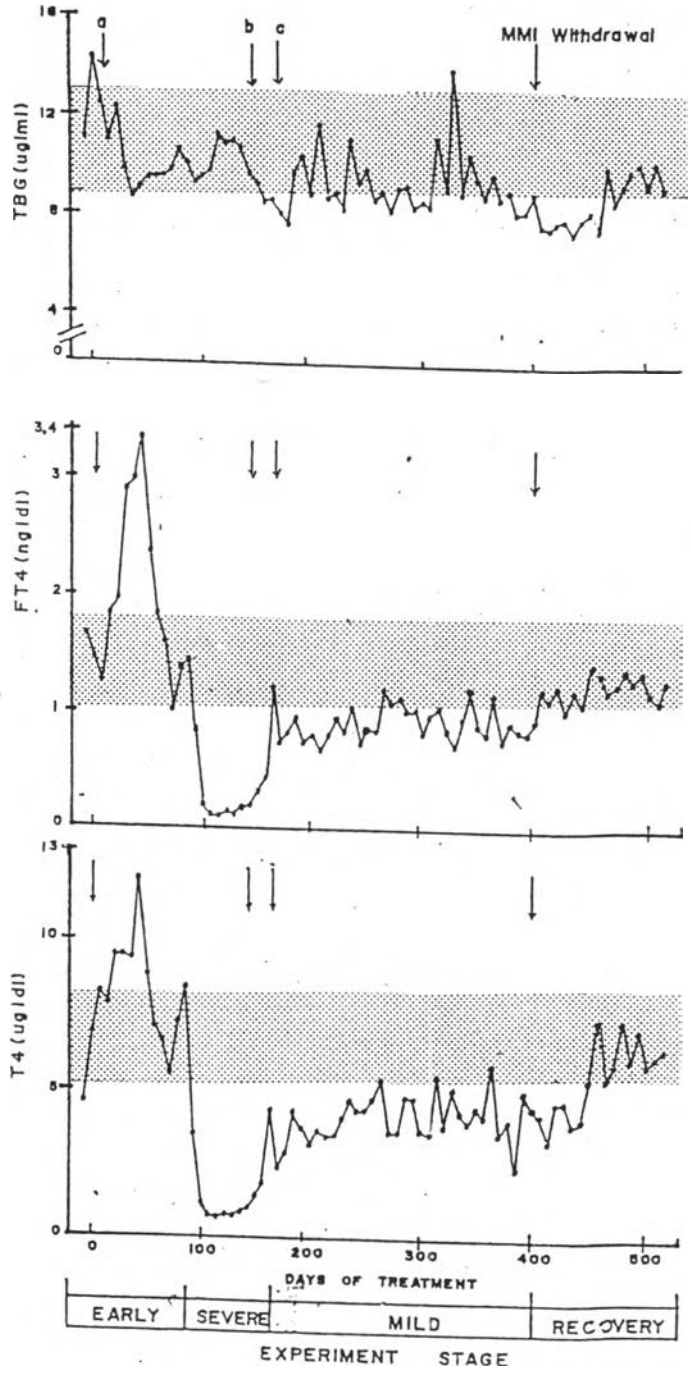

Fig 43. The serum TBG, fT4 and T4 profiles during hypothyroidism in monkey no. 87

Abbreviation : a, MMI 10 mg/day ; ▒ pretreatment value ($\bar{X}\pm SD$)
b, MMI 5 mg/day
c, MMI 2.5 mg/day

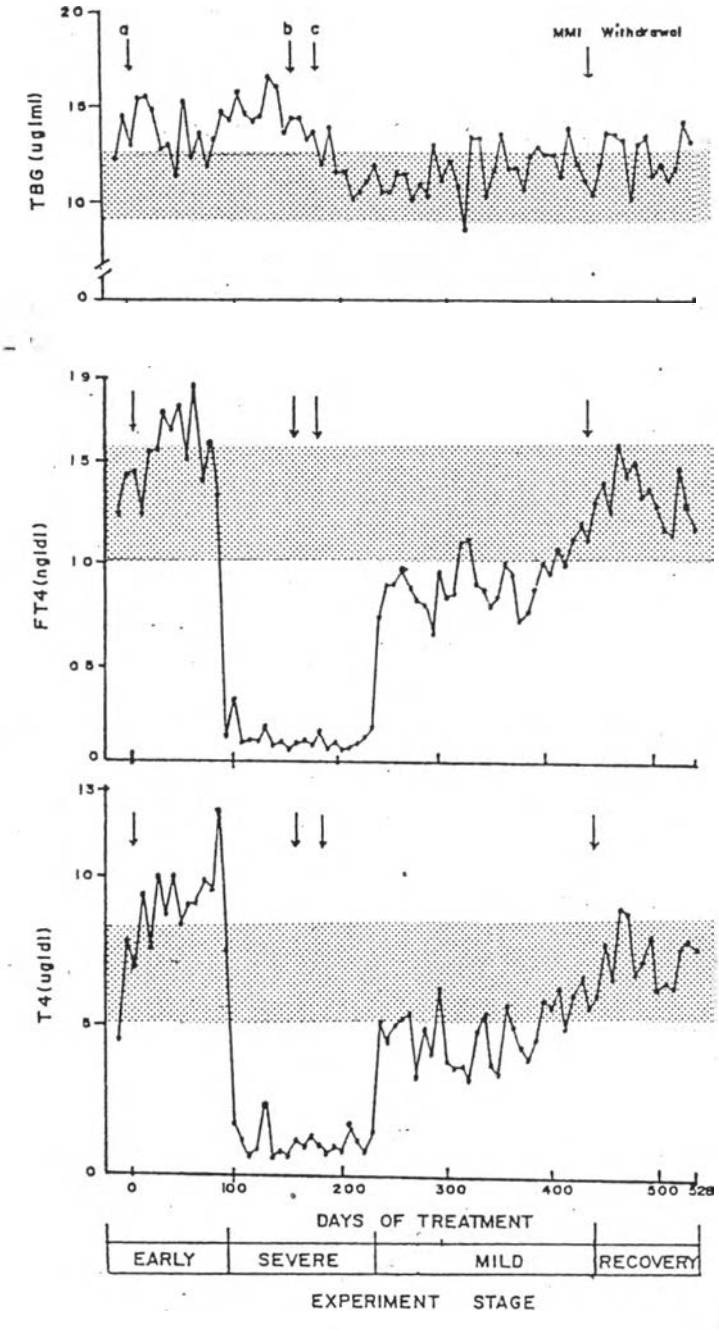

Fig 44. The serum TBG, fT4 and T4 profiles during hypothyroidism in monkey no. 77.

Abbreviation : a, MMI 10 mg/day ; pretreatment value ($\bar{X}\pm SD$)
b, MMI 5 mg/day
c, MMI 2.5 mg/day

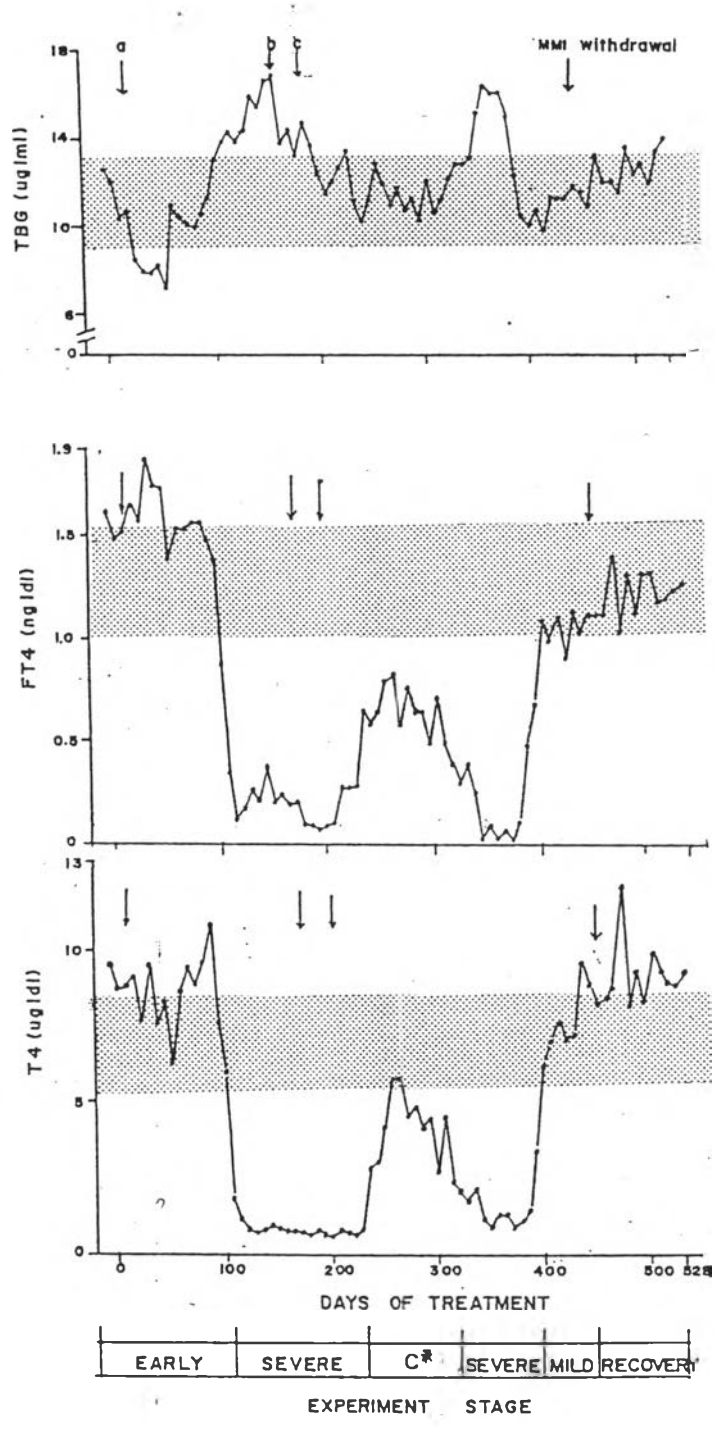

Fig 45. The serum TBG, fT4 and T4 profiles during hypothyroidism in monkey no. 101.

Abbreviation : a, MMI 10 mg/day ; pretreatment value ($\bar{X}\pm SD$)
b, MMI 5 mg/day ; C*, compensatory period
c, MMI 2.5 mg/day

6. Profile patterns of thyroid hormones, TSH, PRL, TBG E_2, and P in normal pregnancy and pregnant monkey previously treated with MMI no.(63).

As showed in fig 46 and 47, the profile patterns of both T3 and T4 during normal gestational period were exhibited. The levels of T4 increased sligthly on D8 but trened to be low at the time of placentation. The levels fluctulated to be high again in late first trimester until term. Peripheral serum T4 levels accentuated on D57.D85,D134,D148 D155 and D162 of gestation and differed significantly from the control value (Do of gestation). The level of T3 was highest on D8 but declined gradually in late first trimester and lowered consistently in the second and third trimester. Significant difference of lower T3 levels was demonstrated on D43, D71, D85, D92, and D106 of gestation. In monkey no. 63, serum levels of T4 on D0 of gestation was higher than normal untreated animal (9.80 ug/dl) and then reduced to similar values found in normal pregnancy until the first month of gestation. Subsequently, T4 levels increased again during late second and third trimesters of gestational period and this differences were greater than those in earlier stage of pregnancy (10.00-14.00 ug/dl). The levels of T3 in this monkey was also extremely high on D0 of gestation but readjusted to be similar to levels found in normal pregnancy during D8 and D15 of pregnancy.Subsequently, T3 levels oscillated to be high again on D22 and gradually

dropped, paralleled with the values found in normal pregnancy on D22-D43 of gestation. The levels further lowered to be similar to the values found in normal pregnancy around 2 weeks prior to increase again during D71-D92 of gestation. During third trimester, the animal readjusted the T3 levels to be normalized. It was also noted that T4:T3 ratio of both normal pregnancy and monkey no.63 declined prominently at the time of implantation and placentation , and then increased sharply in late first trimester (fig. 48). In the second and third trimesters, only the T4:T3 ratio levels of pregnant animals remained high, nevertheless, fluctuated during the latter part of gestation (fig. 48). T4:T3 ratio of no. 63 reduced during second trimester and then increased sharply during third trimester (fig. 48). The fT4 levels also accentuated significantly on D8 and gradually lessened during D15-D29 of gestation (fig.49) .The fT4 levels oscillated and trended to increase slightly again in late first trimester, subsequently, unchanged significantly during the rest of gestation period. The fT4 levels of monkey no. 63 seemed to be similar to those of the other pregnant monkeys except a sharp drop on D8-D22 of gestation. In normal pregnant monkeys, the TBG levels increased strikingly and reached a significant level ($p<0.05$) on D29 and D43 of first trimester; furthermore, showed significantly during the second and third trimesters (fig. 50). Patterns of TBG levels in no. 63 was very similar to

those of normal pregnancy except slightly lessened during the transition period of the first and second trimester and increased sharply during the last trimester (fig. 50). TSH levels rose during D8-D29 and then decreased again during D36-D50 of normal gestation (fig. 51). During early period of second trimester, TSH levels increased prominently on D57-D71 of gestation. The levels of TSH remained high and strong fluctuations during the rest of gestational period. Significant differences ($P<0.05$) of TSH were exhibited (fig. 51). It was noticed that the TSH levels of no. 63 was 6.67 mIU/L on D0 of gestation and higher than normal value of four pregnancy. Moreover, the pattern of TSH levels in no. 63 seemed to be reduced gradually throughout the gestation which contrasted to the normal patterns of TSH levels (fig. 51). As shown in fig. 52. serum levels of E_2 increased sharply during early first trimester reaching significant level on D22 ($P<0.05$). The E_2 levels declined on D29 and D36; consequently, increased gradually again in late first trimester. During second trimester, E_2 levels were increased significantly ($P<0.05$) but declined gradually afterwards and consistently on D134-D162 of gestation. Prior to delivery, serum E_2 levels accentuated again. It was noted that an increase in E_2 levels concided with high TBG levels; eventhough;they performed in first trimester ($r=0.60, P<0.001$) (table 6). During the second trimester, E_2 levels increased gradually whereas the TBG elevated consistently. In addition, the levels of E_2 declined

sharply in early third trimester but the TBG levels tended to be high (fig. 52). Poor correlation between E_2 and TBG during the second and third trimester were noted (table 16). The pattern of TBG levels in no. 63 was similar to those in normal pregnant monkeys. In the case of progesterone, the sudden rise in progesterone levels were also observed in normal pregnant animals as well as in monkey no. 63 (fig. 54). Similarly, all showed a slight decline in progesterone levels in the late first trimester period (fig. 54). Progesterone levels increased slightly from the second until early third trimester and maintained slight changes until term. But the progesterone levels of no. 63 tended to be reduced from the late second trimester until delivery. A few weeks prior to delivery, progesterone levels of normal pregnancy increased sharply and achieved significant values ($P<0.05$). The PRL levels of monkey no. 63 rose on D8 and then fluctuated to be high (D43) in first trimester. During second trimester, Excessive higher PRL levels were exhibited ranging 2300-6500 mIU/L; subsequently; declined to be 2500 mIU/L. The PRL levels fluctuated strongly again and showed to be 5300 mIU/L at term. However, the PRL levels of normal pregnant animal showed to be continuously increased in all periods but rose strikingly again during a few week before delivery (fig. 53).

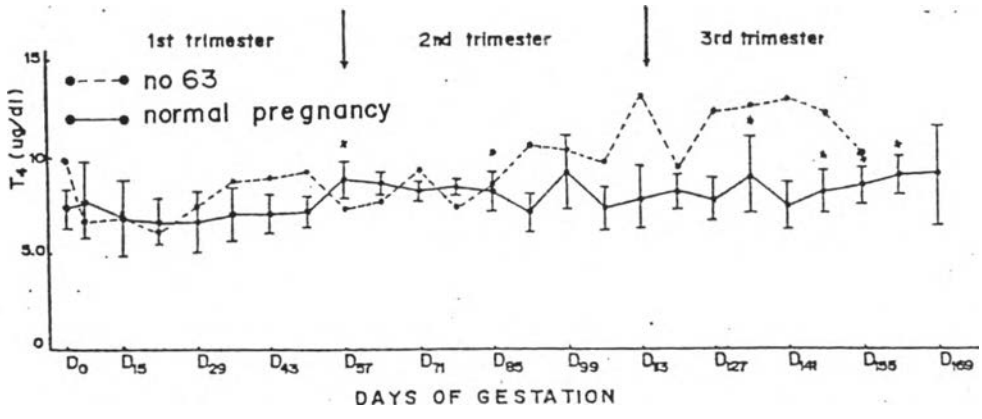

Fig 46. The serum levels of T4 throughout entire pregnancy of both normal pregnant monkeys and MMI- previously treated monkey (no. 63)

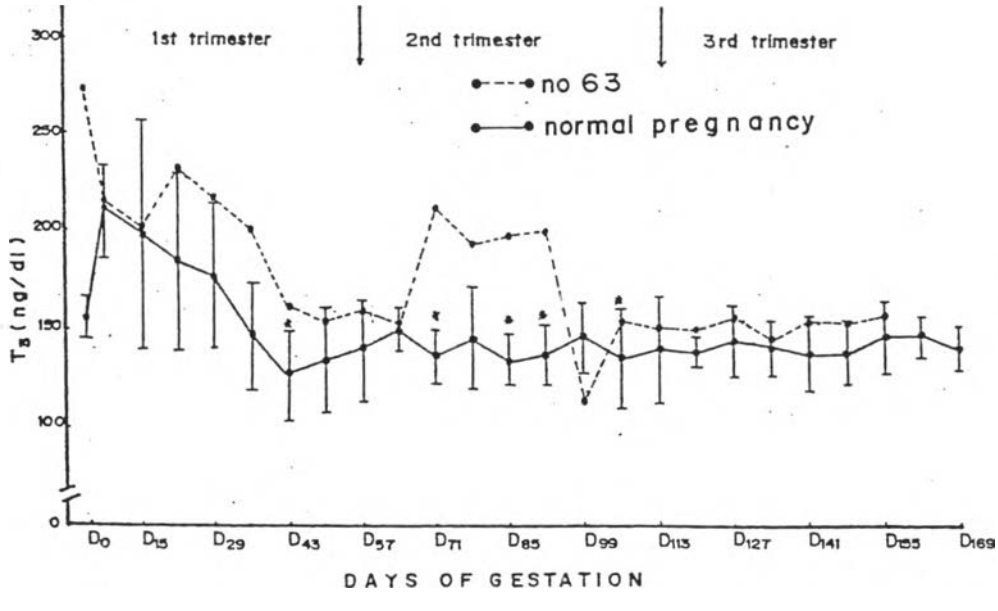

Fig 47. The serum levels of T3 throughout entire pregnancy of both normal preagnant monkeys and MMI-previously treated monkey (no. 63)

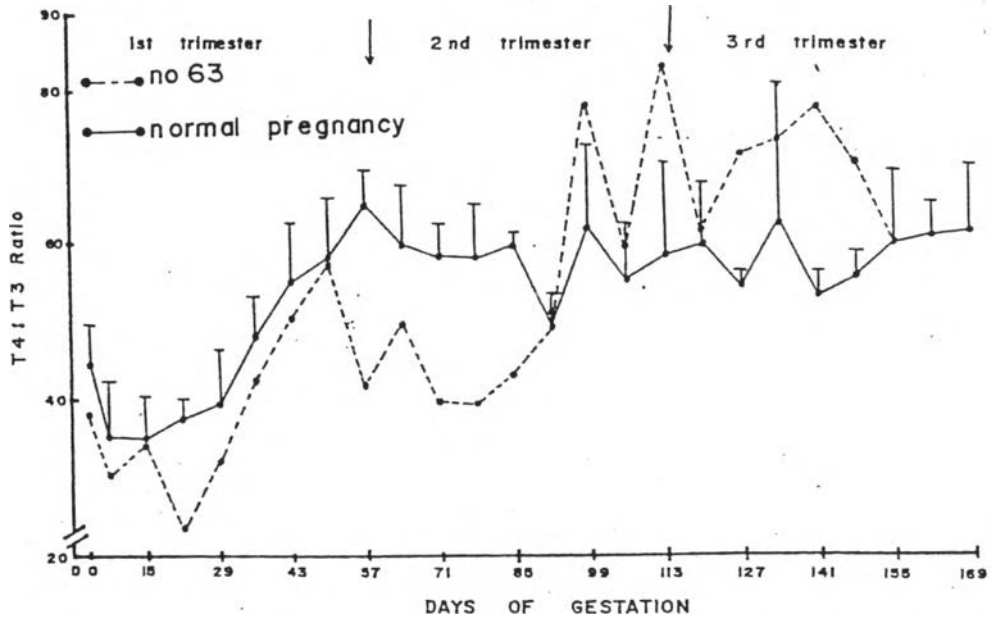

Fig 48. The patterns of T4:T3 ratio throughout entire gestation in both normal pregnant monkeys and MMI-previously treated monkey (no. 63)

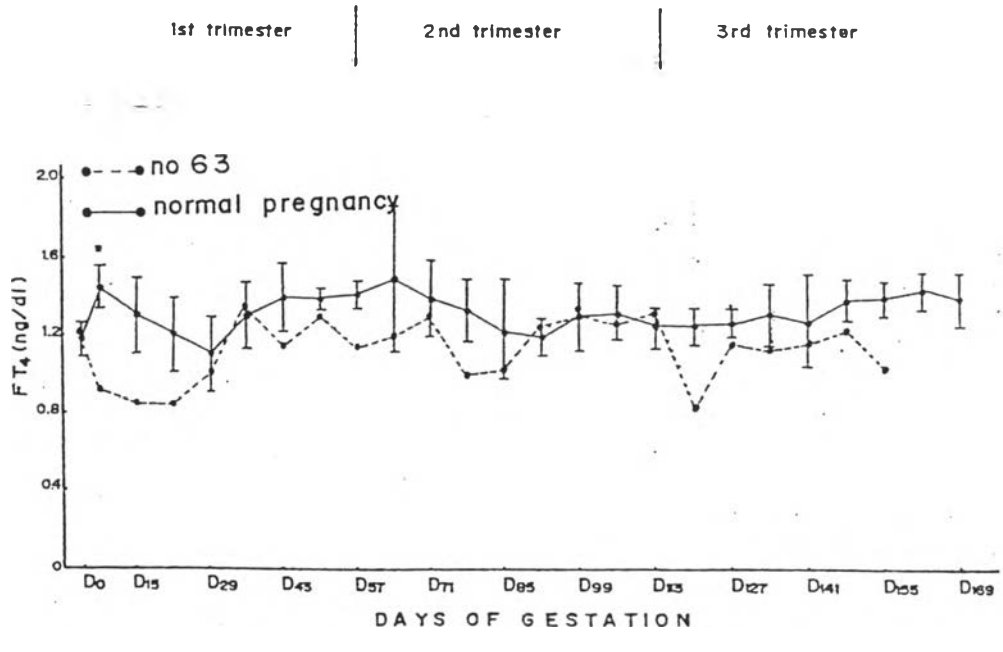

Fig 49. The serum levels of fT4 throughout entire gestation of both normal pregnant monkeys and MMI-previously treated monkey (no. 63)

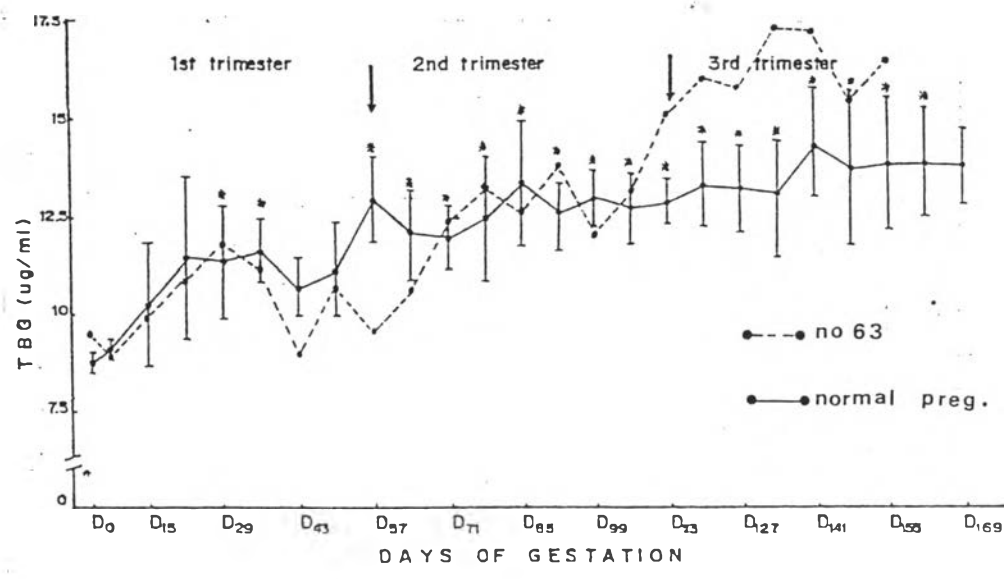

Fig 50. The serum levels of TBG throughout entire gestation of both normal pregnant monkeys and MMI-previously treated monkey (no. 63)

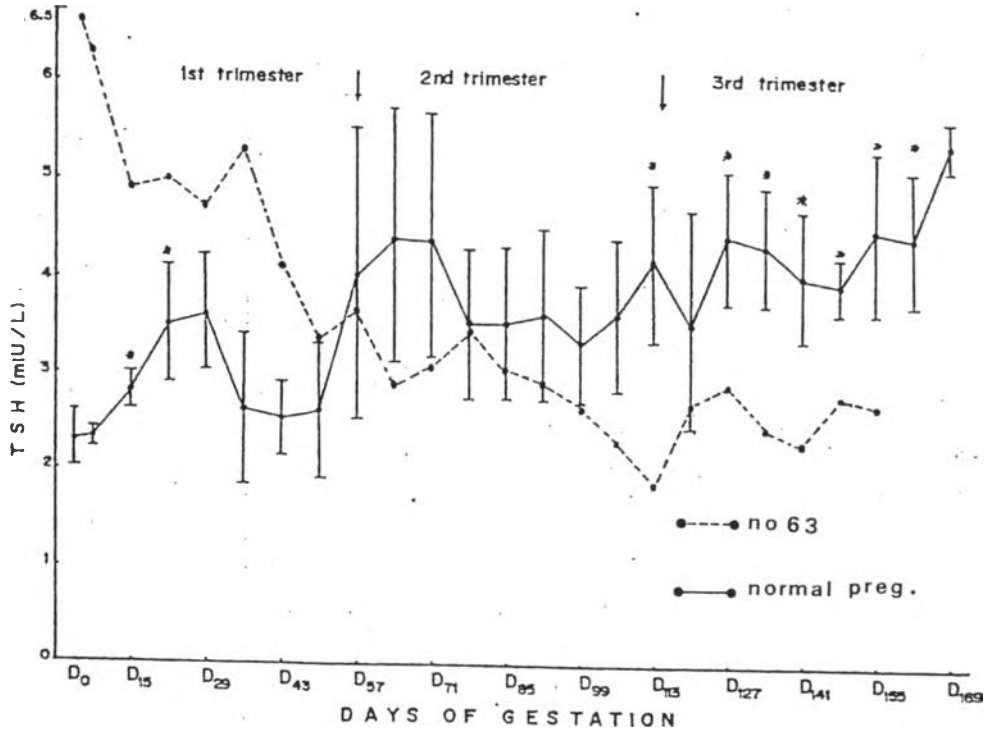

Fig 51. The serum levels of TSH throughout entire gestation of both normal pregnant monkeys and MMI-previously treated monkey (no. 63)

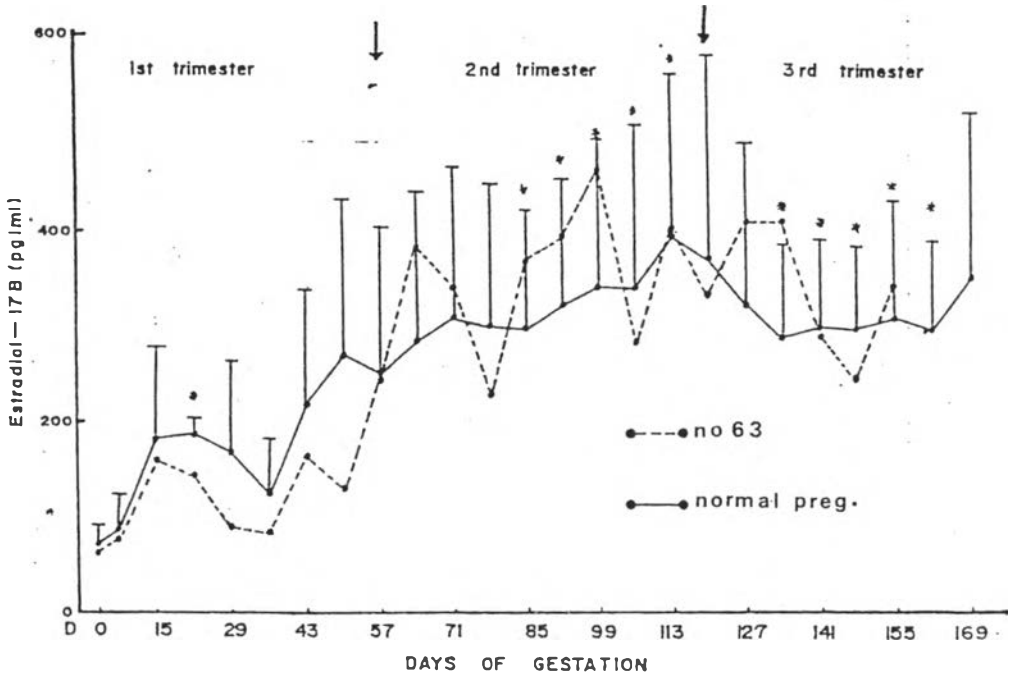

Fig 52. The serum levels of E_2 throughout entire gestation of both normal pregnant monkeys and MMI-previously treated monkey (no. 63)

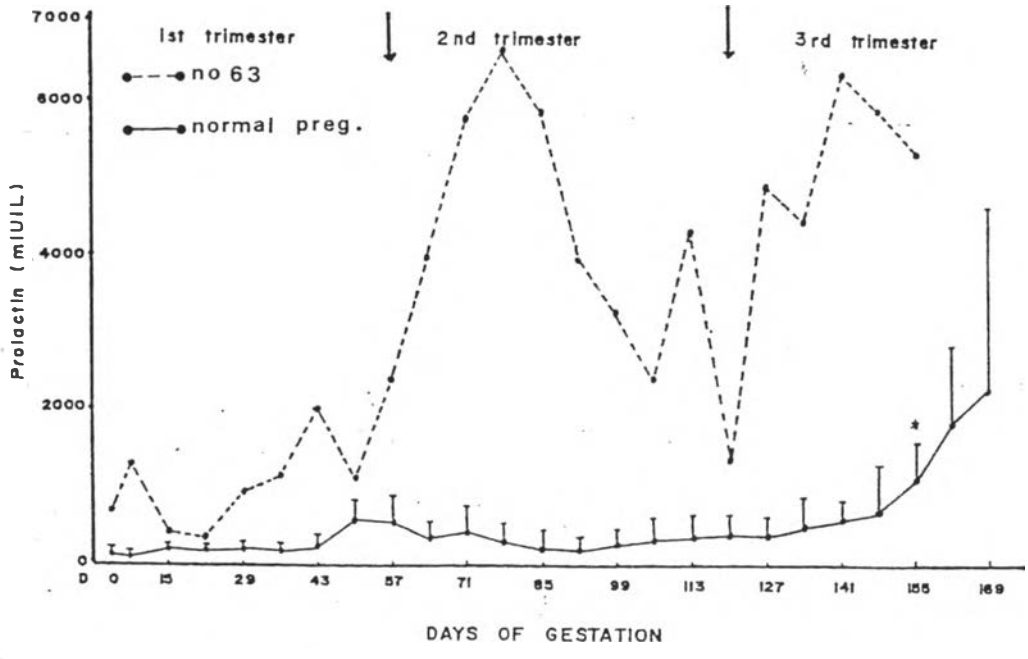

Fig 53. The serum levels of PRL throughout entire gestation of both normal pregnant monkeys and MMI-previously treated monkey (no. 63)

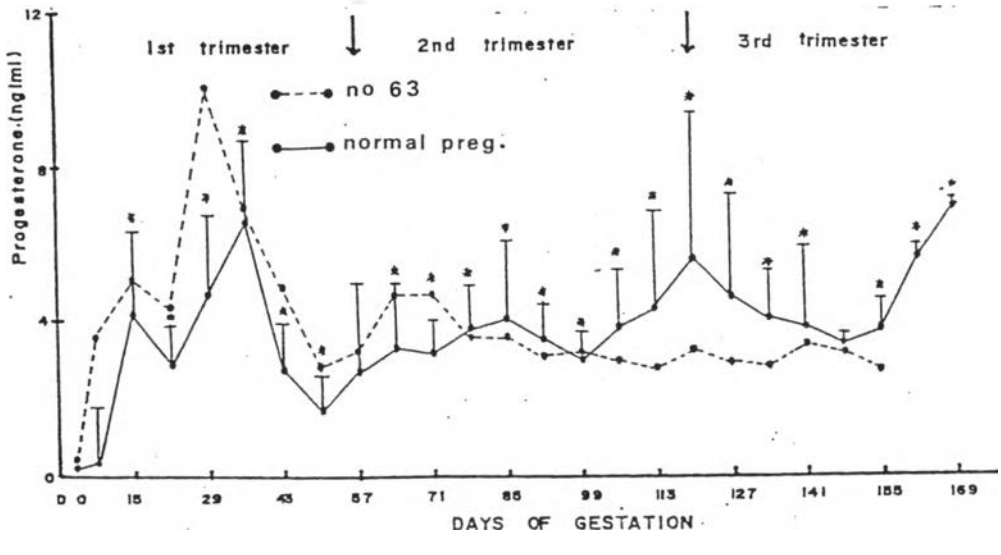

Fig 54. The serum levels of P throughout entire gestation of both normal pregnant monkeys and MMI-previously treated monkey (no. 63)

Table 6. Correlation between E_2 and TBG in early, mid, and late periods of normal pregnancy.

State of pregnancy	early period	mid period	late period
E_2 and TBG	0.60^{**}	-0.19	-0.02

Abbreviation: **, $p < 0.01$