

Chapter IV

CIRCULATING GONADOTROPINS IN PRE-MENOPAUSAL BREAST CANCER PATIENTS : ENDOCRINE CONSEQUENCES AFTER ADJUVANT THERAPY

INTRODUCTION

The hormone dependence of breast cancer is now well established. In the previous Chapters, we have reported that pre-menopausal breast cancer patients had low levels of circulating E with concomitant hyperprolactinaemia. These studies, point² towards a significant role of steroid and peptide hormones in the pathogenesis of human breast carcinoma (Bhatavdekar et al, 1987).

In view of the above, we have further investigated the levels of pituitary gonadotropins in pre-menopausal patients. This might help us to gain a better insight to understand the hormonal dependence of breast cancer.

Long term administration of cytotoxic drugs and antiestrogens, singly or in combination has been increasingly employed as an adjuvant therapy to surgery. These agents exert their primary antitumor effect through a direct inhibition of neoplastic cells, but they have been shown to produce concomitant alterations of the endocrine function (Golder et al, 1976 ; Dnistrian et al, 1983, 1985 ;

Delrio et al, 1986 ; Manni, 1987). We also report here the effect of adjuvant/endocrine treatment on the pituitary gonadotropins in pre-menopausal patients. Along this line, an attempt was made to correlate the circulating levels of Follicle Stimulating Hormone and Luteinizing Hormone with the clinically important prognosticators viz. disease stage, nodal status, histological grade and disease course. These gonadotropins were also correlated with circulating estradiol and prolactin.

STUDY DESIGN

The clinical data collection, pathologic staging and assessment of disease activity was investigated on a cohort of 111 pre-menopausal breast cancer patients attending The Gujarat Cancer and Research Institute, Ahmedabad, India as described in previous Chapters. The surgical procedures were performed by Surgical Oncology units and adjuvant therapy was instituted by Medical Oncology units of the Institute. The treatment schedules were described in Chapter II. Blood samples from patients (N=111) and controls (N=30) were collected in ethylenediaminetetraacetic acid (EDTA), disodium salt (1-2 mg/ml) coated tubes in the morning between 9-11 AM pretherapeutically for pituitary gonadotropins i.e. Follicle Stimulating Hormone and

Luteinizing Hormone (FSH, LH) estimation. Serial blood samples were obtained from 52/111 patients pretherapeutically to obtain baseline level of individual patients and at intervals of 3-6 months for stage II and at monthly / bimonthly intervals for advanced patients. The plasma was separated within 1-2 hours, aliquoted and stored at -70° C until assayed. The assays were performed within one month. Studies were performed retrospectively using frozen plasma. The accurate details of the menstrual cycle length of these patients could not be procured and hence, phase of the menstrual cycle was not considered at the time of gonadotropin estimations. These hormones were estimated sequentially to investigate : (1) usefulness of these hormones as disease monitor and (2) the endocrine consequences after adjuvant therapy. Moreover, we also have estimated these hormones sequentially, in few patients only, and have tried to correlate the circulating levels of FSH, LH with PRL prior to death of the patient.

GONADOTROPIN ASSAYS :

Plasma FSH and LH were assayed using double antibody RIA kits, procured from Diagnostic Products Corporation, Los Angeles, USA, according to manufacturers' instructions. The kits were standardized : (i) for FSH against WHO 2nd IRP-HMG and (ii) for LH against WHO 1st IRP 68/40. The assays were

performed in duplicate with an intrassay and an interassay coefficient of variation (CV) of 3% to 5% and 5% to 8% respectively along with internal quality controls. The sensitivity of the assay was : (i) FSH 1.2 mIU/ml (ii) LH 2 mIU/ml. The normal range in pre-menopausal patients was : FSH - 4.5 to 35.0 mIU/ml and LH - 2.5 to 60.0 mIU/ml plasma.

THERAPY :

The adjuvant therapy instituted to the patients was broadly categorized into :

- A). patients treated only with multidrug chemotherapy (N=22 ; CMF).
- B). patients treated only with endocrine manipulation (N=8 ; bilateral oophorectomy and/or TMX).
- C). patients treated with chemoendocrine therapy (N=11 ; CMF + bilateral oophorectomy and/or TMX).

The details of therapy and assessment of disease activity were described in Chapter II.

STATISTICS :

The differences in gonadotropins were analysed to obtain statistical significance using (i) χ^2 analysis and (ii) an exact contingency table for order data and Fisher's two sided exact test (Mehta and Patel, 1983). P values less than 0.05 were considered to be significant.

RESULTS

PITUITARY GONADOTROPINS IN PRE-MENOPAUSAL BREAST CARCINOMA PATIENTS :

Plasma gonadotropins in pre-menopausal breast cancer patients were elevated as compared to controls. The elevation of LH was statistically significant ($P < 0.001$) while that of FSH was statistically non-significant. 19/111 (17.1%) patients had subnormal and 13/111 (11.7%) patients exhibited LH levels above normal. On the other hand, FSH levels were subnormal in 11/111 (9.9%) patients and above normal in 18/111 (16.2%) patients (Table - 1 ; Fig. 1)

PITUITARY GONADOTROPINS, ESTRADIOL AND PROLACTIN IN RELATION TO STAGE :

Statistically non-significant trend of decrease in FSH and E_2 and increase in PRL and no significant change in LH was observed as stage advanced (Table - 2). A comparison of stage II with the advanced stage also resulted into similar non-significant differences.

15/27 (55.5%) and 12/27 (44.0%) stage II patients exhibited normal and abnormal gonadotropins respectively. On the other hand, 50/84 (59.5%) and 34/84 (40.4%) advanced patients showed normal and abnormal gonadotropins respectively. Moreover, amongst stage II patients,

4/12 (33.3%), 2/12 (16.6%) and 6/12 (50.0%) patients had abnormal FSH, LH and both these hormones respectively. Contrary to the above, amidst advanced patients, 11/34 (32.3%), 15/34 (44.1%) and 8/34 (23.5%) patients reported abnormal FSH, LH and both these hormones respectively. Thus with advancement of stage, the abnormal incidence of FSH + LH as well as only FSH tended to increase. None of the above differences were statistically significant.

PITUITARY GONADOTROPINS IN RELATION TO NODAL STATUS :

The mean values of FSH and LH were increased amongst node positive patients in comparison to node negative patients (Table - 3) These results however, were statistically non-significant.

4/11 (36.3%) and 7/11 (63.6%) node negative patients demonstrated normal and abnormal gonadotropins respectively. On the contrary, 54/89 (60.6%) and 35/89 (39.3%) node positive patients exhibited normal and abnormal gonadotropin levels respectively. The differences however, were statistically non-significant.

PITUITARY GONADOTROPINS IN RELATION TO HISTOLOGIC GRADE :

A statistically significant increase in LH but not FSH was observed in patients with grade II+III tumors as compared with grade I tumors (Table - 4).

Moreover, 13/60 (21.6%) and 9/60 (15.0%) patients with

grade II + III tumors demonstrated LH and FSH levels above normal while 1/8 (12.5%) patients in each group showed elevated levels of FSH and LH amongst grade I tumors. The differences however, were statistically non-significant.

PITUITARY GONADOTROPINS IN RELATION TO DISEASE STATUS:

The pretherapeutic levels of FSH and LH amongst patients who developed recurrence were statistically non-significant from the levels in responders (Table - 5).

Amidst the patients who developed recurrence, the levels of both FSH and LH showed an increase before progression as compared to pretherapeutic levels. The elevations in LH and not FSH were statistically significant (Figs. 2-5). On the other hand, levels of both FSH and LH at last follow-up amongst responders exhibited a statistically significant elevation as compared to pretherapeutic levels (Table - 6 A; Figs. 6-8).

When FSH and LH amongst responders were subgrouped taking stage at diagnosis into consideration, it was observed that the LH elevations at last follow-up in both stage II and advanced stages were statistically significant in comparison to pretherapeutic levels while the FSH elevations in the same group were statistically non-significant (Table - 6 B).

PITUITARY GONADOTROPINS IN RELATION TO THERAPY :

Both chemo - and endocrine - treatment resulted into statistically significant elevations of FSH and LH (Table - 7; Figs. 3-7), however, no change in FSH and non-significant elevations in LH were observed following chemoendocrine therapy. Moreover, these levels even after treatment were significantly high when compared with controls (FSH : $P < 0.001$; LH : $P < 0.01$). The cytotoxic chemotherapy and endocrine treatment resulted into ovarian failure as documented by elevation in pituitary gonadotropins with concomitant decrease in E_2 (Figs. 9-12) and a decrease in the estradiol : gonadotropin ratio (Table - 8).

Interestingly, we also have observed in few patients only that prior to death there was a significant drop in FSH and LH with concomitant rise in PRL. On the other hand, in patients who were in remission the gonadotropins remained elevated with low PRL levels (Figs. 13-16).

DISCUSSION

The mean values of FSH and LH in breast cancer patients obtained in the present study were higher than controls and those obtained by Rose and Davis (1977,1980). We have observed that only 8/111 (7.2%) patients had all 7 hormones within normal limits. Out of these 8 patients, 5 had stage

II and 3 had stage III disease. Therefore, the remaining 92.7% patients had abnormal menstrual function which might be due to advanced disease or hyperprolactinaemia. The high pretherapeutic levels of FSH, LH and PRL with concomitant low E_2 levels in our set of patients might suggest ovarian failure at the time of diagnosis itself which might be due to advanced stage of the disease.

In the present study, statistically non-significant decreased trend in FSH and E_2 , an increase in PRL and unaltered LH was observed as stage advanced. Moreover, it was observed that node negative patients exhibited relatively lower levels of FSH, LH and prolactin and higher levels of circulating steroids as compared to node positive patients. The difference was statistically significant only for prolactin. These findings collectively announce node negative patients as relatively more hormone dependent than node positive patients. This was further validated by the observed low steroid receptor negativity ($ER^- PR^-$ 1/11 ; 9.0%) of the node negative patients as compared to node positive patients ($ER^- PR^-$ 14/89 ; 15.7%). Significant elevation of LH and PRL and non-significant elevation of FSH and E_2 in patients with histologic grade II+III tumors was observed as compared with histologic grade I tumors. Moreover, 88.2% of these patients had grade II + III tumors.

On the other hand, none of the HG I tumors were negative for steroid receptors while 11/60 (18.3%) grade II + III tumors were negative for steroid receptors. This finding collectively explains in part the aggressive biologic behaviour of histologic grade II and III tumors.

We have correlated pretherapeutic levels of these gonadotropins according to disease status : (1) patients who developed recurrence and (2) responders. However, we did not find any significant difference in gonadotropins in non-responders and responders. The FSH elevations amongst responders were statistically significant and non-significant amongst non-responders, while LH elevations were statistically significant in these groups.

Chemotherapy resulted into a significant rise in FSH and LH leading to ovarian failure in pre-menopausal patients. This data clearly indicated that drug-induced amenorrhea is identical to physiologic menopause and that chemotherapy alters the hypothalamic-pituitary-ovarian axis to the extent that it suppresses ovarian activity, but leaving intact hypothalamic and pituitary function as feedback regulatory mechanisms (Delrio et al, 1986). Dnistrian et al (1985) have reported that pituitary function is essentially unaffected by the cytotoxic drugs. Moreover, we have observed decreased ratio of estradiol : gonadotropins.

Ovarian failure was documented by a decrease in estradiol : gonadotropin ratio resulting in hormonal profile characteristic of women after menopause or surgical castration. Thus, CMF induced amenorrhea is generally permanent in older patients but may be reversible in younger patients. Its possible therapeutic benefit in breast cancer patients has been difficult to evaluate. However, it is still not clear whether ovarian failure might potentiate the antitumor effect of adjuvant therapy in pre-menopausal patients. Our results indicate that durg induced amenorrhea in pre-menopausal patients was not responsible for the improvement of disease free survival observed in these patients, because majority of our patients developed recurrances immediately after completion of adjuvant therapy. Chemotherapy culminated into a progressive disease in 17/22 (77.2%) patients.

In pre-menopausal patients, the effect of TMX on E₂ has already been described (Chepter II). TMX might be sensitizing the ovary to the stimulatory effect of gonadotropins or augment the physiologically active fraction of FSH. The endocrine therapy resulted into significant elevation in FSH and LH. It may be recalled at this point that the endocrine therpay concluded into significant decline in PRL and T levels. Delrio et al (1986) suggested

that exaggerated FSH-LH release by the pituitary Gn-RH stimulation supports the existence of a failure of the normal feedback control mechanism of gonadotropin synthesis during the treatment with TMX.

A combination of chemoendocrine therapy was useful in patients who despite the presence of ER and PR, had a very aggressive disease. In pre-menopausal patients treated with CMF +TMX the time of onset and incidence of amenorrhea as well as fall of circulating estrogens, were similar to those patients treated with CMF alone. The chemoendocrine therapy resulted into non-significant elevations of FSH and LH.

Chemotherapy and endocrine manipulation resulted into statistically significant elevations of both FSH and LH after treatment, while chemoendocrine therapy exhibited no change in FSH levels with non-significant elevations in LH. However, these levels even after treatment were significantly higher when compared with controls (FSH : $P < 0.001$; LH : $P < 0.01$). The high pretherapeutic levels of FSH, LH and PRL with concomitant reduced E_2 levels clearly suggests ovarian failure at the time of diagnosis itself due to advanced stage of the disease.

Interestingly, we have observed in few patients only that prior to death there was a significant drop in the FSH and

LH with concomitant rise in PRL. On the other hand, in patients who were in remission, the gonadotropins remained elevated with low PRL levels. we would like to confirm this finding by analysing some more samples.

ABSTRACT

Chapter 4 elaborates the incidence of pituitary gonadotropins in breast carcinoma. The prevalence of gonadotropins had no relation to stage and nodal status. In addition, the gonadotropins amongst responders were not different from non-responders. Pretherapeutic levels of LH, however, were significantly elevated as compared to controls ($P < 0.001$).

Part B details the fluctuations in gonadotropins with prograssion and response during the course of breast cancers. Pretherapeutic gonadotropin levels were compared with the levels before progression and at progression. Similarly, amidst responders, the pretheraeutic levels were compared with the levels at last follow-up.

The levels of FSH at last follow-up in responders were significantly elevated ($P < 0.01$). Contrary to that, FSH elevations in nonresponders were statistically not significant. This was in contrast to LH levels which were significantly elevated in both, responders and nonresponders

at last follow-up and at progression respectively. Also depicted here are some graphic representations on variations in pituitary gonadotropins during the course of breast cancers.

Section C enumerates the variations in gonadotropins with the type of therapy instituted to the patients.

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TABLES

Table 1 : Pituitary gonadotropins in pre-menopausal breast carcinoma (M \pm SE)

		FSH mIU / ml	LH mIU / ml
Control	30	11.48 \pm 00.78	10.32 \pm 0.35 *
Breast Cancer Patients	111	42.12 \pm 15.67	26.61 \pm 3.50 *
Below normal limit		11/111 (09.9%)	19/111 (17.1%)
Above normal limit		18/111 (16.2%)	13/111 (11.7%)

* - P < 0.001

Table 2 : Pituitary gonadotropins , estradiol and prolactin in relation to stage (M \pm SE)

Stage	N	FSH mIU / ml plasma	LH mIU / ml plasma	E 2 pg / ml serum	PRL ng / ml plasma
II	27	87.17 \pm 58.67	27.60 \pm 6.66	110.20 \pm 19.39	859.43 \pm 17.96
III	57	33.35 \pm 88.84	28.61 \pm 5.82	885.19 \pm 14.55	854.92 \pm 18.39
IV	16	11.55 \pm 81.81	19.78 \pm 4.42	888.72 \pm 23.38	139.17 \pm 99.91
Entered at relapse	11	15.57 \pm 84.22	24.87 \pm 7.84	877.98 \pm 16.31	145.69 \pm 96.72
Advanced stages	84	26.78 \pm 86.84	26.27 \pm 4.13	884.98 \pm 18.93	882.86 \pm 23.67
Controls	38	11.48 \pm 88.78	18.32 \pm 8.35	167.28 \pm 24.18	888.43 \pm 88.78

Table 3 : Pituitary gonadotropins, estradiol and prolactin in relation to nodal status (M \pm SE)

Nodal status	N	FSH mIU / ml plasma	LH mIU / ml plasma	E 2 pg / ml serum	PRL ng / ml plasma
Node negative	11	26.18 \pm 08.72	18.88 \pm 8.34	114.24 \pm 41.83	24.64 \pm 07.85
Node positive	89	47.56 \pm 19.68	27.90 \pm 4.15	890.52 \pm 10.84	75.18 \pm 19.64

* - P < 0.02

Table 4 : Pituitary gonadotropins, estradiol and prolactin in relation to histologic grade (H \pm SE)

Histologic grade	N	FSH mIU / ml plasma	LH mIU / ml plasma	E ² pg / ml serum	PRL ng / ml plasma
I	68	22.20 \pm 11.08	14.76 \pm 07.94	071.90 \pm 23.66	038.34 \pm 18.28
II	37	23.94 \pm 06.08	33.89 \pm 06.23	111.40 \pm 20.98	072.09 \pm 16.89
III	23	38.85 \pm 12.43	39.68 \pm 11.56	065.50 \pm 19.32	147.65 \pm 69.16
II+III	60	29.39 \pm 05.97	35.59 \pm 05.80	094.68 \pm 15.17	101.05 \pm 28.52

‡ - P < 0.05

Table 5 : Pretherapeutic pituitary gonadotropins in relation to
disease status (M \pm SE)

	N	FSH mIU / ml plasma	LH mIU / ml plasma
Patients who developed recurrence	31	35.56 \pm 13.78	26.60 \pm 05.37
Responders	21	29.27 \pm 11.82	29.28 \pm 11.34

Table A A : Pituitary gonadotropins, estradiol and prolactin in relation to disease status (M \pm SE)

Disease	N	FSH	LH	E	PRL
status		mIU / ml plasma	mIU / ml plasma	pg / ml serum	ng / ml plasma

Patients who					
developed recurrence 31					
Pretherapeutic		35.56 \pm 13.78	26.60 \pm 05.37 ^{2,§}	78.14 \pm 22.22 [‡]	149.39 \pm 60.73 [‡]
Before progression		47.40 \pm 08.04 [@]	084.39 \pm 18.00 [@]	46.68 \pm 10.06 [‡]	019.48 \pm 04.54 ^{‡,§}
At progression		86.95 \pm 24.85 [@]	103.87 \pm 15.29 [§]	13.60 \pm 02.31 [‡]	060.86 \pm 10.40 [§]
Responsive disease 21					
Pretherapeutic		29.27 \pm 11.82 [@]	029.28 \pm 11.34 [@]	76.53 \pm 14.20 [‡]	047.49 \pm 11.80 [‡]
At last F / U		85.28 \pm 15.67 [@]	100.71 \pm 17.83 [@]	39.38 \pm 08.41 [‡]	007.98 \pm 01.10 [‡]

1, @ - P < 0.01 § - P < 0.001 ‡ - P / 0.05

Table 6 B : Pituitary gonadotropins in responders.

Relation to stage (M \pm SE)

Stage		N	FSH mIU / ml	LH mIU / ml
II	Pretherapeutic	10	26.40 \pm 10.38	024.58 \pm 09.28 @
	At last F / U		73.74 \pm 21.12	090.21 \pm 23.67 @
Advanced	Pretherapeutic	11	32.46 \pm 22.95	033.55 \pm 20.41 \$
	At last F / U		96.82 \pm 23.68	110.26 \pm 27.15 \$

@ - P < 0.02 \$ - P < 0.05

Table 7 : Pituitary gonadotropins, estradiol and prolactin in relation to therapy (M \pm SE)

Therapy	N		FSH mIU / ml plasma	LH mIU / ml plasma	E ² pg / ml serum	PRL ng / ml plasma
Chemo	22	Prethera	017.14 \pm 06.52 ^x	026.06 \pm 05.35 ^z	096.43 \pm 29.96 ⁺	122.02 \pm 049.99
		After therapy	132.15 \pm 44.70 ^x	149.81 \pm 32.02 ^z	021.75 \pm 04.43 ⁺	030.69 \pm 008.83
Endocrine	08	Prethera	025.31 \pm 10.81 ^z	016.13 \pm 07.70 ^z	052.45 \pm 30.95	071.17 \pm 021.37 ⁺
		After therapy	115.22 \pm 13.82 ^z	157.76 \pm 22.16 ^z	041.33 \pm 16.10	012.23 \pm 002.41 ⁺
Chemo-Endo	11	Prethera	060.10 \pm 33.30 ^z	033.44 \pm 11.63 ^z	051.84 \pm 15.18	173.18 \pm 144.67
		After therapy	062.05 \pm 11.73 ^z	083.41 \pm 21.30 ^z	052.27 \pm 33.05	017.37 \pm 004.65
Controls	30		011.48 \pm 00.79 ^z	010.32 \pm 00.35 ^z	167.20 \pm 24.18	008.43 \pm 000.70

+ , z - P < 0.02 z , z , z , z - P < 0.001 # - P < 0.01

Table 8 : Estradiol : gonadotropin ratio in relation
to therapy (M \pm SE)

Therapy	N		E : FSH 2	E : LH 2
Chemo	22	Prethera	40.06 \pm 29.60	26.52 \pm 14.19
		After therapy	02.02 \pm 01.15	00.68 \pm 00.33
Endocrine	08	Prethera	04.78 \pm 01.85 *	07.75 \pm 02.83 @
		After therapy	00.37 \pm 00.20 *	00.25 \pm 00.12 @
Chemo-Endo	11	Prethera	05.95 \pm 03.27	06.76 \pm 02.87
		After therapy	01.18 \pm 00.63	01.35 \pm 00.77

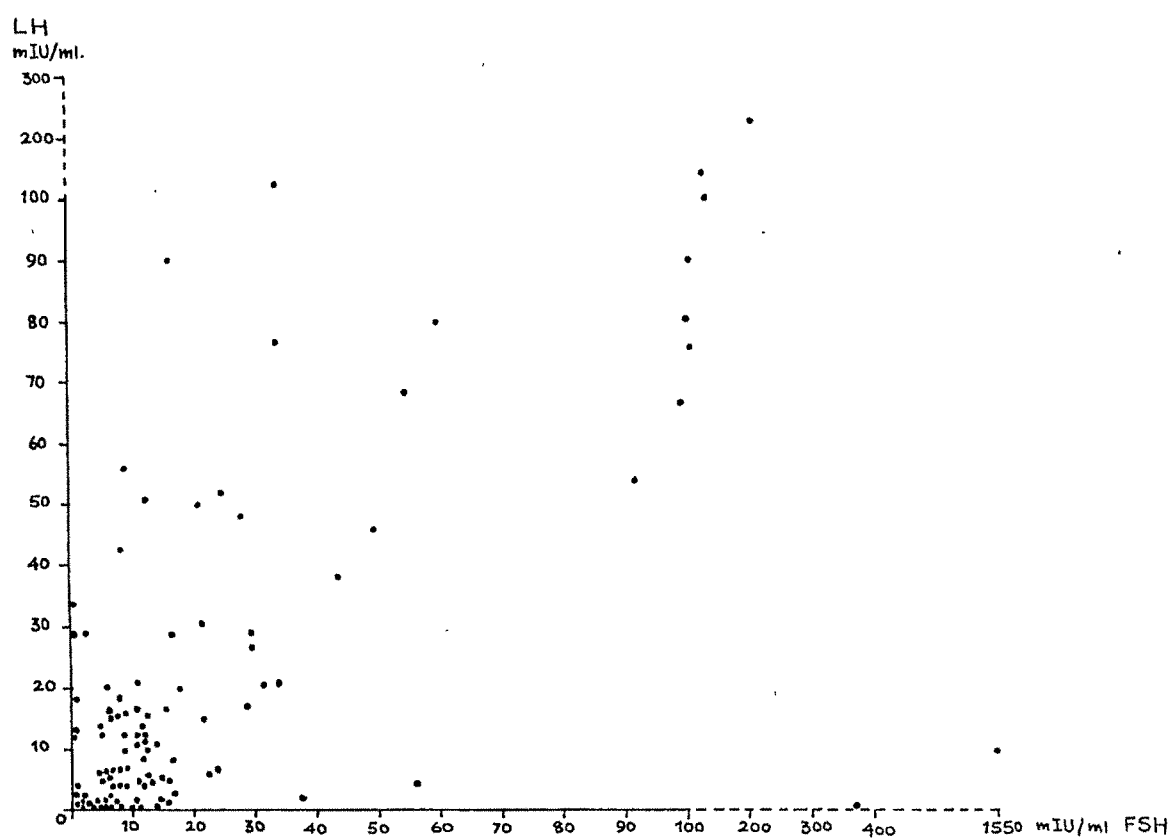
* - P < 0.05 @ - P < 0.02

FIGURES

Fig. 1

Scatterogram showing FSH, LH pre-menopausal breast carcinoma patients.

Fig. 1



I : GONADOTROPINS IN PATIENTS WHO DEVELOPED PROGRESSIVE
DISEASE :

Fig. 2

stage II, grade III patient was treated with surgery followed by radiotherapy and was disease free for 20 months. However, she developed local recurrence at the end of 21st months.

FSH was undetectable while LH showed an increasing trend post-operatively but resulted into decreased levels at last follow-up.

Stage II
HG III

— FSH
- - - LH

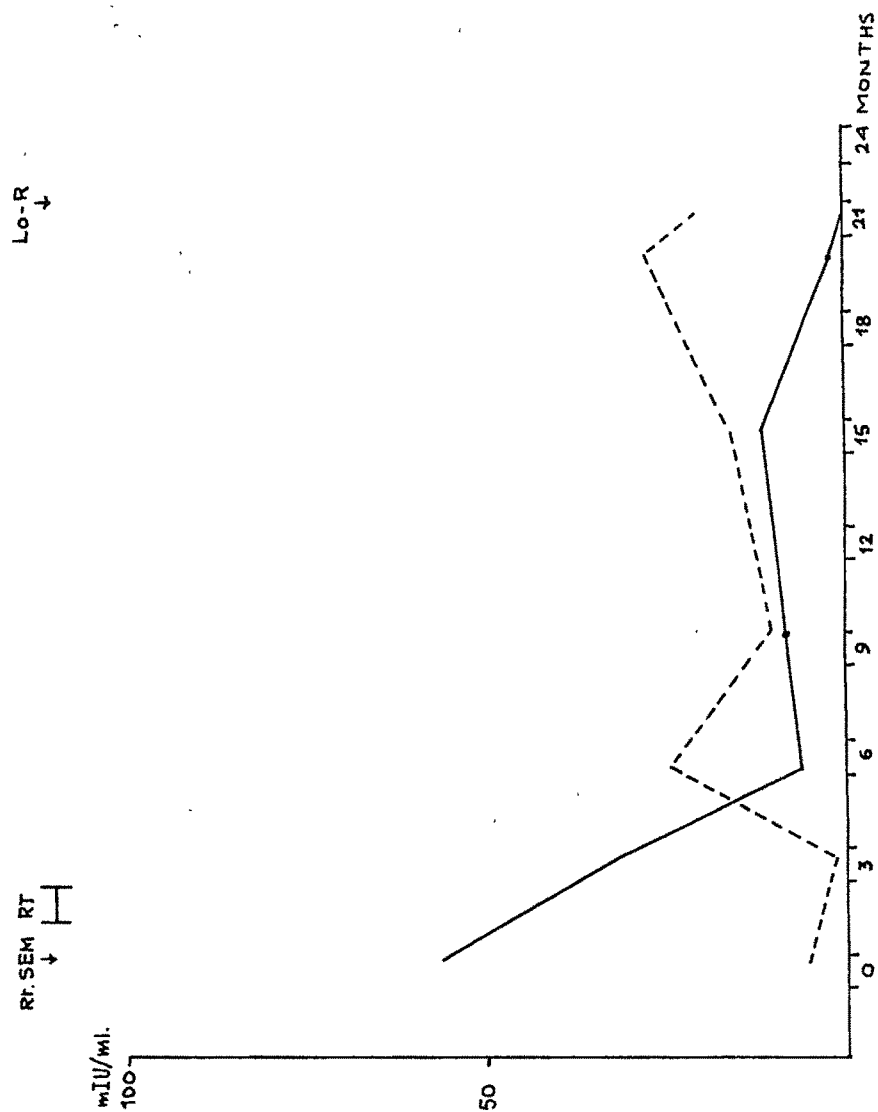


Fig.2

Fig. 3

A stage II, grade II patient treated with surgery followed by CMF. she responded to it but within 8 months. She developed metastasis in lungs and bone. She was treated with 2^o line chemotherapy + TMX. She responded in the beginning but again developed brain metastasis and was given cranial radiotherapy. She finally died after 1 month.

We have observed an interesting finding i.e. after the development metastasis in lungs and bone, the FSH, LH levels dropped significantly in spite 2^o line chemoendocrine therapy finally leading to death.

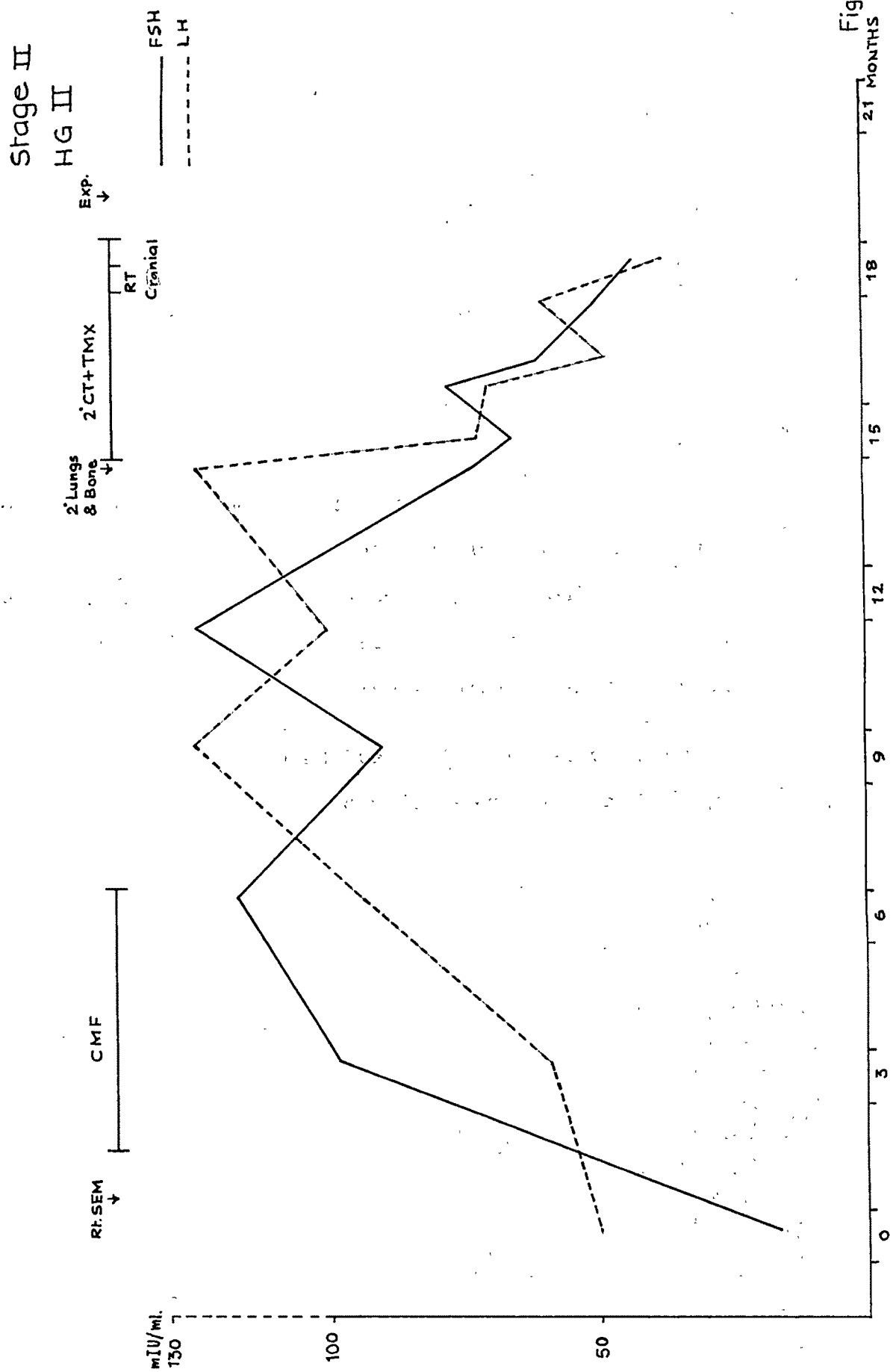


Fig.3

Fig. 4

A stage IV, grade III patient with disseminated disease was treated with chemotherapy and later on with 2^o line chemotherapy. She did not respond to it and developed metastasis in the brain. She was given cranial radiotherapy but ended to death within 1 month.

FSH and LH levels were elevated throughout disease course but significantly dropped prior to death.

Stage IV
HG III

FSH
LH

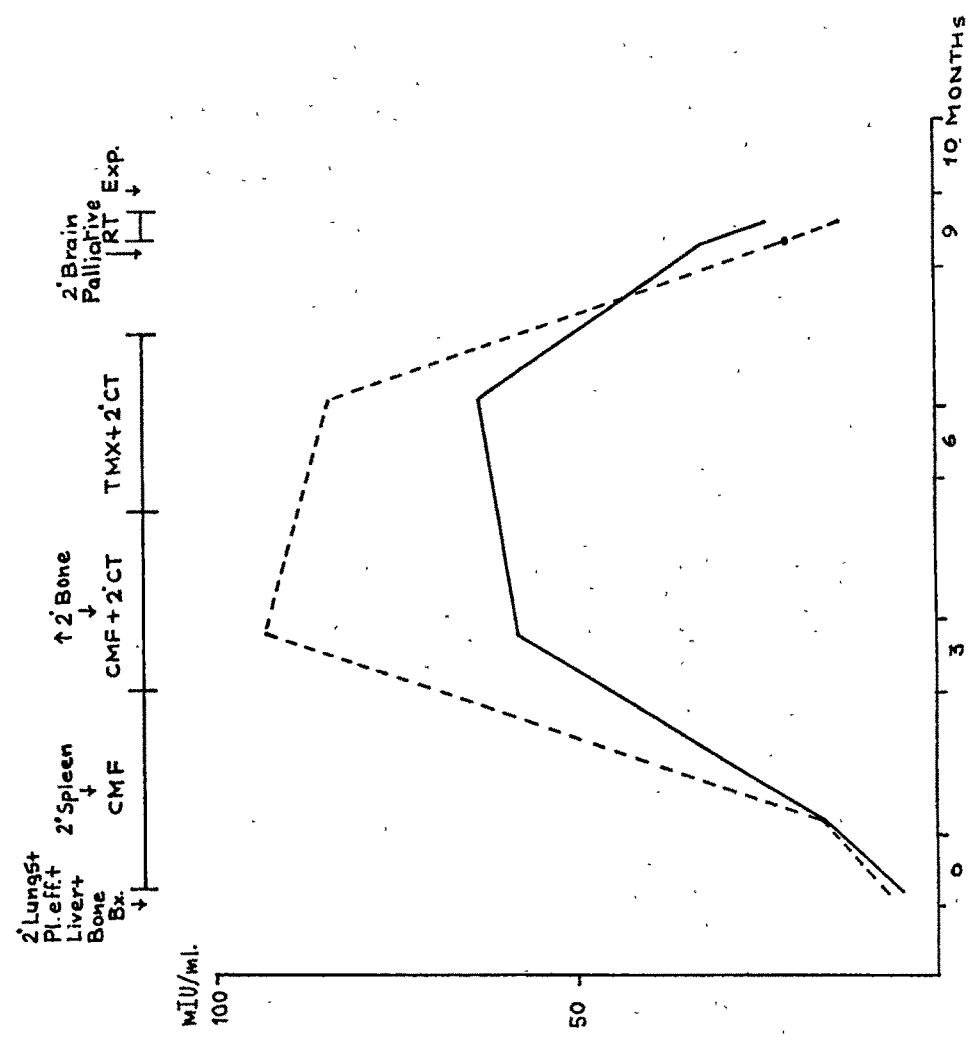


Fig.4

Fig. 5

A patient reported with local recurrence in axilla. The treatment offered was axillary clearance followed by radiotherapy and CMF. Initially she responded to it but after 4 months developed metastasis in the brain. She expired within a couple of weeks. 2 months after treatment, elevations in FSH and LH were observed which dropped significantly prior to death.

Rec. Ca.
HG II

— FSH
- - - LH

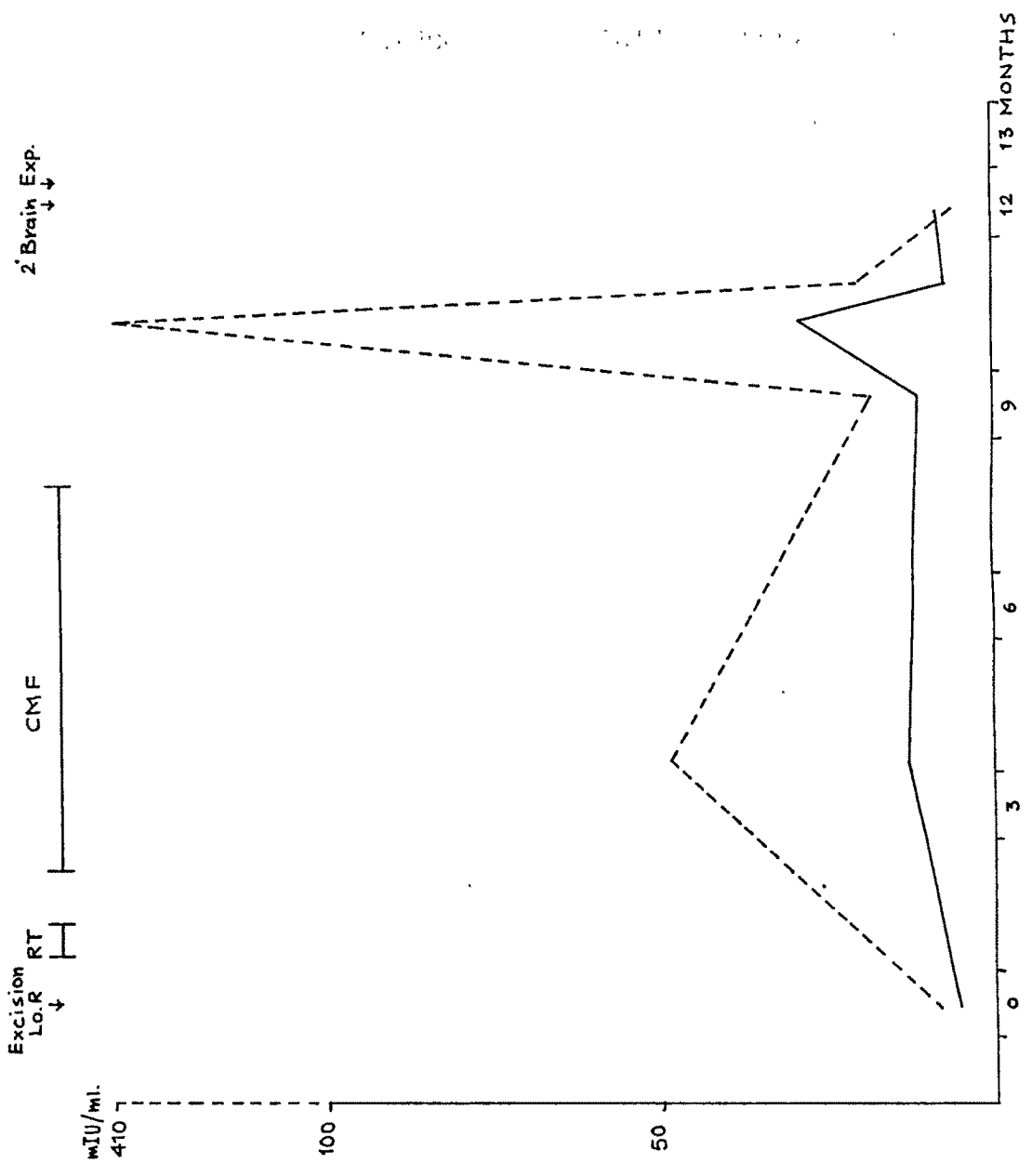


Fig. 5

II. GONADOTROPINS IN RESPONDERS :

Fig. 6

A stage II, grade II patient was treated with surgery and followed by CMF.

Very high levels of FSH and LH were recorded with CMF and remained high at the end of 2 years.

Stage II
HG II

— FSH
- - LH

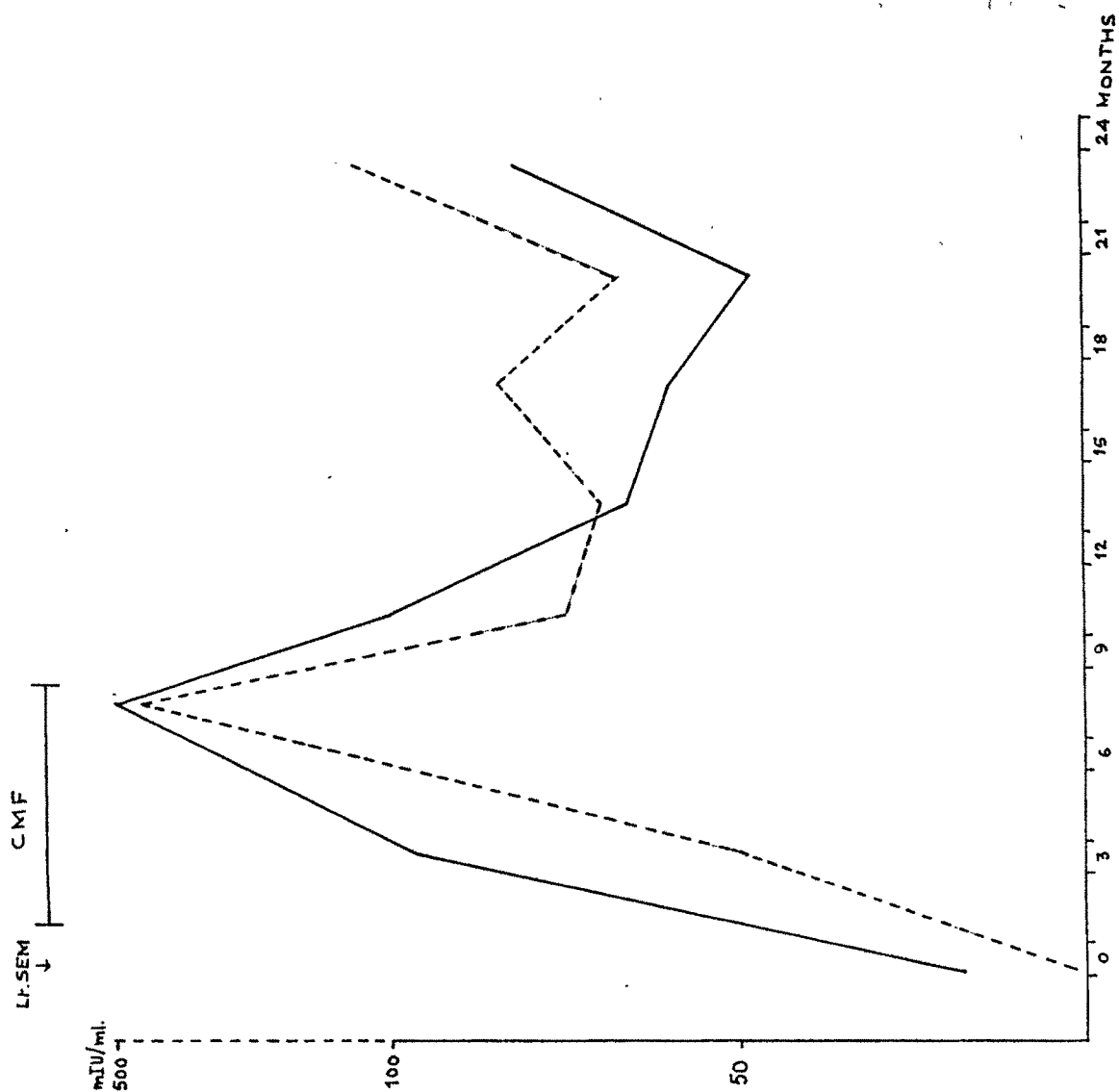


Fig. 6

Fig. 7

Stage II, grade II patient was treated with surgery + CMF + RT followed by bilateral oophorectomy.

FSH and LH levels were high with treatment. The patient remained disease free throughout the follow-up period of 2 years.

Stage III
HG II

— FSH
- - - LH

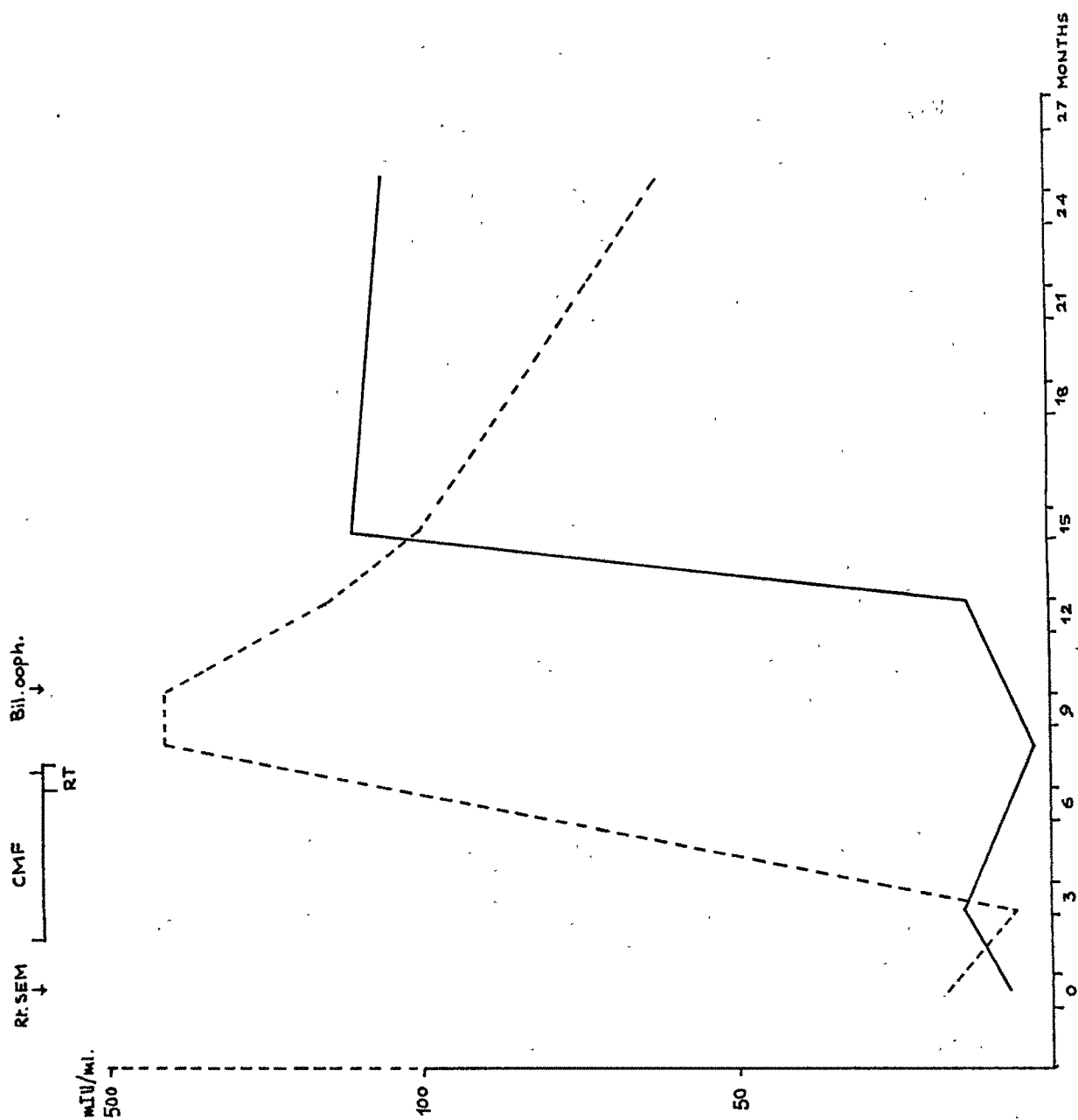


Fig.7

Fig. 8

Stage II, grade III patient was treated with surgery followed by radiotherapy. The FSH, LH levels remained high throughout the follow-up period and the patient was disease free at the end of 2 years.

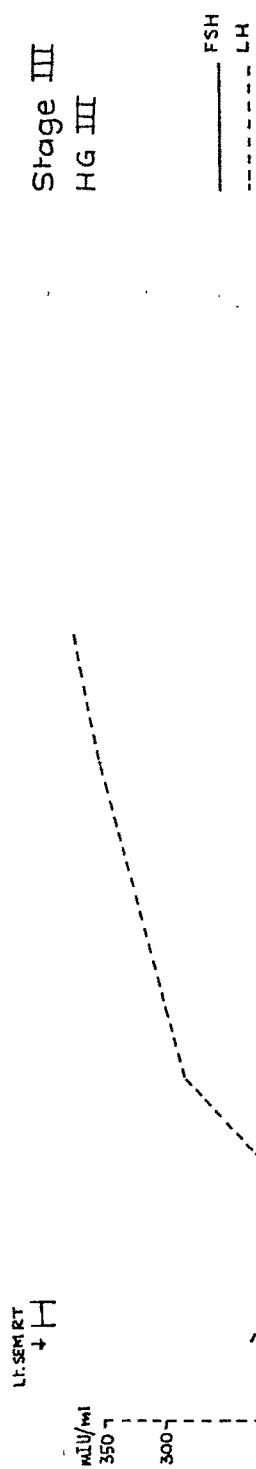


Fig. 8

III. GONADOTROPINS, E AND PRL IN RELATION THERAPY ;
2

Fig. 9

A stage II, grade II patient treated with surgery followed by CMF. CMF resulted into high LH, FSH levels with concomitant low E and PRL levels.

Stage II
HG II

FSH
LH
PRL
E₂

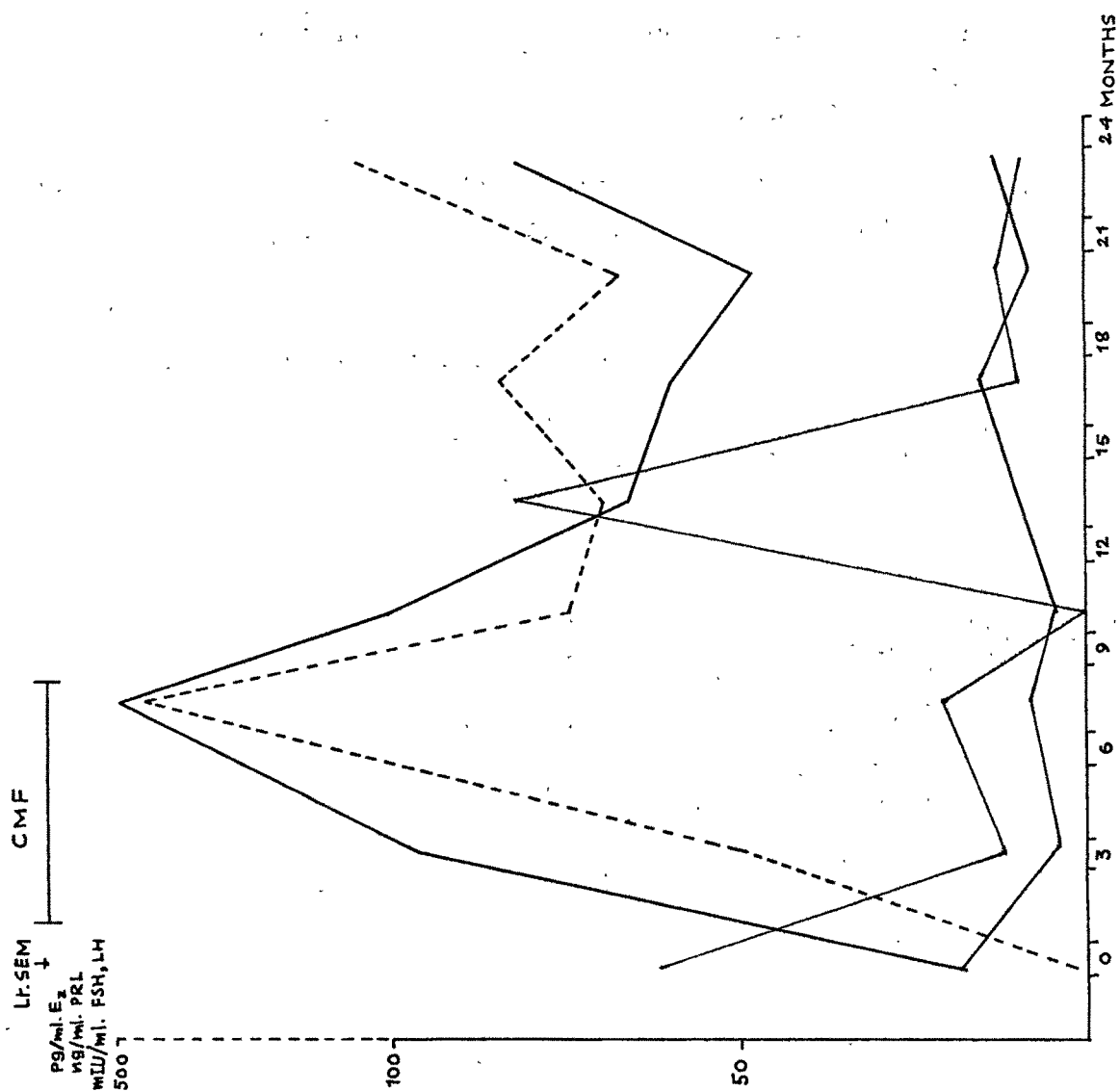


Fig. 9

Fig. 10

A stage II, grade II patient treated with surgery and CMF.

The FSH, LH levels elevated and E₂ and PRL levels dropped with CMF and the disease was in remission. With the appearance of metastatic disease in lungs and bone, FSH and LH levels decreased with a concomitant elevation of PRL.

Stage II

HQ II

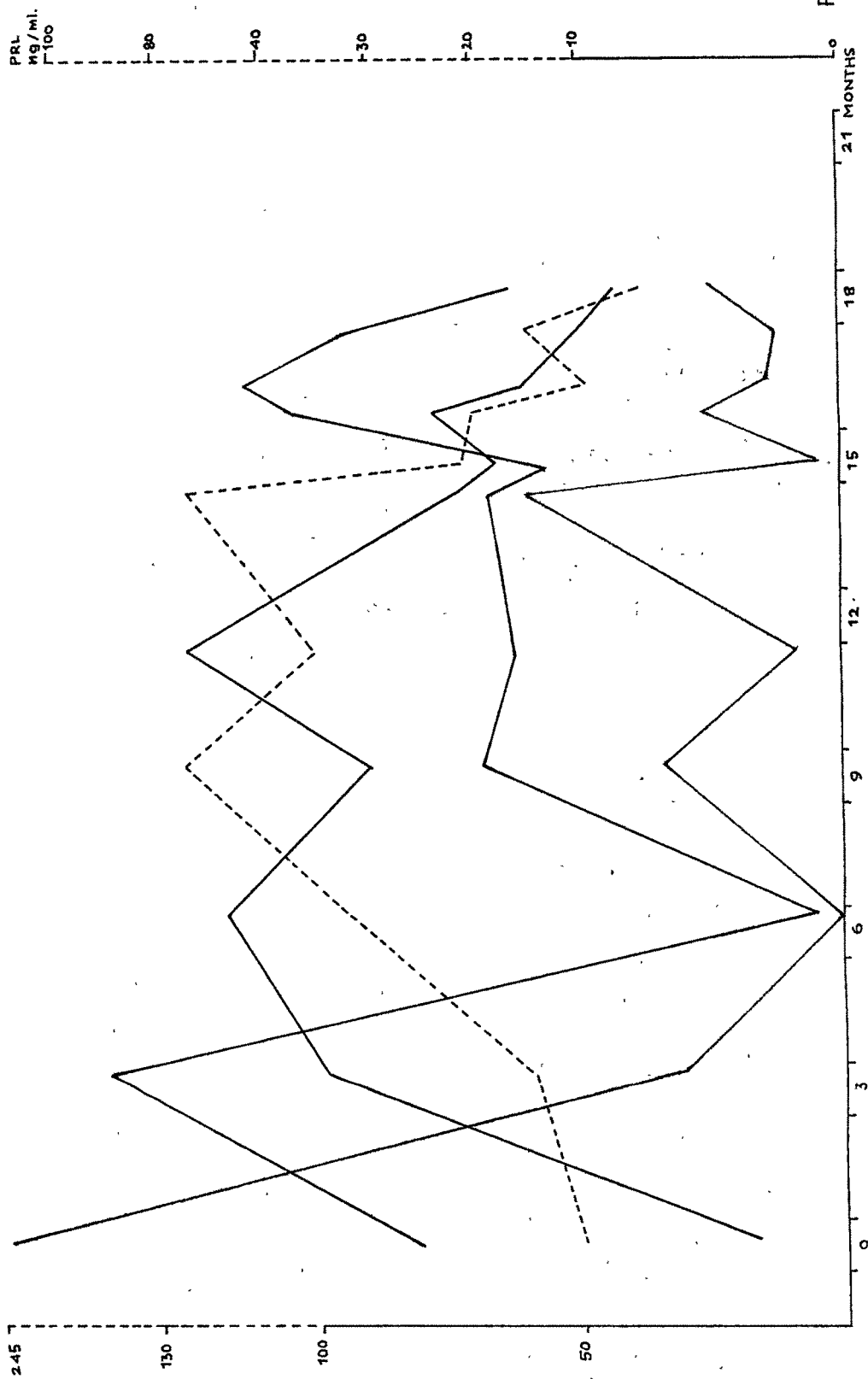
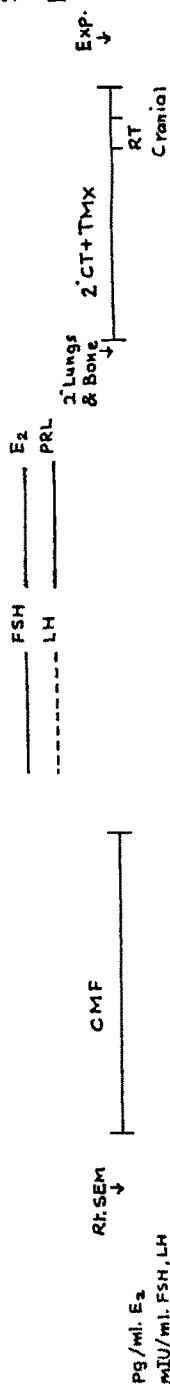


Fig.10

Fig. 11

A stage IV, grade III patient, when treated with CMF followed by chemoendocrine therapy, a rise in FSH, LH with low E₂ (100 ng/ml) was observed. However, with disease progression, PRL levels showed an elevation.

Stage IV
HG III

FSH
LH
PRL
E₂

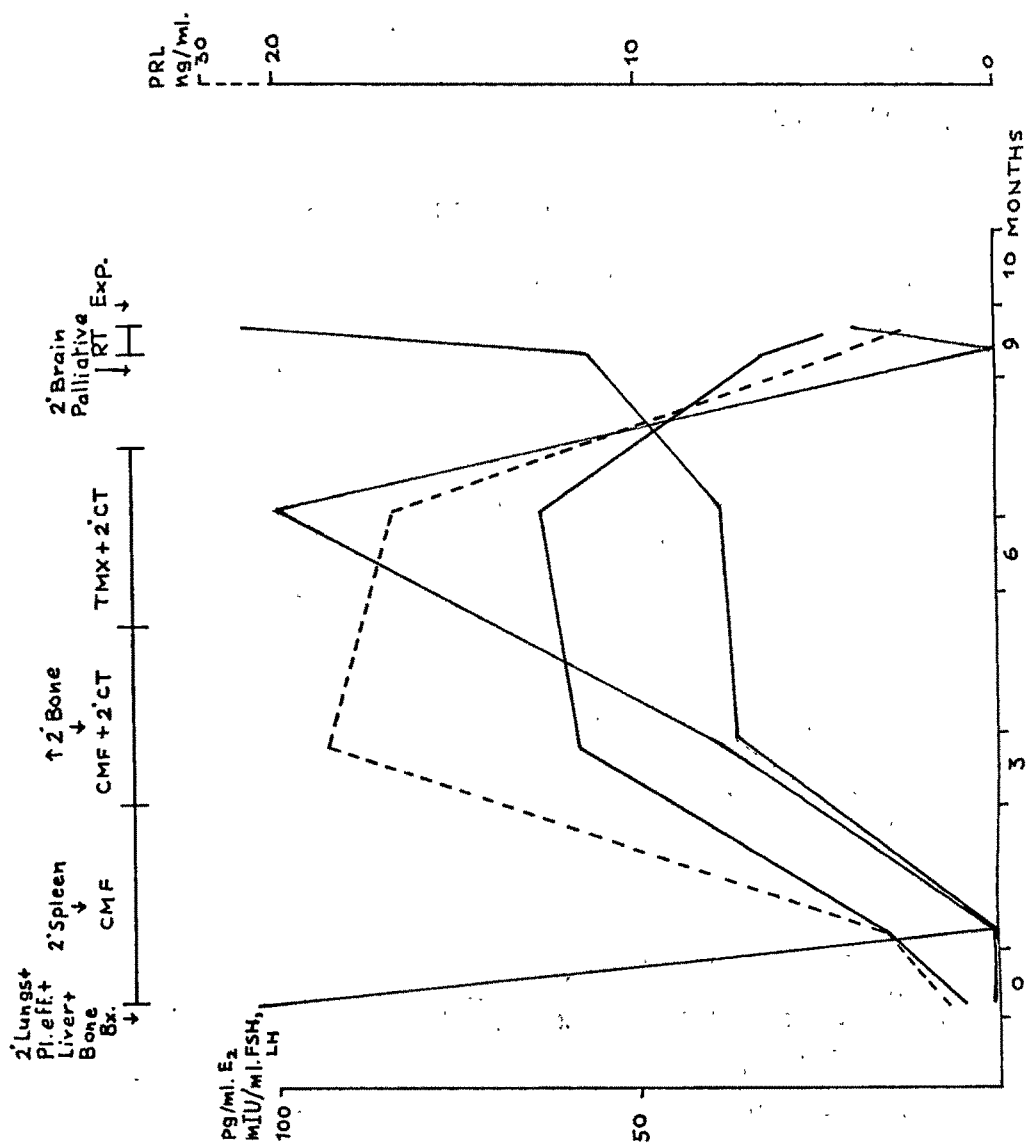


Fig. 11

Fig. 12

The patient has taken CMF only for 1 month which resulted into homonal imbalance.

Rec. Ca.
HG III

FSH
LH
E2
PRL

Bil. ooph.
2 Lungs
↓

RT

CMF

Rt SEM
↓

mg/ml. PRL
pg/ml. E2
mIU/ml. FSH, LH

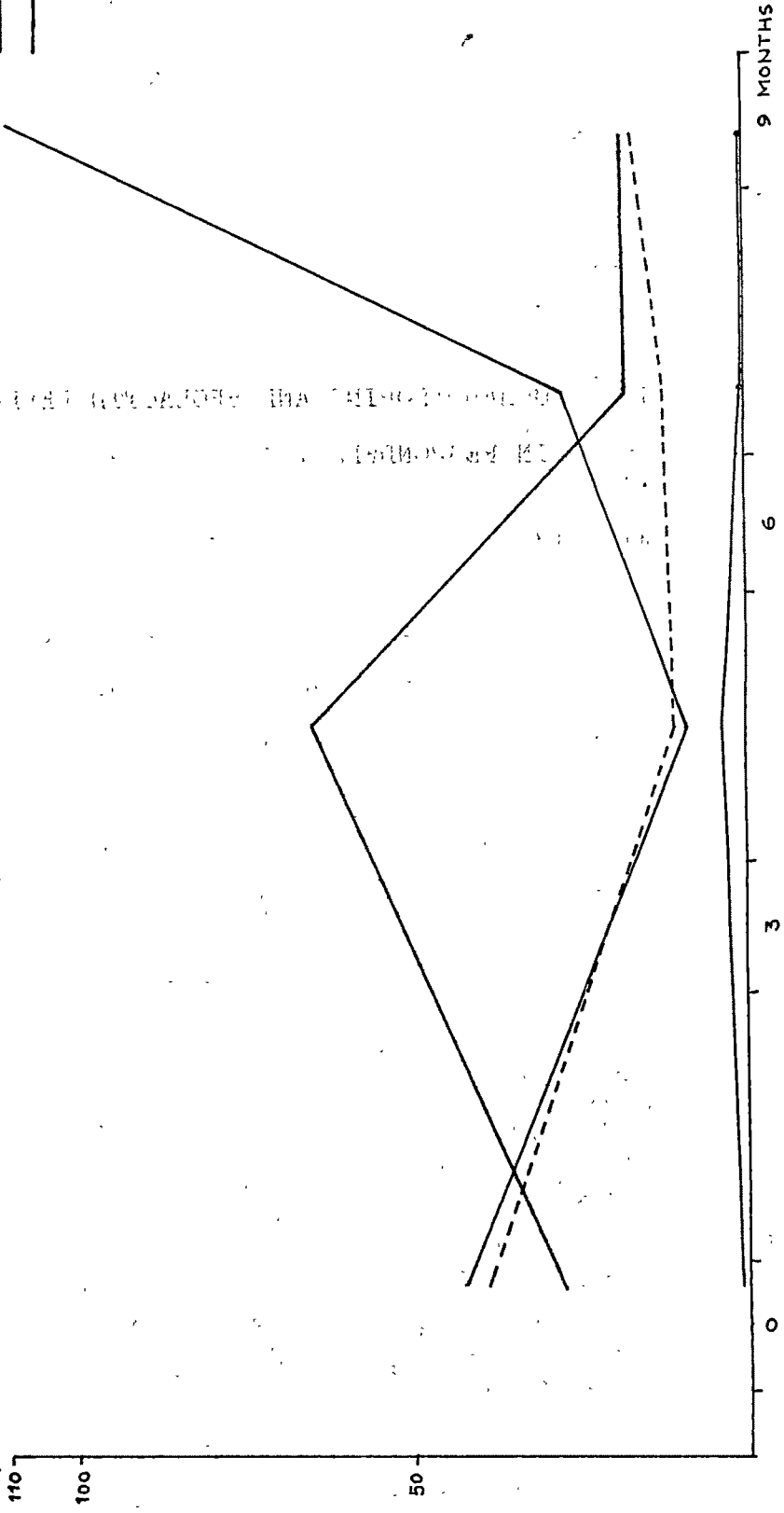


Fig.12

IV GONADOTROPINS AND PROLACTIN LEVELS PRIOR TO DEATH AND
IN RESPONDERS :

Fig. 13

In a stage II, grade II patient , the FSH and LH levels showed a sharp drop prior to death. The prolactin levels were high during this period.

Stage II
HG II

FSH
LH
PRL

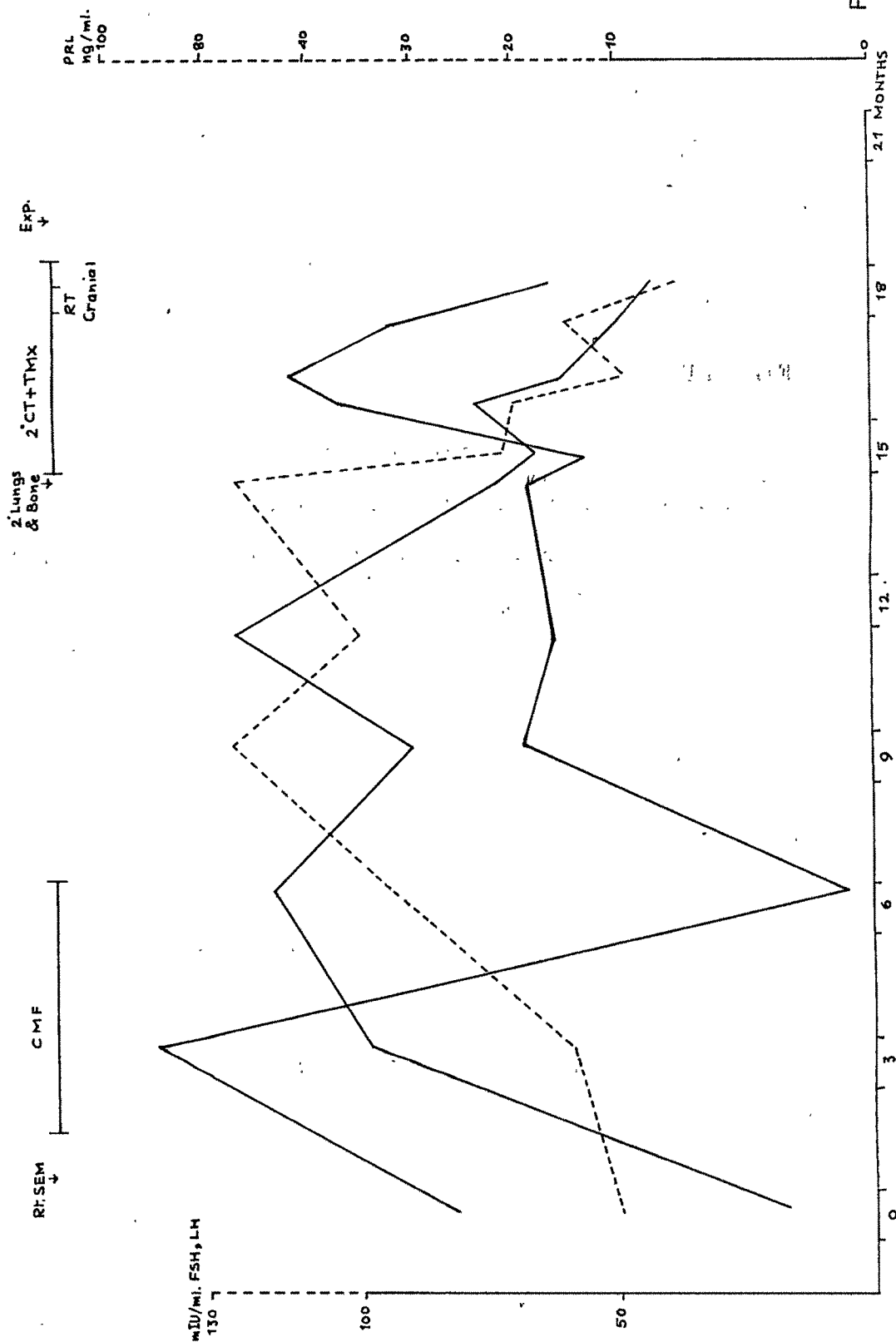


Fig. 13

Fig. 14

Stage IV, grade III patient showed a sharp decline in FSH, LH levels before the development of metastasis in brain. A further drop in FSH, LH was seen prior to death. PRL levels remained high during this period.

Stage IV
HG III

FSH
LH
PRL

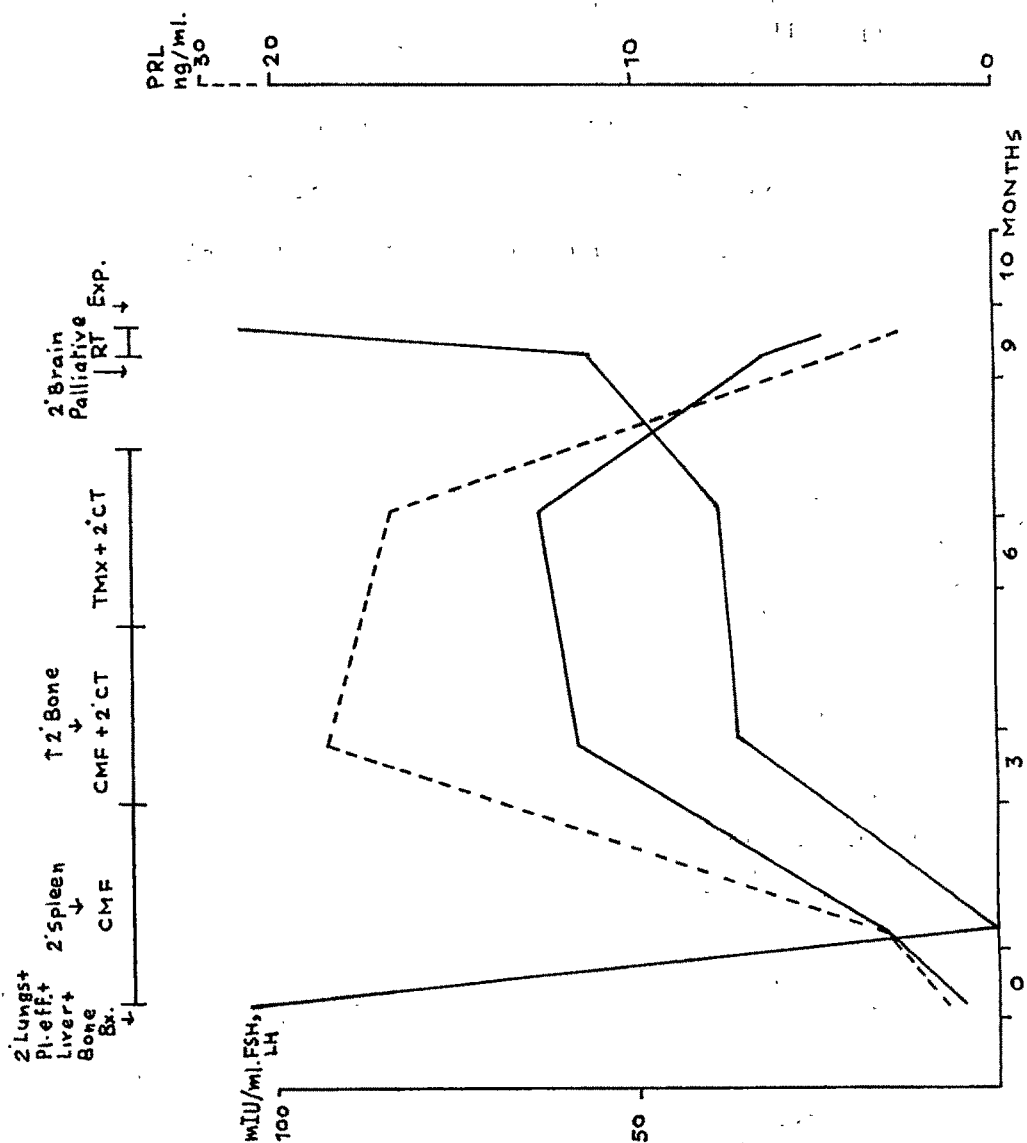


Fig.14

Fig. 15

A locally recurrent patient with grade II tumor was treated with CMF. A very sharp drop in FSH and LH was seen prior to death with concomitant elevation in PRL.

Rec. Ca.
HG II

FSH
LH
PRL

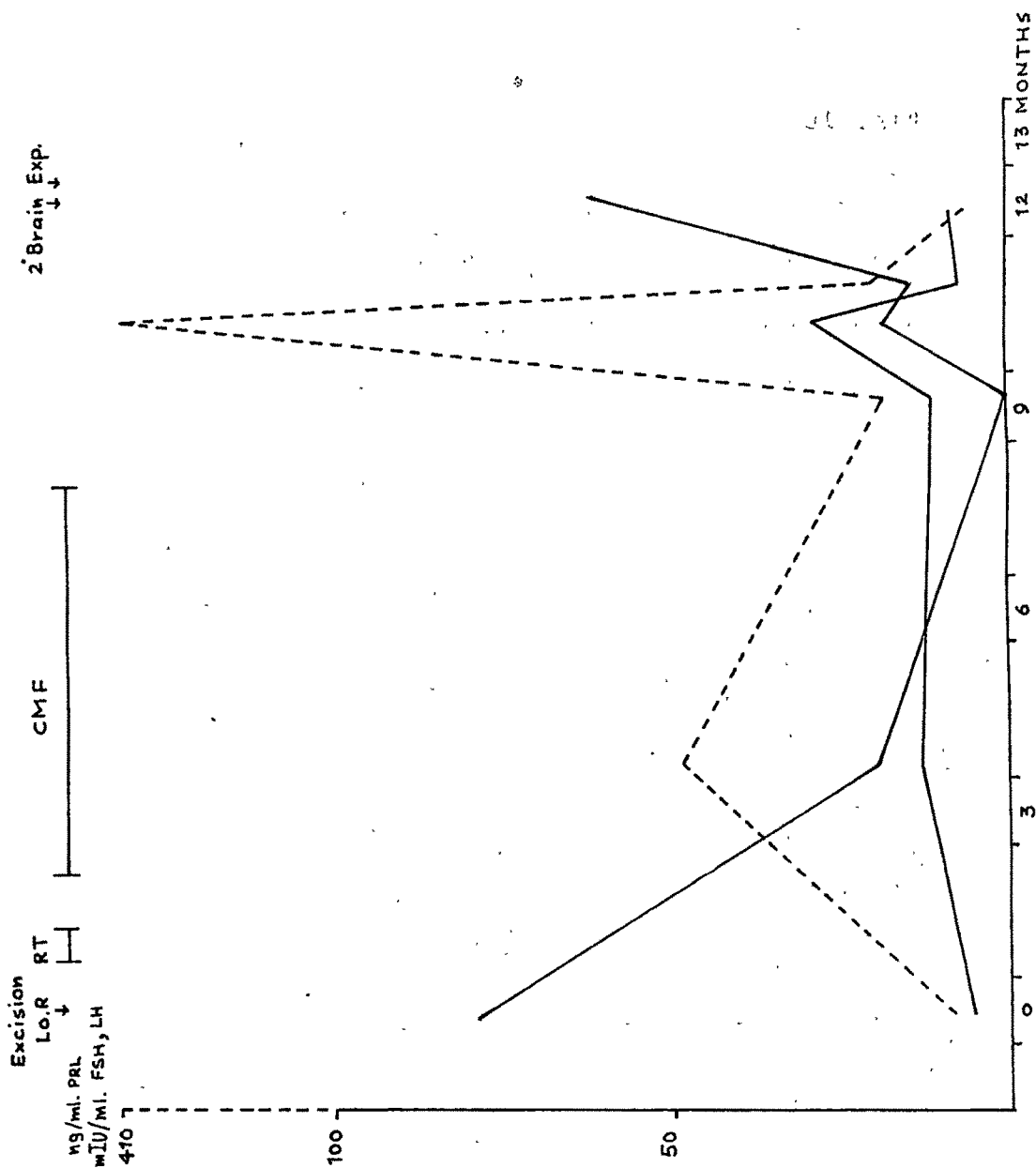


Fig.15

Fig. 16

A stage II, grade II patient remained in remission at the end of 2 years. The high LH, FSH levels were concomitantly accompanied by low PRL levels.

Stage II
HG II

— FSH
--- LH
— PRL

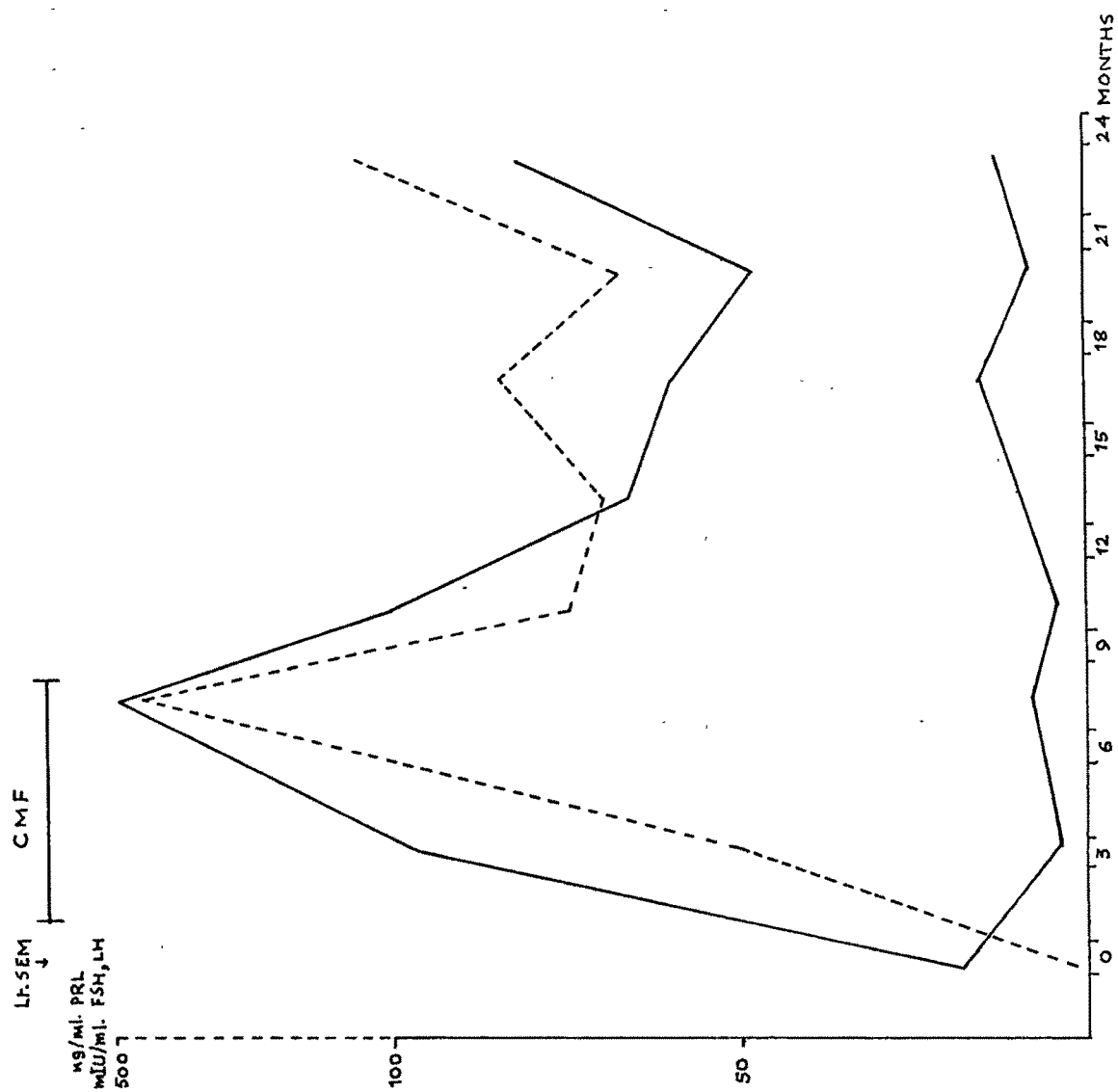


Fig.16