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Pituitary function in women with postpartum hemorrhage

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To my wife, Maria Carmen

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INTRODUCTION

The syndrome of ischemic necrosis of the anterior pituitary gland subsequent to postpartum hemorrhage was first described by the British pathologist, H.L. Sheehan, in 1937.[1] Sheehan stated that the causal relationship of postpartum hemorrhage to anterior pituitary necrosis was first suggested by the coincidental autopsy findings of pituitary necrosis in two patients who had chronic hypopituitarism:

> "The first case was a woman aged 35, who had attacks of hypoglycemia and had a laparotomy for suspected pancreatic tumor. At autopsy two days later we found that the anterior lobe was replaced by a thin layer of fibrous tissue. She had been ill since her last baby was born, but we did not check her obstetric history! The second case was a woman who died of unexplained shock two hours after delivery. At autopsy, we found that her pituitary was reduced to a small patch in front of the stalk; all the rest was fibrous scar. She had nearly died at the previous delivery two years before; the cause was retained placenta with severe hemorrhage. These two cases of chronic hypopituitarism suggested that the original lesion leading to scarring of the anterior lobe might be found in obstetric patients. So we examined the pituitary in all obstetric autopsies and found a number of fresh necroses of the anterior lobe."[2]

Sheehan wrote that as of 1937, about 60 cases of anterior pituitary necrosis had been reported in the literature. Those patients with postpartum hemmrrhage comprised the largest group and had the most severe degree of necrosis; in only four cases unassociated with pregnancy was necrosis widespread. He concluded that necrosis of the anterior

pituitary was a relatively frequent finding in females dying in the puerperium, that necrosis began at about the time of delivery, and that it was due to thrombosis rather than embolus, that is, that it was not a secondary event.[3]

Although Sheehan was the first physician to attribute anterior pituitary necrosis to the concurrent obstetrical accident, the first observer to report a case of acute extensive necrosis of the anterior pituitary in a patient with a severe obstetrical hemorrhage was the Polish pathologist, Glinski, in 1913. He described the case of a 37 year old female who suffered severe uterine bleeding secondary to uterine atony at the time of delivery. A Caesarean section was performed and nine days later the patient succumbed to puerperal sepsis. On post mortem examination, extensive pituitary necrosis was found. Glinski concluded that the necrosis was the cause and not the result of the uterine atony, hemorrhage, and collapse in women at the time of delivery. Had he reasoned differently, this clinical entity might have been named Glinski's Syndrome.[4]

Sheehan stressed that anterior pituitary necrosis secondary to postpartum hemorrhage was not a rare occurrence. Upon examination of the pituitaries of 127 patients who had died 12 hours to 35 days postpartum, he discovered 22 large and 19 small or medium-sized cases of pituitary necrosis.[5] He observed that anterior hypopituitarism,

which is most commonly secondary to postpartum hemorrhage[6], was not rare in the general population. In 1939, he estimated that there were two severe cases and seven less severe cases per ten thousand people and that these cases often went unrecognized[7]. Sheehan and Summers noted that among 95 cases of histologically proven chronic hypopituitarism, 62 cases were related to postpartum hemorrhage[8]. In a survey of 128 females who sustained hemorrhage and collapse at the time of delivery, 41(32%) showed some degree of diminished pituitary function[9].

There is no general agreement about the pathogenesis of Sheehan's Syndrome. The special vulnerability to ischemia of the pituitary gland during pregnancy is probably related to the two to three-fold increase in size of the adenohypophysis during pregnancy[10], as it is rare for reduced blood flow to cause pituitary necrosis in the non-pregnant female[11]. Indeed, reversible physiologic bitemporal hemianopsia can occur secondary to pituitary enlargement during pregnancy[12]. Sheehan contends that necrosis is produced by local ischemia due to vasospasm in the arterial supply. This results from any severe circulatory collapse at the time of delivery, most commonly due to obstetrical hemorrhage[13]. Sheehan and Standfield propose that during pregnanacy the vascular system of the pituitary becomes especially sensitive to vasoconstrictive stimuli and that

pregnancy therefore predisposes to pituitary necrosis. However, Kopaniky and Cann have found in dogs that pituitary vasculature responds quite differently to hypoperfusion. Using a miniature thermoelectric probe to continuously record blood flow in the anterior pituitary in the anesthetized dog, they have demonstrated that as hemorrhage increases, pituitary blood flow falls initially but then increases to rates greater than control. "Since cerebral blood flow in the dog is maintained but not significantly increased following hemorrhage, it appears that the rise above control level in the anterior pituitary is not secondary to maintenance of blood flow to the cerebral vascular tree. Instead, this change appears to be localized to the hypothalamo-hypophysial vasculature.[14] Gottshalk and Tilden have emphasized the importance of the physiologic increase in pituitary size during pregnancy and have noted that a massively enlarged gland confined within a limited space (the rigid sella turcica) would be exposed to considerable pressure and would suffer some degree of vascular compression. In this setting, a sudden drop in blood pressure due to postpartum hemorrhage would allow the increased tissue pressure to cause collapse of the pituitary vasculature and ischemic necrosis[15]. Consistent with this hypothesis, the patient Gottshalk and Tilden describe in their article was found on autopsy to have a segment of the anterior lobe of the

pituitary protruding from the sella and no necrosis was found in this area. The importance of the role of the sella in confining the enlarged pituitary gland of pregnancy has received further emphasis from the studies of Meador and Worrell. By using lateral sella turcica area measurements of skull reontgenograms, they have found that the sella turcica in 10 of 14 (71%) patients with Sheehan's Syndrome was significantly smaller (P less than .001) than it was in normal controls. They suggest two possible explanations for the small sella in patients with Sheehan's Syndrome: either the pituitary fossa decreases in size after the necrosis and atrophy of the gland, or the sella turcica is already small at the time of obstetrical hemorrhage. The postulate of a decrease in gland size causing a decrease in pituitary fossa size is questionable as small lateral fossa areas were detected in their patients as early as eleven months after the postpartum hemorrhage, presumably too early for such shrinkage to occur. However, if the sella is already small at the time of hemorrhage, this would further augment the pressure on the pituitary and this abnormality in configuration of the sella would predispose a bleeding patient to pituitary necrosis[16].

A classical case of Sheehan's Syndrome presents as complete anterior hypopituitarism. In 1938, Sheehan and Murdoch found that their patients with Sheehan's Syndrome characteristically had "absent or scanty menses, asthenia, hypothermia, and

sometimes change in weight."[17] Murdoch, in 1962, presented his clinical findings in 57 patients with Sheehan's Syndrome. 44 had total amenorrhea since the obstetrical accident, 9 had oligomenorrhea, 3 gave no information about their menstrual status, and 1 had regular menses. 41 had cold intolerance. 51 had obvious pallor. 56 had loss of body hair and of pubic, axillary, and eyebrow hair. 9 of 9 patients examined had genital atrophy. 23 patients complained of slow or monotonous speech.[18] Other signs and symptoms of Sheehan's Syndrome are failure of lactation postpartum, infertility, breast atrophy and decreased pigmentation of the areolae, increasing fatigue and lethargy, deep hoarse voice, thick coarse or waxy skin, macroglossia, decreased libido, and chronic constipation. Although severe pituitary necrosis usually causes total loss of anterior pituitary function, isolated or partial deficiencies of pituitary hormones may occur[19], and there is no definite sequence of loss of hormone function[20]. There have been numerous reports of patients with Sheehan's Syndrome having normal pregnancies and deliveries[21-28].

Sheehan's Syndrome does not develop within a predictable period of time after the obstetrical accident. It often emerges insidiously and exposes the patient to considerable risk[29,30]. Sheehan admonishes that endocrine changes should be carefully evaluated in every case where obstetrical

circumstances suggest that pituitary necrosis may have occurred[31]. Although a minimum blood loss of 500 cc. at the time of delivery and shortly thereafter is probably necessary to cause Sheehan's Syndrome[32], There is no correlation between the amount of postpartum hemorrhage and the likelihood of developing pituitary insufficiency[33]. Therefore, it is possible that apparently normal woemn with minimal postpartum blood loss may have impaired anterior pituitary function. As Sheehan's Syndrome is readily amenable to successful treatment with hormonal replacement therapy, it would be useful to know the incidence among asymptomatic patients at risk of laboratory evidence of anterior pituitary insufficiency and to identify these patients before they develop overt clinical disease.

METHODOLOGY

A. Patient Selection

All patients at Yale New Haven Hospital with a discharge diagnosis of postpartum hemorrhage within the past ten years were identified through chart review of Yale New Haven Hospital records. Postpartum hemorrhage was defined in this study as a minimum estimated blood loss of 500 cc.[34]. One hundred forty patients were identified. Patients were grouped according to the responsible obstetrician at the time of their postpartum hemorrhage. Those obstetricians (7) with the largest number of patients (80) were contacted and the study was discussed with them. After obtaining the obstetricians' consents, 38 of the 80 patients could be located; each received a description of the project and their participation was solicited. Patients in this group of 38 who were pregnant, breast-feeding, on drug therapy other than estrogen-progesterone compounds, taking medication which would interfere with laboratory determination of hormone levels, or who had a history of hypertension or diabetes mellitus were excluded from the study (4). Twelve patients from the initial group of 38 agreed to participate. Three of these patients were taking estrogens: Orthonovum 1/80 for contraception (two patients), and Premarin 1.25 mg. daily for three weeks of each month (one patient who was status post bilateral salpingo-oophorectomy and hysterectomy for pelvic actinomycosis). A thirteenth

patient, a research technician at the Yale New Haven Hospital, volunteered to participate, met the criteria for inclusion in the study, and was accepted. Patients were not selected according to age, parity, obstetrical or medical history, amount of estimated blood loss in excess of 500 cc., duration of hemorrhage, presence of hypotension or shock, interval between delivery and time of hemorrhage, or obstetrical cause of hemorrhage. The nature of the study was discussed in detail with each patient and all subjects gave written informed consent.

B. Protocol

All patients arrived at 8 AM after an overnight fast and were interviewed and examined. Formal fields of vision examination was obtained using the Goldmann perimeter. All patients had sella turcica x-rays, twenty-four hour urine collections for 17-hydroxycorticosteroids, 17-ketosteroids, and creatinine, 8 AM and 8 PM serum cortisols, unstimulated 8 AM serum FSH and LH samples, and fasting thyroid function tests. Each patient then underwent an insulin tolerance test as follows: with a constant intravenous infusion of normal saline through an indwelling scalp vein needle placed in the antecubital fossa, a bolus of regular insulin 0.1 units/kg body weight was injected over 30 seconds at time 0. Serum samples were obtained at -30,0, 30,45,60,90,

and 120 minutes for glucose, cortisol, growth hormone (GH), prolactin (PRL), and thyrotropin (TSH) determination. Patients were carefully monitored for hypoglycemic reactions which consisted of lightheadedness, fatigue, warmth, hunger, sweating, and drowsiness. Vital signs were taken frequently throughout the test. Concentrated intravenous glucose solution was available but not required. The test was terminated at 90 minutes for one patient (patient 3) as serum could not be successfully obtained thereafter. Two patients (patients 1 and 2) required an insulin dose of 0.15 units/kg body weight in order to acheive significant hypoglycemia (defined as a fall in blood glucose of greater than 50% from baseling to below 40 mg/100 ml and hypoglycemic symptomatology). All patients received ample glucose repletion upon completion of the test and left the hospital only after a stabilization of vital signs for one hour. On the following day, a thyrotropin-releasing-hormone (TRH) stimulation test for evaluation of TSH and PRL response was performed as follows: with a constant intravenous infusion of normal saline through an indwelling scalp vein needle placed in the antecubital fossa, a bolus of 100 micrograms of TRH was injected over 30 seconds at time 0. Serum samples were obtained at -15,0,15,30,45,60,90, and 120 minutes for TSH and PRL determination. Some patients transiently experienced nausea, facial flushing, urinary urgency, or a

metallic taste at the time of TRH injection; there were no other adverse reactions.

Additionally, one patient (patient 7) required a metapyrone test and an ACTH stimulation test. Metapyrone at a dose of 750 mgs. orally every four hours was given for twenty-four hours; twenty-four hour urines for 17-hydroxy-corticosteroids, 17-ketosteroids, compound S, and creatinine were obtained the day before, the day of, and the day after metapyrone administration. Vital signs were carefully monitored. Two days later, the patient received an ACTH stimulation test as follows: intravenous Cortrosyn^{R} 0.5 mgs. in 0.5 liters of a five % dextrose-water solution was infused at a constant rate over eight hours from 9 AM and 5 PM. Beginning at 8 AM, a twenty-four hour urine collection for 17-hydroxycorticosteroids, 17-ketosteroids, compound S, and creatinine was obtained. Serum cortisol levels were obtained at 8 AM, 2 PM, 4 PM, and 6 PM. The patient experienced no adverse effects.

This protocol was approved by the Human Investigation Committee of the Yale New Haven Hospital.

C. Assays

Radioimmunoassay determinations of serum levels of GH, PRL, and TSH were performed by Dr. Richard K. Donabedian. Burroughs-Welcome, Inc. provided the antisera for the GH assays, the National INstitute of Health provided antisera

for the PRL assays, and Cal-Biochem, Inc. provided antisera for the TSH assays. Serum cortisol determinations were performed by the Yale New Haven Hospital Department of Clinical Chemistry according to the fluorimetric method of DeMoor[35]. 17-hydroxycorticosteroids were determined spectrophotometrically by the Yale New Haven Hospital Department of Clinical Chemistry according to the metho described in Standard Methods of Clinical Chemistry, vol. 4, Academic Press, 1963. 17-ketosteroids and compound S were determined spectrophotometrically by the Yale New Haven Hospital Department oc Clinical Chemistry according to a modification of the method of James[36]. Serum thyroxine and thyroid-binding capacity were determined by the method of Seligson[37].

D. Statistics

P values were calculated by a paired student "t" test method.

RESULTS

The present age, date of postpartum hemorrhage, estimated blood loss (EBL), transfusions of units of whole blood received, interval between delivery and postpartum hemorrhage, cause of hemorrhage, and degree of hypotension are presented for each patient in Table I(pp.14-15).

Table I. Obstetrical Data for Each Patient.

Patient	Age	Date of hemorrhage	Interval between delivery and hemorrhage	Etiology of hemorrhage	EBL* in cc.	Transfusions in units of whole blood	Hypotension blood pressure in mm. Hg
1	38	10/64	1 hour	uterine atony	500	0	80/? right arm 30/0 left arm
2	39	5/66	less than 1 day	"	600	0	no hypotension
3	33	6/67	" " " "	"	1000	0	" "
4	29	3/70	" " " "	bilateral vaginal lacerations	600	0	" "
5	29	5/70	1 day	? uterine atony	1750	0	50/0
		8/73	10 days	retained placental fragments	800	0	no hypotension
6	27	7/71	10 days	"	greater than 1000	2	" "
7	23	11/67	1 hour	heavy 3rd stage bleeding	600	0	" "
		12/68	less than 36 hours	uterine atony	1000	0	" "
8	40	4/64	less than 2 days	retained placental fragments	500	0	" "
9	34	2/67	less than 1 day	uterine atony	1000	2	" "
10	24	10/69	6 hours	"	1000	0	" "

* EBL=estimated blood loss

Patient	Age	Date of hemorrhage	Interval between delivery and hemorrhage	Etiology of hemorrhage	EBL* in cc.	Transfusions in units of whole blood	Hypotension blood pressure in mm Hg
11	37	11/70	less than 1 day	?	1500	3	70/40
12	34	4/66	3-72 hours	retained placental fragments	1500 to 2000	3	90/60
13	27	12/69	less than 1 day	uterine atony	700 to 800	0	no hypotension

EBL*=estimated blood loss

All patients with the exception of patient 7 had unremarkable medical histories and physical examinations. Patient 7 had idiopathic galactorrhea. Patients 5 and 12 had been receiving Orthonovum 1/80 for oral contraception for one and one half years and twelve years, respectively. Patient 1 underwent a bilateral salpingo-oophorectomy and hysterectomy for pelvic actinomycosis in 1971 and since then had been receiving Premarin 1.25 mg. orally each day for the first three weeks of each month. All patients had normal x-ray evaluation of the sella turcica and normal fields of vision as determined by Goldmann perimetry. The results of 8 AM and 8 PM serum cortisol levels, thyroid function tests, and 24 hour urinary 17-hydroxycorticosteroids, 17-ketosteroids, and creatinine collections are shown in Table II(p.17).

Table II. 8 AM and 8 PM Cortisol, Thyroid Function Tests, and 24 Hour Urinary Steroids For Each Patient.

	8 AM cortisol	8 PM cortisol	thyroxine	thyroid binding capacity	17OHCS	17KS	total urine volume	creatinine
normal values	12-24 micrograms per dl.	6-12 micrograms per dl.	4.6-9.2 micrograms per dl.	16.8-25.6 micrograms per dl.	3-10 mgs. per total volume	5-15 mgs. per total volume	------	800-1700 mgs. per day
Patient								
1	16	8	10.8	25.5	3.2	5.8	1600	1024
2	16	6	7.2	18.3	3.0	4.6	1300	931
3	15	18	8.2	19.9	3.1	8.7	570	638
4	16	10	6.5	17.5	3.9	7.8	1420	1221
5	27	21	11.9	30.1	3.0	9.1	1120	1322
6	10	7	7.5	14.6	5.3	8.4	1860	856
7	15	6	5.3	19.1	2.3	8.6	1040	1102
8	16	10	6.8	15.9	4.0	6.9	920	948
9	16	6	5.4	13.2	2.8	8.6	660	950
10	10	6	6.3	15.0	3.4	12.0	1260	1386
11	14	9	8.1	18.3	4.9	9.5	1900	1311
12	23	17	10.6	26.0	5.0	16.1	1475	513
13	11	10	8.9	13.0	2.9	8.6	1005	874

The elevated levels of serum cortisol in patients 5 and 12 and of thyroxine and thyroid binding capacity in patients 1,5, and 12 are ascribed to the effect of their estrogen-containing medications[38,39]. The abnormally high 8 PM cortisol of patient 3 is attributed to her great anxiety and near hysterical syncopal espisode at the time of venipuncture. The low level of 17-hydroxycorticosteroid production by patient 7 was further investigated as described below (p 25).

Table III (p 19) indicates each patient's unstimulated serum FSH and LH values, the date of the menstrual cycle at the time of sampling, and the use of estrogen-containing medications. No abnormalities in gonadotrophic function were found.

Table III. Gonadotrophin Levels for Each Patient.

Patient	Estrogen	Stage of menstrual cycle (day of cycle/ total days of average cycle	LH in milliunits per ml.	FSH in milliunits per ml.
normal values			premenopausal: less than 25. postmenopausal: greater than 25. midcycle peak 3 times basal levels	premenopausal: 4-30 postmenopausal: 40-250 midcycle peak 2 times basal levels
1	Premarin 1.25 mgs. QD	postmenopausal	68	128
2	none	15/26	13	13
3	none	1/28	13	14
4	none	17/28	71	31
5	Orthonovum 1/80	14/28	7	6
6	none	5/28	20	14
7	none	4/26	9	7
8	none	11/32	12	7
9	none	1/28	6	10
10	none	5/29	15	16
11	none	12/30	7	7
12	Orthonovum 1/80	13/28	7	8
13	none	14/28	62	12

An insulin tolerance test was done in all patients and determinations made for glucose, cortisol, GH,PRL, and TSH and a TRH stimulation test was also done in all patients and PRL and TSH levels were determined. All patients developed hypoglycemia with a fall in glucose to less than 40 mgs per dl. and associated sweating. Two patients, patients 1 and 2, required regular insulin 0.15 units per kg body weight in order to achieve significant hypoglycemia.

Although it has been reported that the TRH stimulation test for TSH and PRL and the insulin tolerance test for GH, PRL, and cortisol can be performed simultaneously without modification of the hormonal responses to either TRH or insulin[40], it was decided to perform each test on a separate day. Besser et. al. state that there is no evidence for competition between pituitary mechanisms involved in GH and TSH secretion in man in response to simultaneous TRH and insulin-hypoglycemia stimulation[41]. However, Guansing et. al. have observed a statistically significant rise in TSH to hypoglycemia in patients with pituitary disease[42] while there is no TSH response in normal patients[43,44]. Therefore, the two tests were performed on separate days to avoid the possible uncertainty of whether a marked TSH response in a patient with pituitary disease who received insulin and TRH simultaneously was due

solely to hypoglycemia, therefore indicating no response to TRH, or whether the TSH rise was due to TRH alone or to a combination of both stimuli. A TSH response to insulin, observed only in patients wtih pituitary disease[45], could therefore be clearly separated from a TSH response to TRH. Additional reasons to perform the tests on different days were: 1) a large increase in serum levels of GH may inhibit TRH stimulation of TSH[46], and 2) cortisol modulates TSH levels and may do so by diminishing the TSH response to TRH [47,48].

Individual patient responses for the TSH stimulation test and the insulin tolerance test appear in Appendix I (pp 54-60) with calculations of the mean, the standard error of the mean (SEM), and the standard deviation (SD). Results are also grouped according to whether or not the patient was receiving estrogen; three patients (patients 1,5, and 12) were receiving estrogens, ten patients were not. Means, SEMs, and SDs are indicated for each group. Results for each test are presented in two figures. The first figure shows the baseline and peak response of all thirteen patients as well as the mean and SEM for all thirtenn patients and the grand mean (a pooling of mean and SEM values derived from a series of normal control groups presented in the literature), the standard error of the grand mean, and the 95 per cent confidence limits derived from normal control values

reported in the literature. The second figure compares the means and SEMs for all thirteen patients, for the three patients receiving estrogens, the ten patients not receiving estrogens, and the grand mean, the standard error of the grand mean, and two standard deviations of a single observation of the grand mean which defines a 95% confidence range. These confidence limits are derived from the literature and although they approximate a true definition of the range of normal values, they cannot be precisely statistically compared to the results obtained in this study. The relative newness of TRH as a diagnostic agent and of the radioimmunoassays for pituitary hormones, the great variation in methodology, technique, and standardization of these radioimmunoassays, the difference in methods of clinical testing among clinical researchers, and the differences in statistical analysis and presentation are all potential sources for discrepant results. Explanations of the selection of normal control groups from the literature as well as statistical methods used to determine the grand mean, standard error of the grand mean, and standard deviation of a single observation are presented in Appendix II (pp 61-65).

Cortisol response to insulin hypoglycemia

The results of cortisol response to hypoglycemia are presented in Figure 1(p29) and Figure 2 (p30). One patient (patient 7) had an

inadequate response and three patients (patients 1,5, and 12) had a heightened response. The patient with the inadequate cortisol response underwent further evaluation of her pituitary-adrenal axis as described below (p 25). In comparison to the 95% confidence limits, all patients not receiving estrogen fell approximately within these limits. The three patients receiving estrogen as indicated in Figure 1 (p 29)(patients 1,5,and 12) all have peak values far outside of the confidence limits. As indicated in Figure 2 (p 30), there is a marked difference between the mean peak values for those patients not receiving estrogen and those patients receiving estrogen. Comparison of these values by a paired "t" test showed that the difference was significant with P less than .0001. The elevated baseline values of patients 5 and 12 are attributable to the effect of estrogen on serum cortisol[49].

Growth hormone response to insulin hypoglycemia

The results of GH response to hypoglycemia are presented in Figure 3(p 31) and Figure 4(p 32). All patients responded with an increase in GH although the response of patient 2 was modest. The breadth of the 95% confidence limits for this test is such that it is not useful to discriminate between normal and abnormal responses. As shown in Figure 4 (p 32), the mean peak responses of patients receiving estrogen and not receiving estrogen were comparable and were not significantly different. As a single group of thirteen

patients, the mean peak response was adequate and compared favorably to that derived from the literature.

Prolactin response to insulin hypoglycemia

The results of the PRL responses to hypoglycemia are presented in Figure 5 (p33) and Figure 6(p34). Nine patients had adequate PRL responses while patients 7,8,9, and 13 showed minimal increases in PRL. However, this second group of four patients did show an adequate PRL response to TRH stimulation. Unfortunately, no 95% confidence limits could be derived from the literature. Figure 6(p34) indicates that the mean peak responses of the group receiving estrogen and the group not receiving estrogen were different; however, this difference was not significant. As a single group of thirteen patients, the mean peak PRL response was adequate and compared favorably to that derived from the literature.

Prolactin response to TRH

The results of the PRL responses to TRH are presented in Figure 7(p35) and Figure 8(p36). All patients responded with an increase in PRL and all were approximately within the 95% confidence limits. As shown in Figure 8(p36), the difference between the mean peak of the patients receiving estrogen and not receiving estrogen was insignificant. As a single group of thirteen patients, the mean peak PRL response was adequate although lower than that of the mean peak PRL responses derived from the literature. However, the mean

PRL increments derived from the literature and from this study, 19.3 ng/ml and 17.3 ng/ml, respectively, are quite comparable.

Thyrotropin response to TRH

The results of the TSH response to TRH are presented in Figure 9(p37) and Figure 10(p38). All patients responded with an increase in TSH and all were approximately within the 95% confidence limits. As shown in Figure 10(p38), there was no apparent effect of estrogen. As a single group of thirteen patients, the mean response was adequate and almost identical to that derived from the literature.

Thyrotropin response to insulin hypoglycemia

The TSH response to hypoglycemia is presented in Figure 11 (p39) and Figure 12(p40). The majority of the patients (a total of 8) had no detectable levels of TSH at any time during the test. Minimal TSH responses were observed among those patients with detectable levels of TSH and there was only insignificant fluctuation in these values during the test. This is comparable to the insignificant response of TSH to insulin hypoglycemia reported in the literature [50,51] and used for supplying a normal control group. Estrogen had no effect on TSH response as seen in Figure 12(p40).

One patient, patient 7, failed to manifest a rise in cortisol to adequate insulin hypoglycemia. Additionally, she had a subnormal 24 hour production of 17-hydroxycortico-

steroids. She therefore underwent a metapyrone test and an ACTH stimulation test as described above. Baseline urinary steroids were obtained eight days before and two days after the testing period. The results are presented in Table IV(p27).

Table IV. Patient 7's Metapyrone and ACTH Tests.

Date	Test	17OHCS	17KS	Compound S	Creatinine	Total Volume
11/25	baseline	less than 1	15.5	not done	1690	1160
12/3	Metapyrone	2.7	20.5	18.5	1470	1160
12/4	Metapyrone	4.7	41.2	36.5	1680	1630
12/5	ACTH	30.1	51.9	20.2	1540	2200
12/7	baseline	4.9	15.6	less than 1	1340	890

ACTH stimulation of serum cortisol

time	8 AM	2 PM	4 PM	6 PM
cortisol level	17	54	80	60

The results presented in Table IV indicate that patient 7 has a normal pituitary response to metapyrone and a normal adrenal response to ACTH stimulation. These tests are not confirmatory for pituitary disease.

FIGURE 1. CORTISOL RESPONSE TO INSULIN HYPOGLYCEMIA

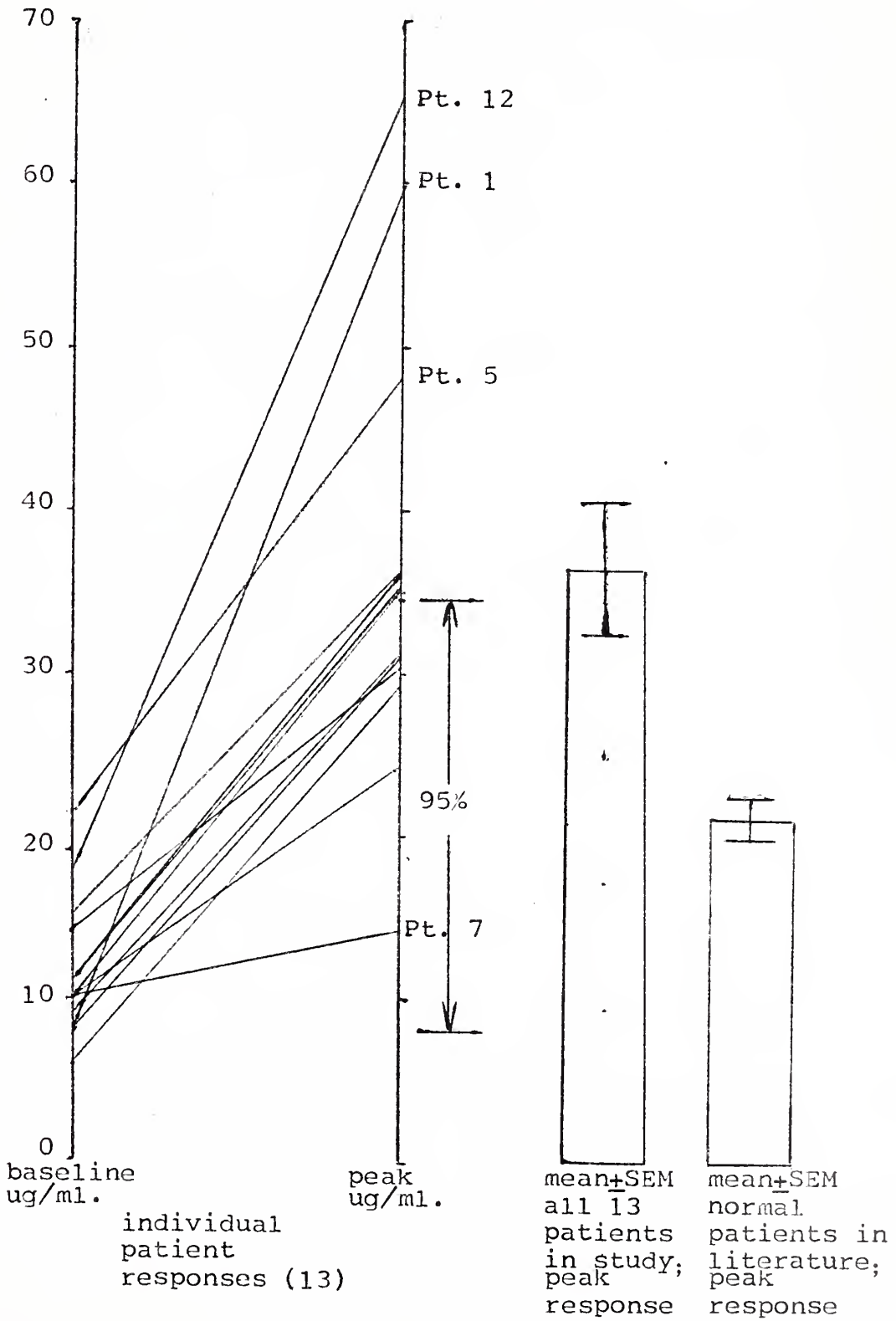


FIGURE 2. CORTISOL RESPONSE TO INSULIN HYPOGLYCEMIA

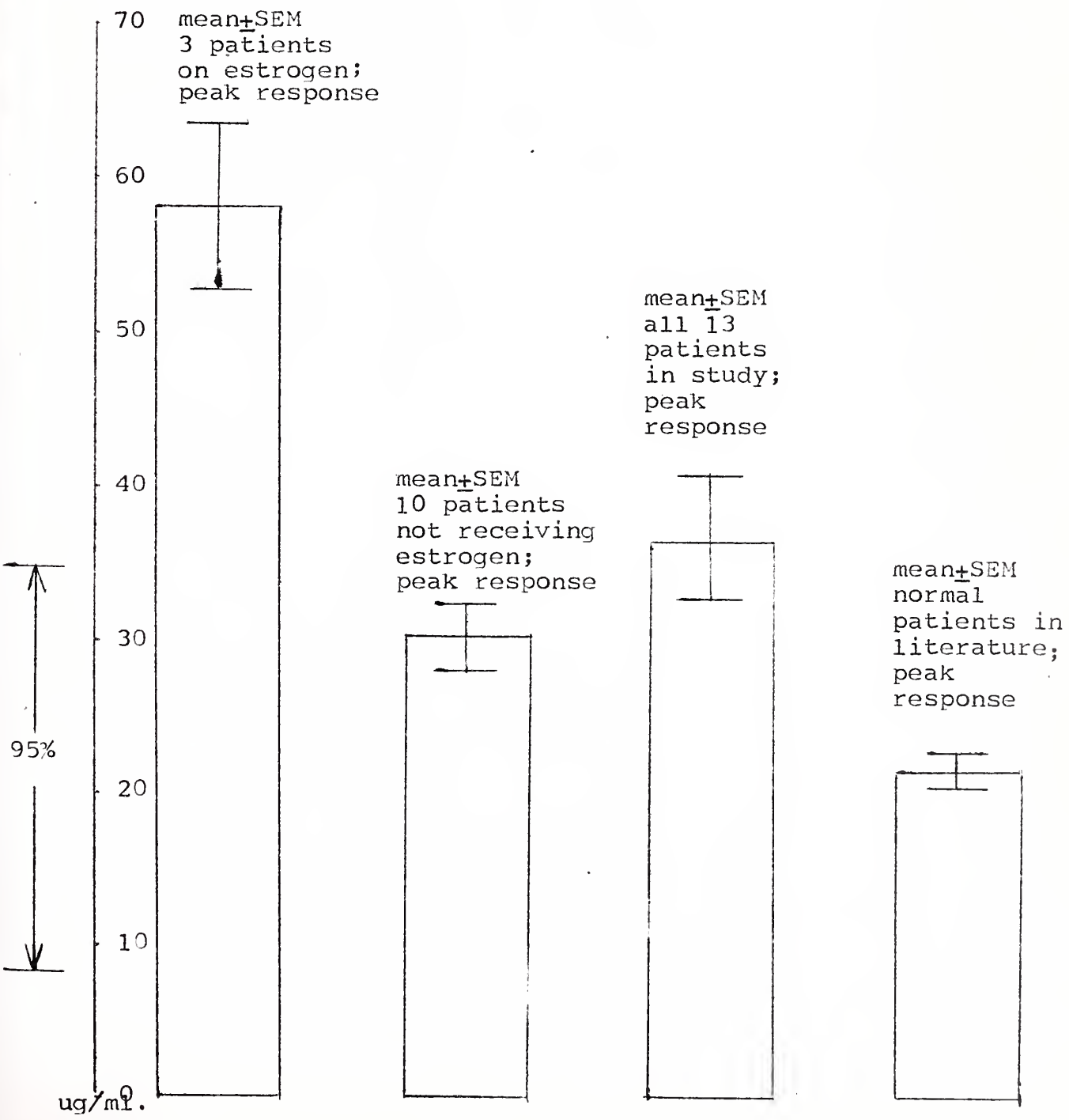


FIGURE 3. GROWTH HORMONE RESPONSE TO INSULIN HYPOGLYCEMIA

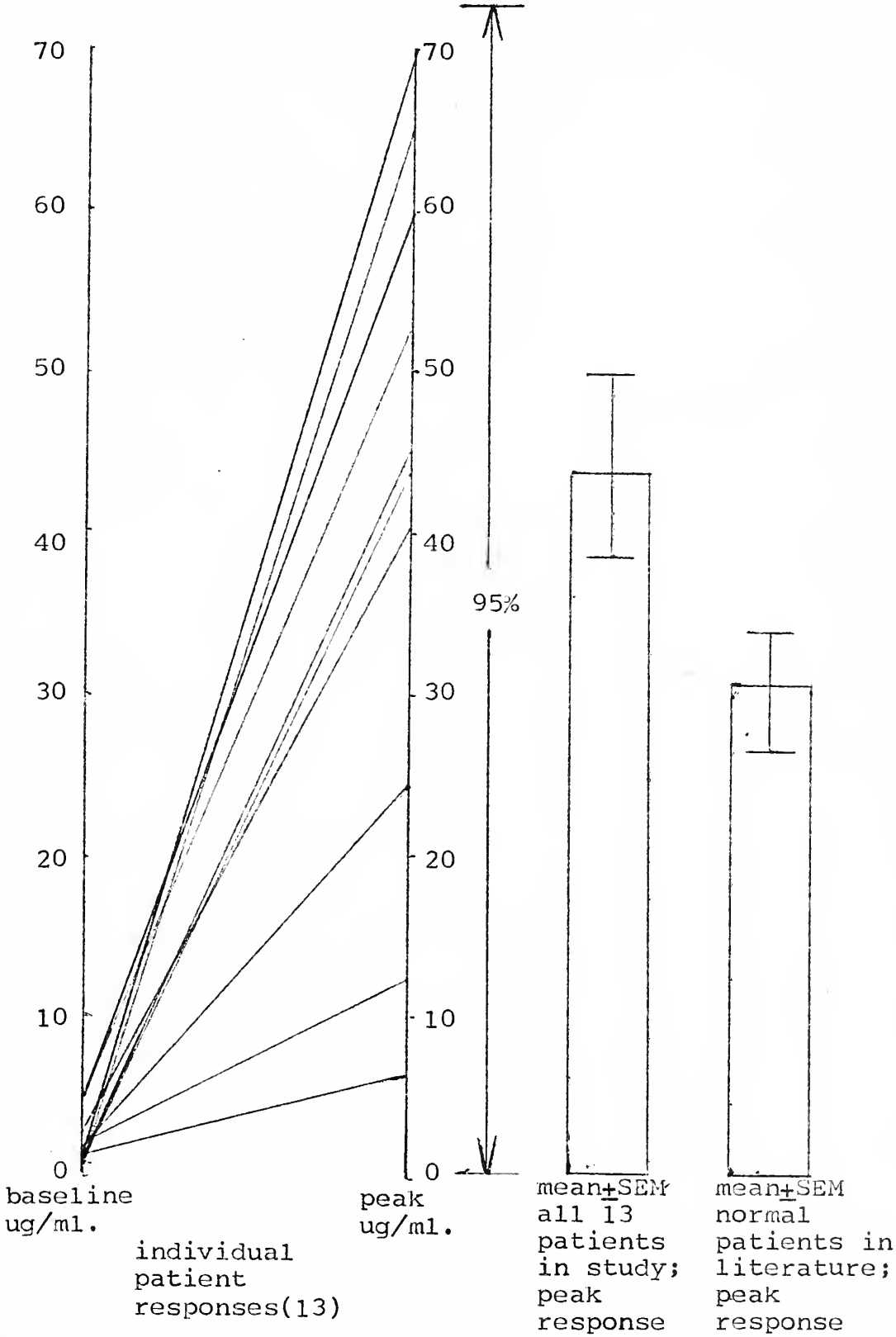


FIGURE 4. GROWTH HORMONE RESPONSE TO INSULIN HYPOGLYCEMIA

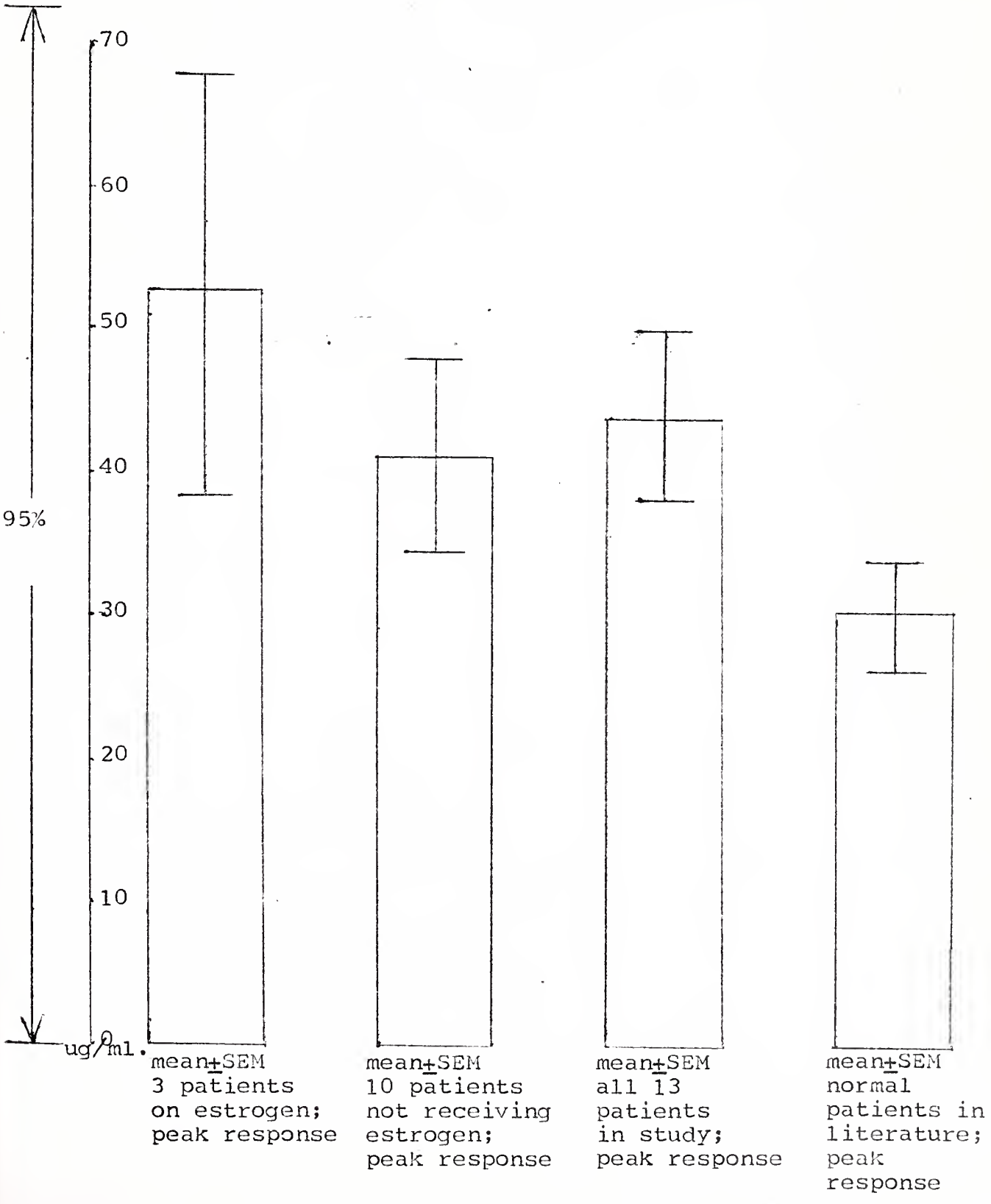


FIGURE 5. PROLACTIN RESPONSE TO INSULIN HYPOGLYCEMIA

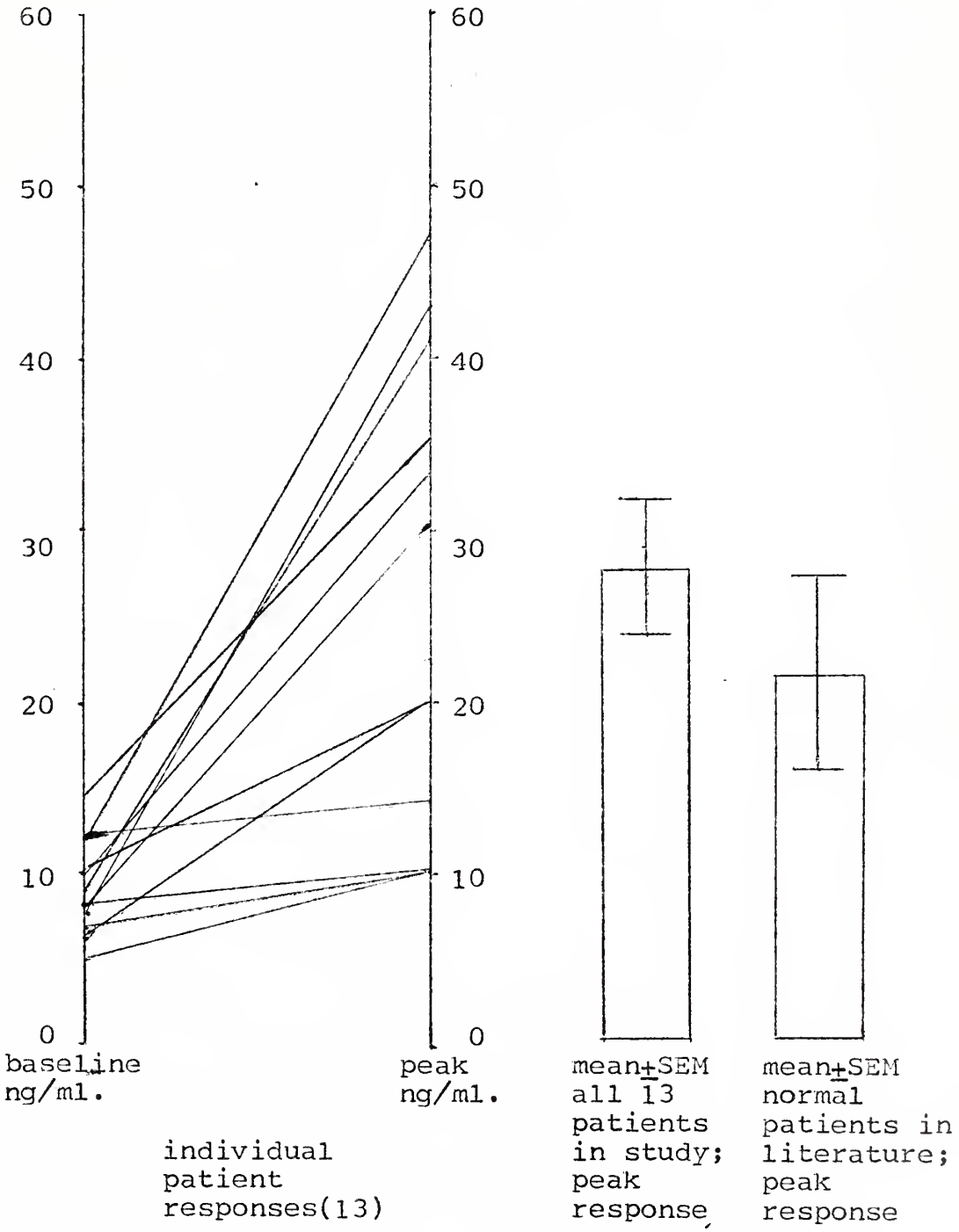


FIGURE 6. PROLACTIN RESPONSE TO INSULIN HYPOGLYCEMIA

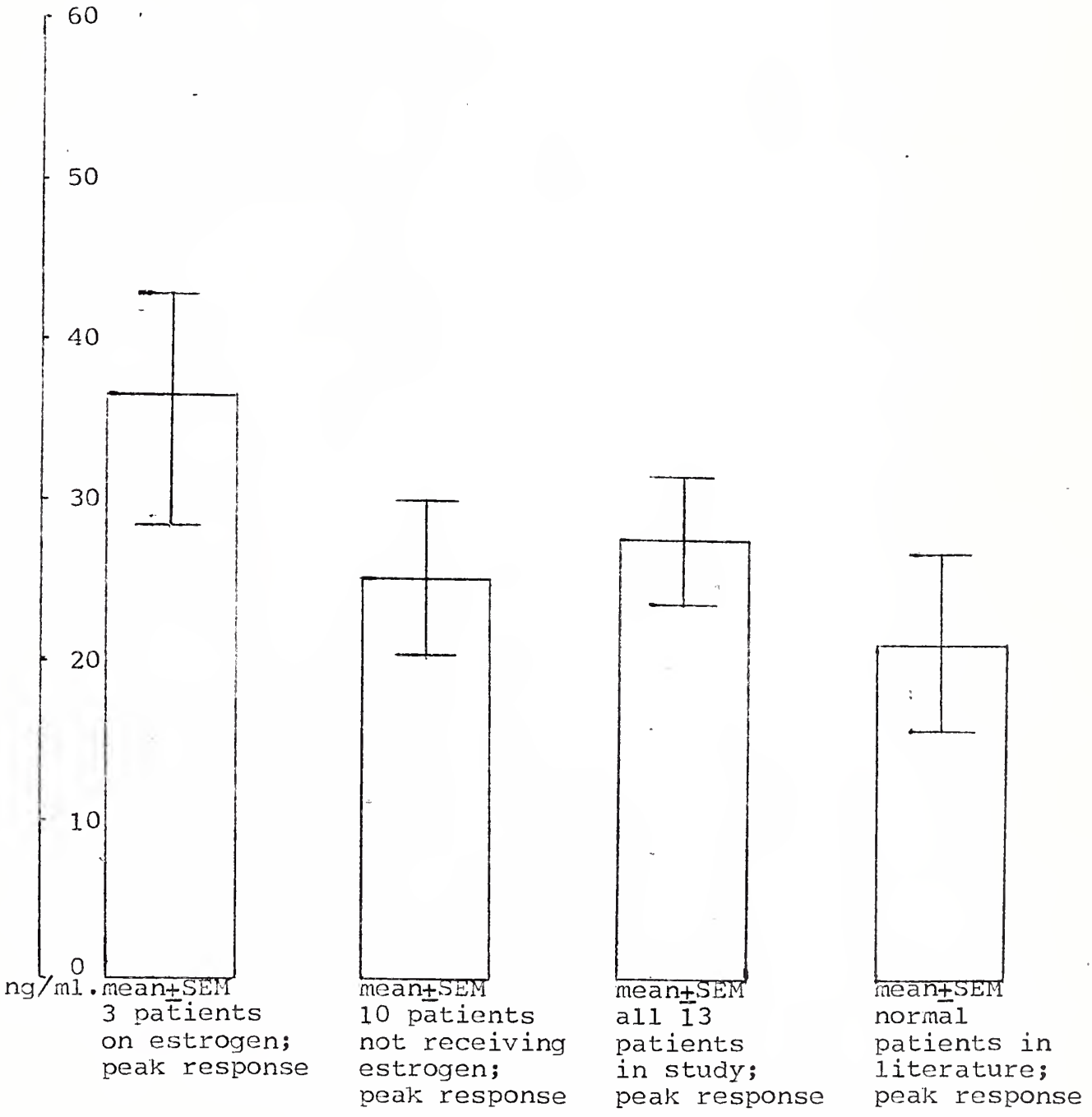


FIGURE 7. PROLACTIN RESPONSE TO TRH

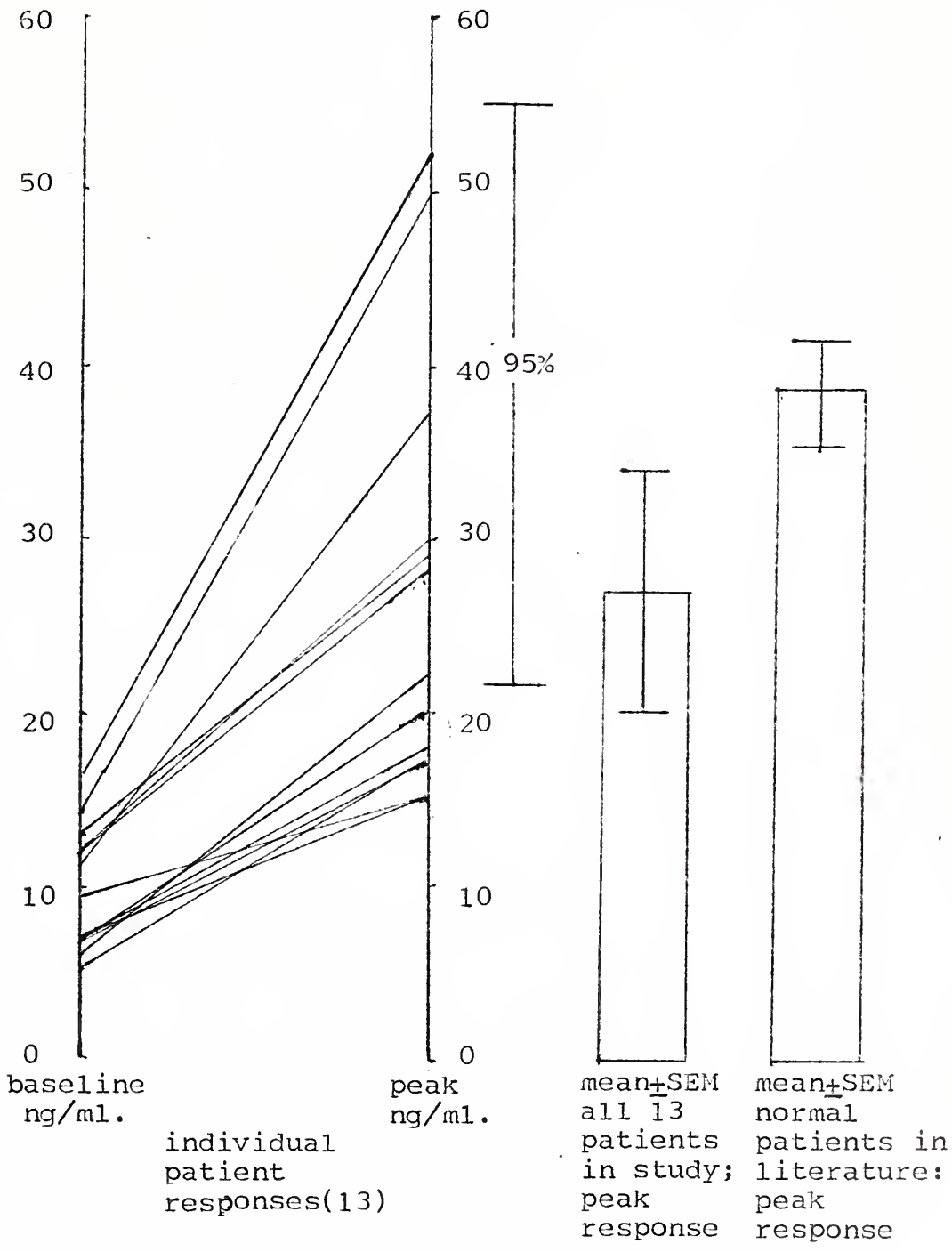


FIGURE 8. PROLACTIN RESPONSE TO TRH

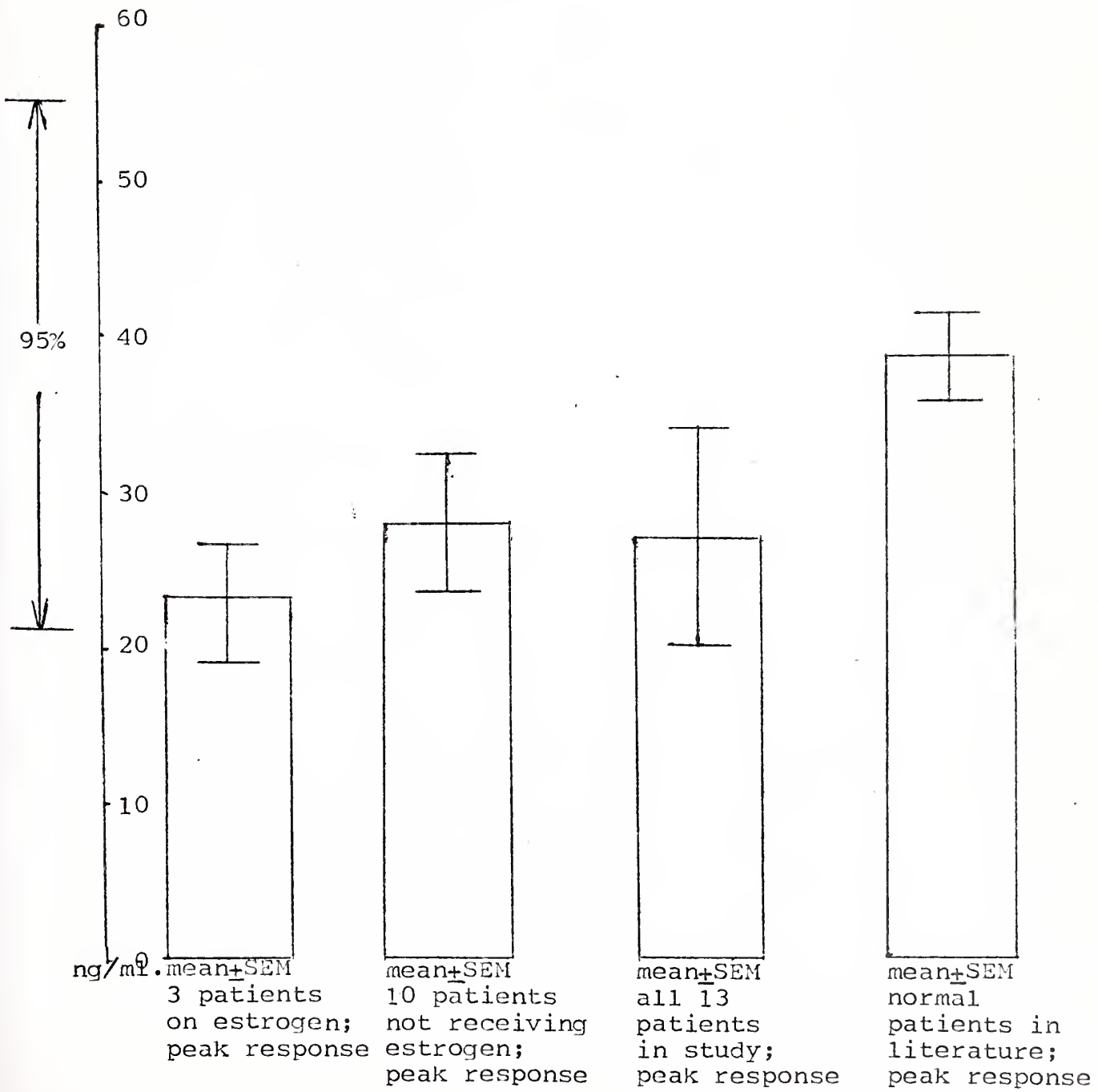


FIGURE 9. THYROTROPIN RESPONSE TO TRH

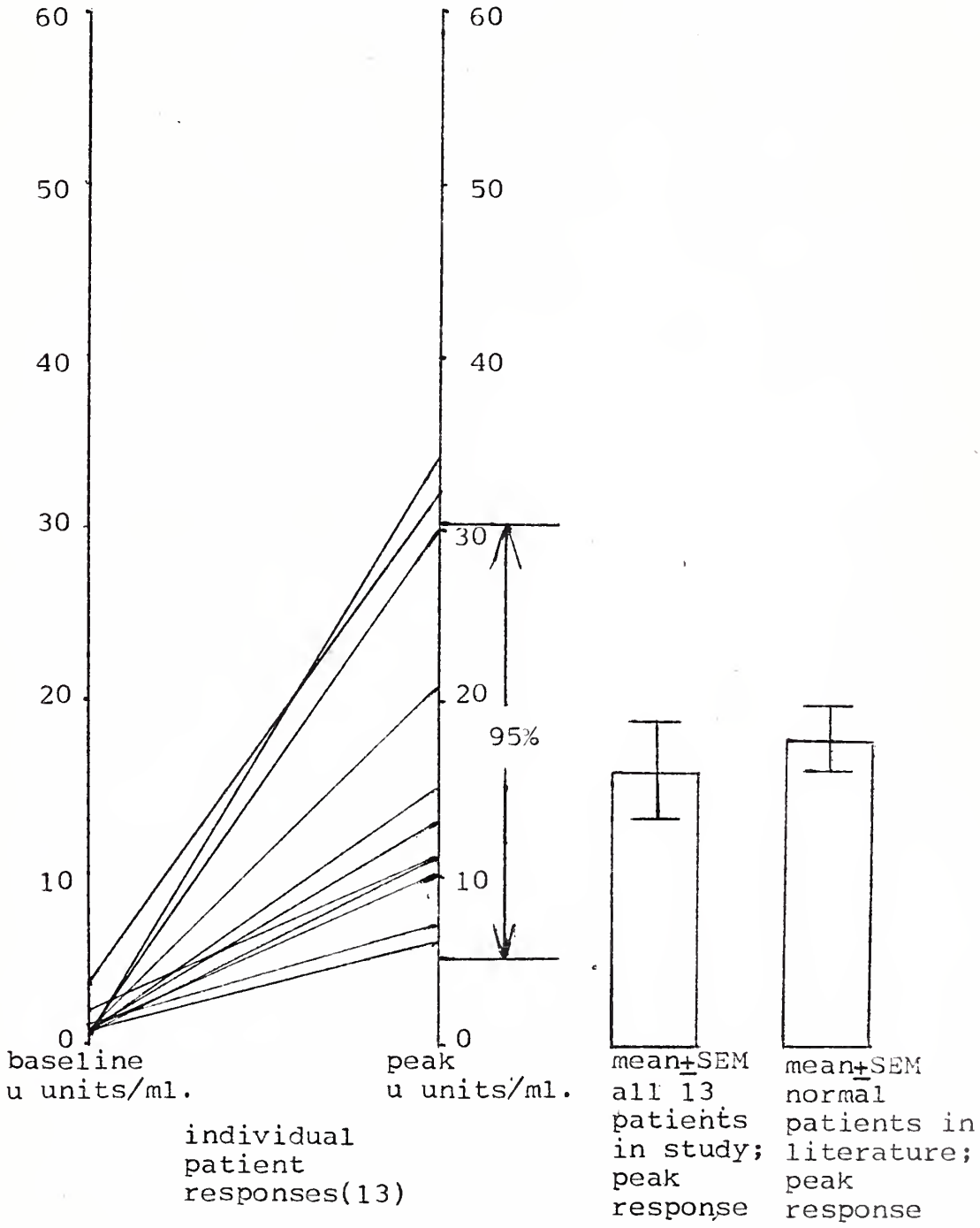


FIGURE 10. THYROTROPIN RESPONSE TO TRH

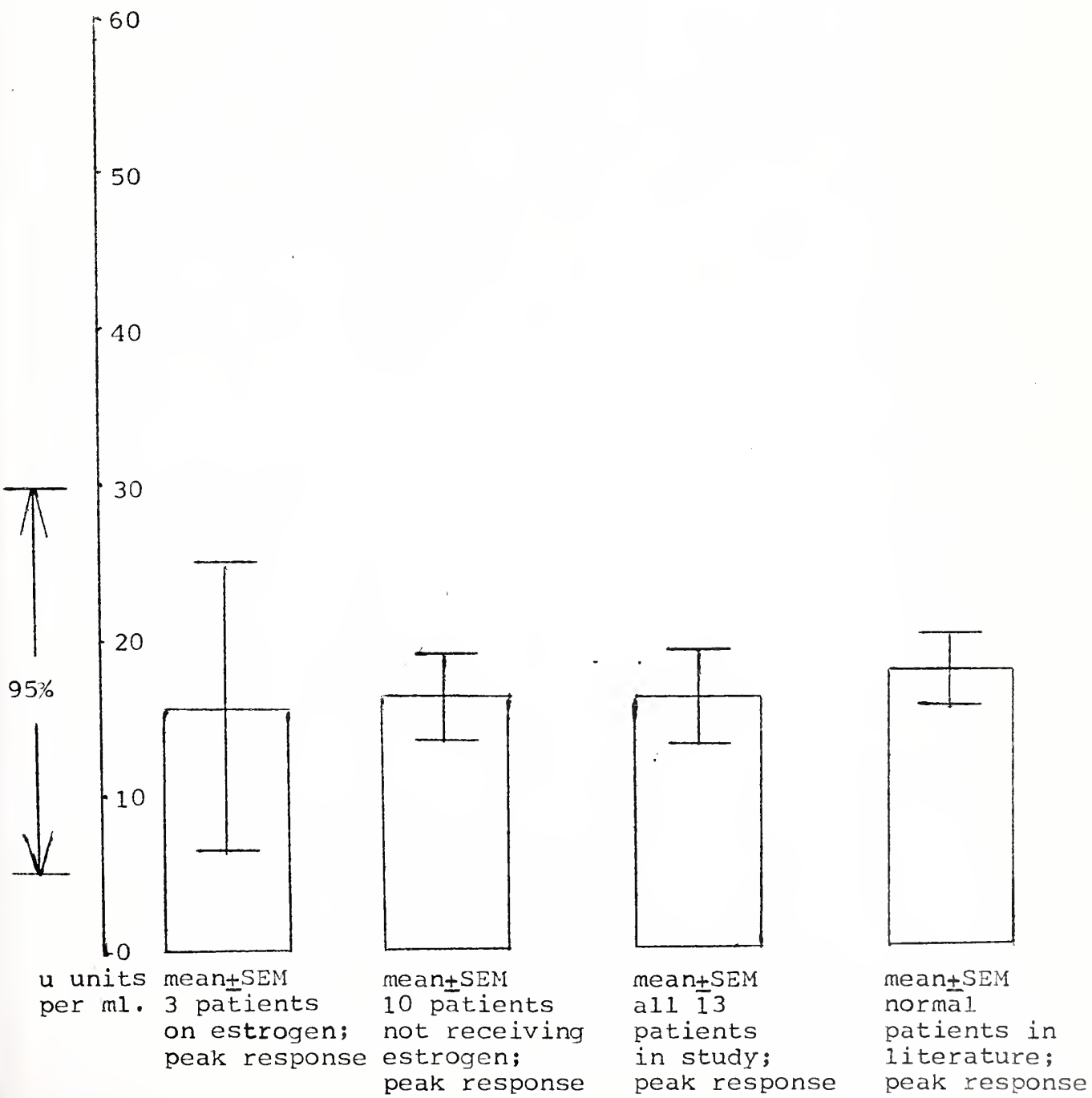


FIGURE 11. THYROTROPIN RESPONSE TO INSULIN HYPOGLYCEMIA

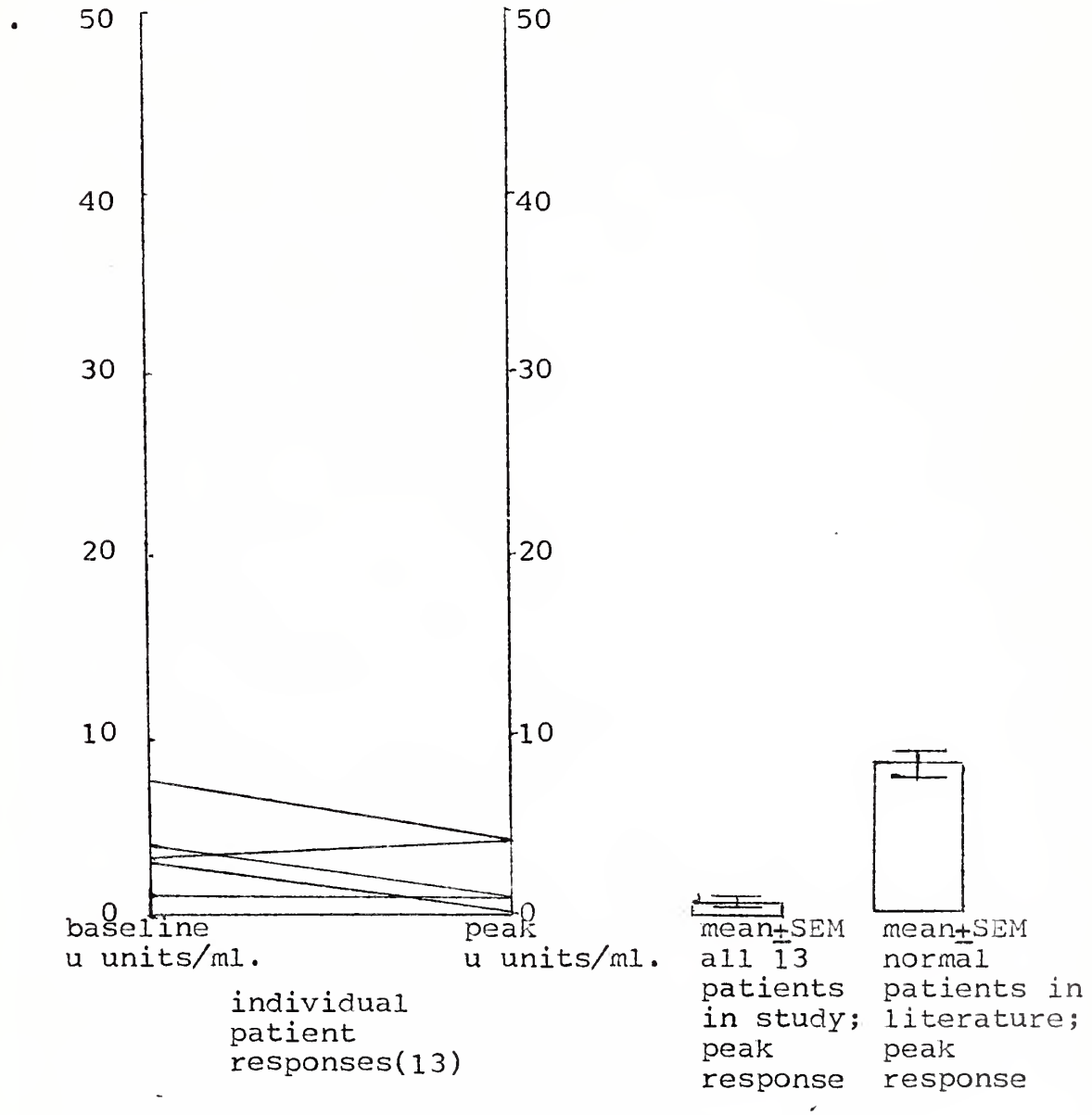
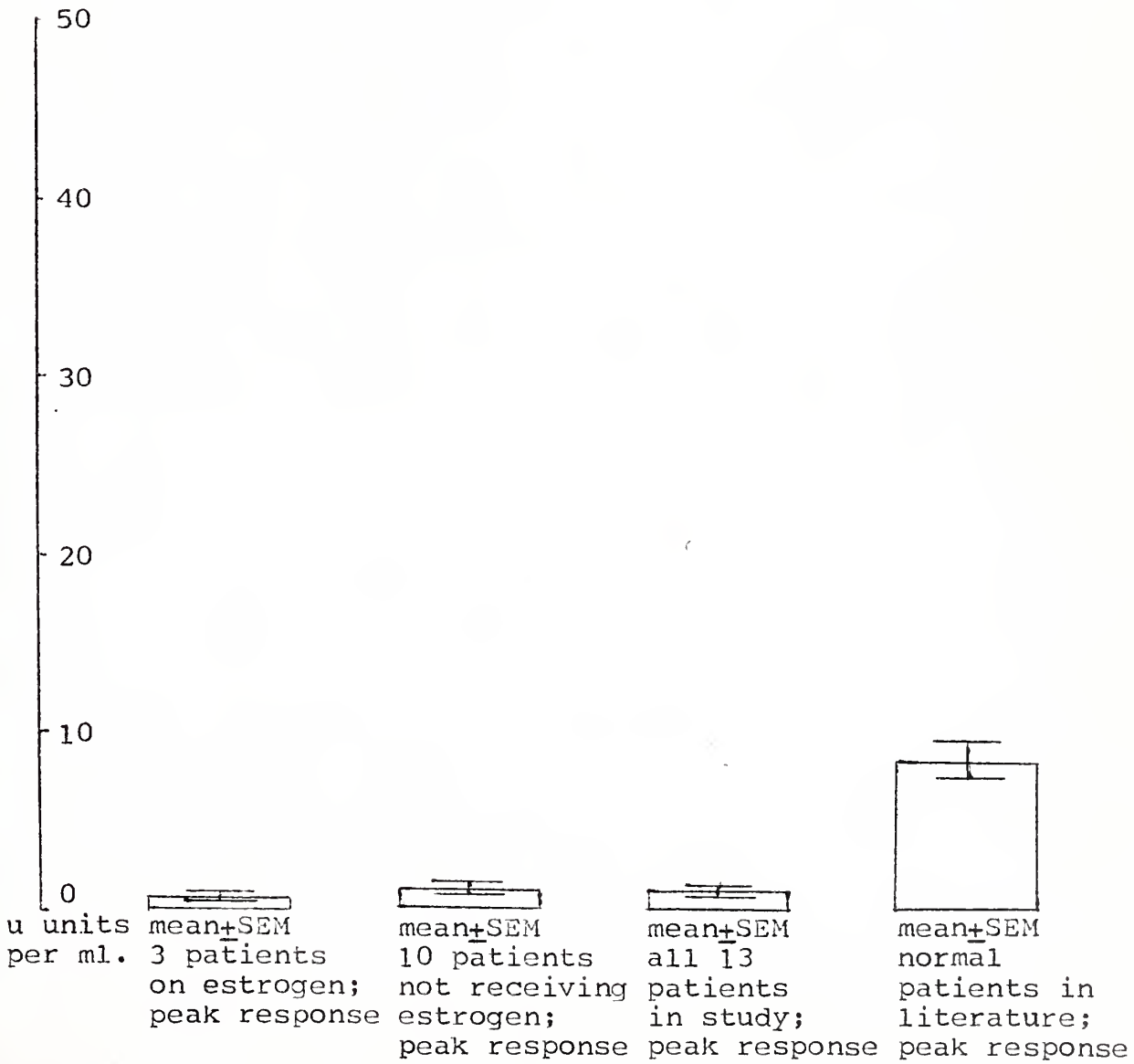


FIGURE 12. THYROTROPIN RESPONSE TO INSULIN HYPOGLYCEMIA



DISCUSSION

Sheehan's Syndrome is the major cause of anterior pituitary insufficiency[52]. As there is no correlation between the amount of blood loss and the development of pituitary insufficiency[53], it is possible that apparently normal women with minimal blood loss may have impaired pituitary function. Anterior pituitary function was evaluated in thirteen patients. This study failed to demonstrate any evidence of pituitary disease in this patient population at the present time. (This does not mean that hypopituitarism may not develop in the future[54].) It seems probable that subclinical defects in asymptomatic patients at risk for Sheehan's Syndrome are uncommon. Perhaps pituitary disease does not exist in the absence of clinical symptoms or perhaps the subclinical state of hypopituitarism is too subtle to be detected with the present level of sophistication of endocrine testing. Nevertheless, because mild instances of Sheehan's Syndrome are often overlooked and the diagnosis considered progressively less often as the date of postpartum hemorrhage becomes more remote, all survivors of this obstetrical complication, however small the quantity of hemorrhage, should be continually observed[55]. It may be argued that the degree of blood loss in this patient group was too small to cause pituitary damage. However, Effkemann and Muller-Jager found that in a group of 84 patients who lost between 800 and 1600 cc. of blood at the time of delivery, sixty per cent of the twenty patients who lost

between 1200 and 1600 cc of blood suffered decreased menstrual function and fifty per cent of these twenty women became permanently sterile[56].

The endocrine status of patient 7 must be clarified in order to conclude that there was no evidence of pituitary disease among these thirteen patients. Although this patient failed to manifest a rise in cortisol in response to insulin hypoglycemia, further testing revealed a normal response of the pituitary to metapyrone, indicating normal ACTH stimulation. Confirmation of adequate adrenal response to stimulation was obtained by a satisfactory ACTH test. As all of patient 7's other pituitary hormones responded adequately to stimulation, there was no evidence of pituitary disease. Failure of insulin hypoglycemia to produce a rise in cortisol is not inconsistent with a normal pituitary response to metapyrone. Indeed, the results of these two tests may be helpful in localizing this patient's endocrine defect to her hypothalamus. Hypoglycemia very likely acts at the hypothalamic level[57-60] to stimulate corticotropin-releasing-factor (CRF)[61] which in turn stimulates ACTH secretion which causes cortisol release. Metapyrone acts by blocking the synthesis of cortisol[62] which acts in a negative feedback fashion to inhibit ACTH and probably CRF. (It is not clear whether cortisol is inhibitory ar the level of the pituitary or the hypothalamus or at both sites; Ganong includes both sites as its possible

loci of action[63]. However, Upton et. al. believe that there is strong evidence that CRF is regulated solely by ACTH and therefore that cortisol would inhibit ACTH at the pituitary level only[64].) Metapyrone, by lowering cortisol levels, would therefore stimulate the pituitary and perhaps the hypothalamus as well to increase cortisol synthesis and release while hypoglycemia would stimulate only the hypothalamus. Thus a negative cortisol response to hypoglycemia coupled with a normal metapyrone response might indicate normal pituitary function but abnormal hypothalamic function. One might then hypothesize that a hypothalamic defect in the production of CRF, which largely controls ACTH secretion[65], might lead to a lower "turn-off" point for the ACTH-cortisol "thermostat" which would be reflected by lower levels of cortisol metabolites such as 17-hydroxycorticosteroids. Such a hypothesis might satisfactorily explain the low levels of 17-hydroxycorticosteroids observed twice in patient 7 (less than 1 and 2.3 mg/ total volume) and relate this abnormality to the absent cortisol response to hypoglycemia and the normal response to metapyrone. The patient's galactorrhea may also be due to hypothalamic disease; certainly there was no evidence for a pituitary casue of galactorrhea. Furthermore, since it seems likely that TRH acts at the pituitary to release PRL in man[66,67], and since it is known that hypoglycemia acts on the hypothalamus to stimulate PRL[68-71], this patient's failure to respond with an increase in PRL to hypoglycemia

despite a normal PRL response to TRH may be a further indication of adequate pituitary function and hypothalamic disease.

Several interesting aspects of the nature of tests of endocrine function were apparent in this study. It is evident that a blood glucose level of less than 40 mg/dl. must be obtained before a patient can be assumed to have pituitary dysfunction on the basis of an abnormal insulin tolerance test. The variability of individual response to the "standard" initial dose of regular insulin 0.1 units/kg body weight makes it necessary to employ a larger dose of insulin before diagnosing pituitary insufficiency. Landon et. al. have demonstrated that there was no cortisol response to insulin hypoglycemia in normal patients in whom the blood sugar did not fall below 40 mg/dl.[72]. Glick has shown that in normal patients the hypoglycemic threshold for GH release is a fall in blood glucose of between 20 and 30 mg/dl. unassociated with the subjective manifestations of stress[73]. Greenwood et.al. have studied the effect of varying the dose of regular insulin from 0.025 to 0.15 units per kg. body weight and found that the responses of GH and cortisol were directly proportional to the dose of insulin administered[74]. While Cohen and Gala failed to demonstrate a rise in PRL in response to a mean fall in blood glucose to 25 mg/dl.[75], Wilson et. al. found that at a hypoglycemic level of 25 mg/dl. obtained by constant infusion of regular insulin 0.04 units/kg body weight/hour there was no significant PRL response; however, with the use of regular

insulin 0.2 units/kg body weight as a bolus a mean glucose level of 9 mg/dl. was obtained and the mean PRL response was quite high[76]. Similarly, Noel et.al., using regular insulin 0.2 units/kg body weight, obtained a mean glucose level of 15 mg/dl which caused a striking rise in PRL[77]. Two patients in this study required an insulin dose of 0.15 units rather than 0.1 units. Patient 1 had no response to 0.1 units and clearly required a larger dose. However, patient 2 responded to a dose of 0.1 units with a fall in glucose from 87 to 42 mg/dl., a fall of 52% from baseline, and experienced sweating, hunger, lightheadedness, drowsiness, and modest changes in pulse and blood pressure. Nevertheless, the patient had no cortisol, GH, or PRL response. If an adequate and diagnostic insulin tolerance test had been defined as a fall inglucose of 50% and associated symptomatology, then this patient would have been considered abnormal. A second test was performed, this time with 0.15 units, and the glucose fell 76% to 20 mg/dl.; adequate cortisol and PRL responses were obtained but the GH response remained modest. The duration of maximal hypoglycemia may also correlate with the height of the hormonal response; Patient 1 had sustained maximal hypoglycemia and responded with marked secretion of all hormones. As it is apparent that the hormonal response correlates with the degree of hypoglycemia, it would be useful to present the results of the insulin tolerance test as a ratio of the change in each hormone value over the change in glucose levels: $\frac{\Delta \text{ hormone}}{\Delta \text{ glucose}}$.

Such a ratio would define the slope of a straight line as indicated in Figure 13(p47). Figure 14(p48) is an attempt to apply this suggestion to the cortisol results obtained in this study. The ten patients not taking estrogen are represented in this figure along with the mean and SEM for this group. The three patients receiving estrogen are not included here because the effect of estrogen on cortisol response (p 23) precludes comparison with patients not taking estrogen. It can be seen that with the exception of patient 7, who did not respond to insulin hypoglycemia and therefore can be excluded from consideration, these patients' responses fall quite close to the mean $\pm$ SEM. This method of reporting the results of insulin tolerance tests would allow patients with varying degrees of hypoglycemia to be compared and would also provide a useful definition and range of normal responses of each hormone to hypoglycemia. However, it may be necessary to take into account the duration of maximal hypoglycemia in order to more clearly unify data. It would be useful to evaluate the results of hormonal responses to hypoglycemia in a large population of normal age and sex-matched controls and to present those results in the manner described above.

In their study of PRL responses to insulin hypoglycemia, Cohen and Gala conclude that "insulin hypoglycemia is not a useful diagnostic test for prolactin secretion and cannot be used as such for assessment of pituitary reserve." and that the"use of insulin hypoglycemia as a diagnostic aid for promoting prolactin secretion should be discontinued."[78]

FIGURE 13. $\frac{\Delta \text{ HORMONE}}{\Delta \text{ GLUCOSE}}$

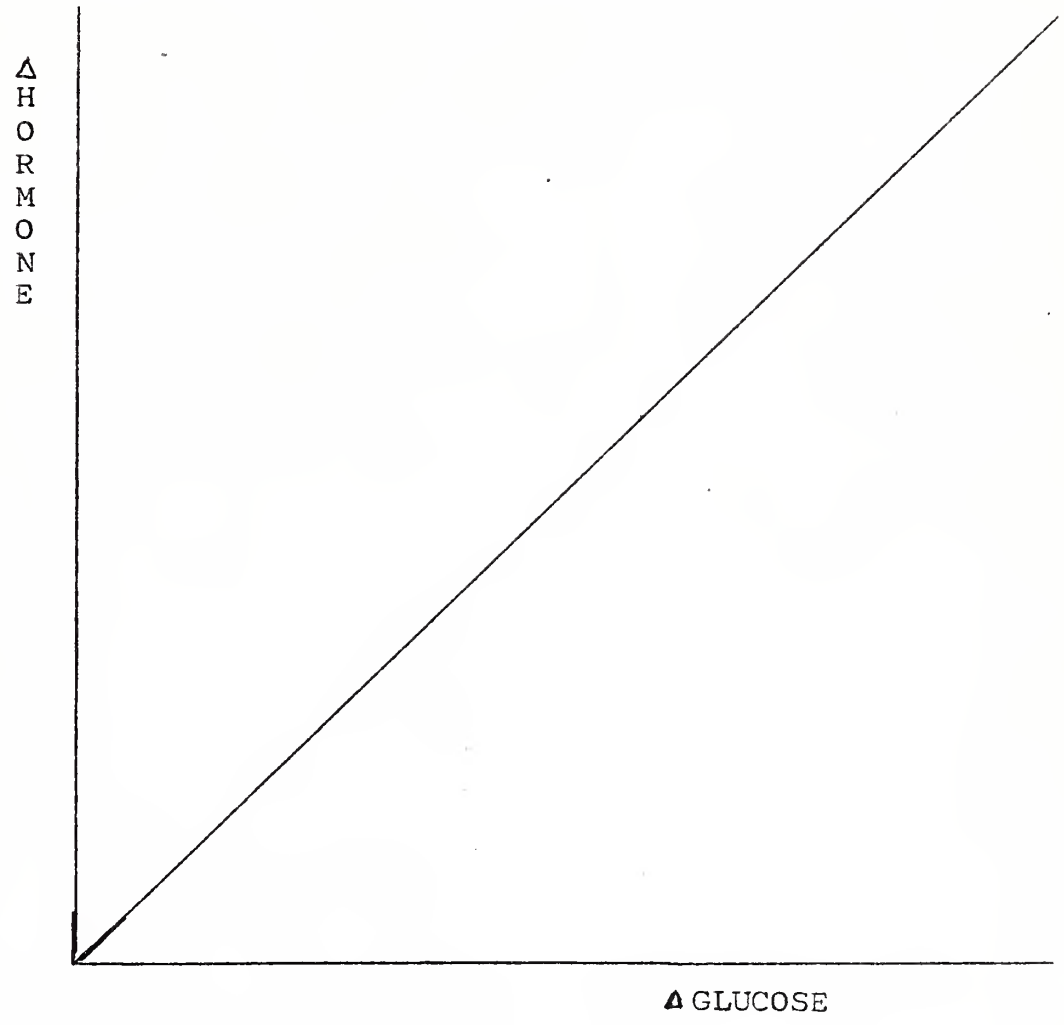
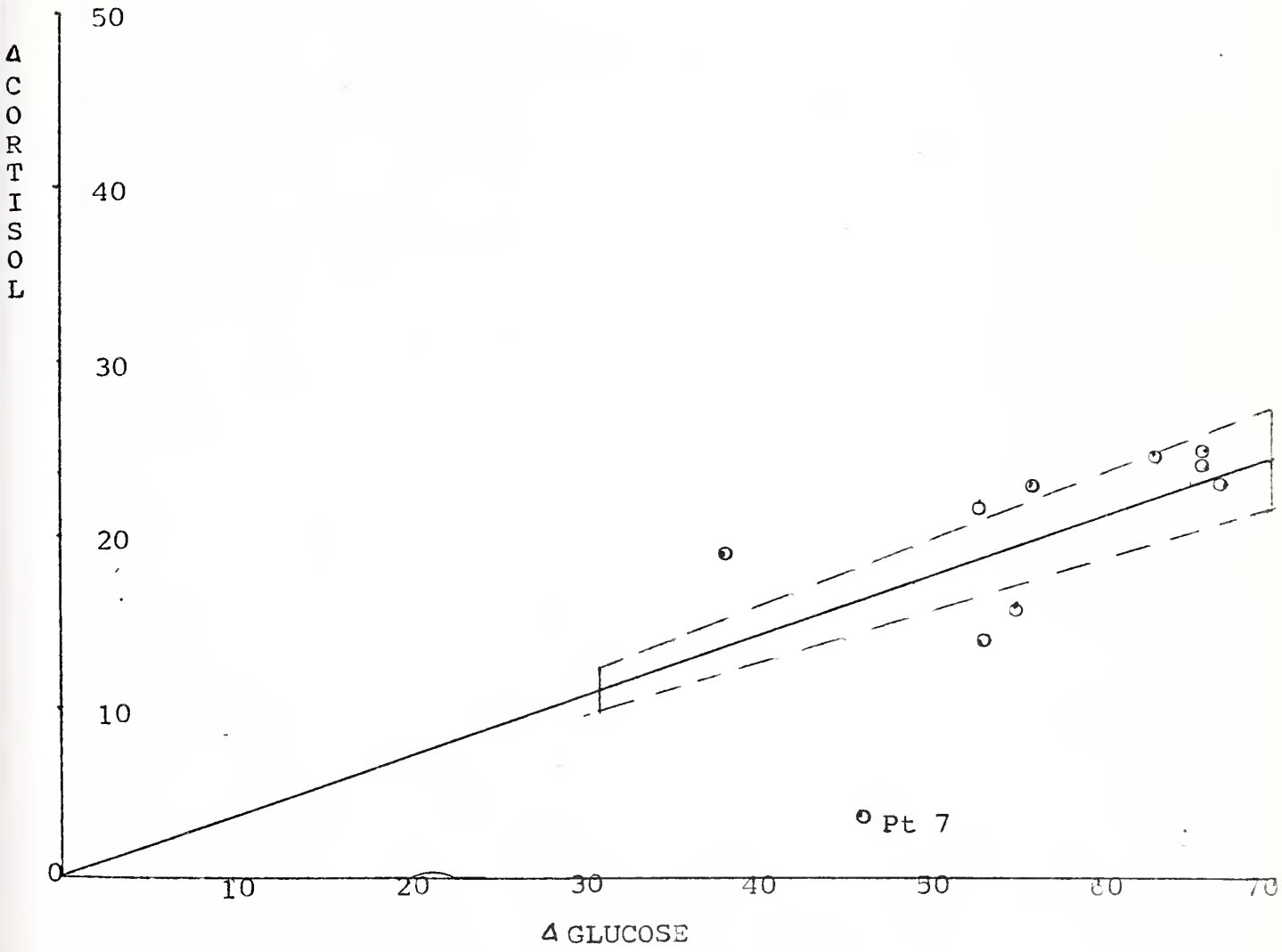


FIGURE 14. $\frac{\Delta \text{ CORTISOL}}{\Delta \text{ GLUCOSE}}$



mean±SEM 10 patients not receiving estrogen
_____=mean
- - -=SEM
o=individual patient

Using regular insulin 0.1 units/kg body weight in three normal mean and two normal women, they obtained a mean blood glucsoe level of 25 mg/dl. but did not observe any increase in PRL levels. Further, two patients who received the same insulin dose had significant PRL rises either before the glucose nadir was achieved or in absence of adequate hypoglycemia. If the differences in the two PRL radioimmunoassays can be disregarded, the results for their five patients, who had a mean level of hypoglycemia almost identical to that of the present study, are quite discrepant with those of the present study and of Copinschi et. al., who showed a significant PRL response in sixteen patients to a mean hypoglycemia of 28 mg/dl.[79] Although four of the thirteen patients in the present study failed to increase PRL levels in response to hypoglycemia, the other nine patients had significant PRL responses and the mean peak PRL for the entire group was 27.4 ng/ml. with a mean peak increment of 18.4 ng/ml. and a mean peak percentage increment compared with baseline of 214%. It is possible that the five patients reported by Cohen and Gala had other evidence of hypothalamic-pituitary dysfunction and were therefore not normal patients. It would have been useful to perform a TRH stimulation test for PRL in this group of five patients to see if hypoglycemia was ineffective in stimulating PRL in otherwise normal patients or if these patients had abnormalities as might have been shown by the TRH test. Phenothiazine stimulation of PRL would also give important information[80].

It is difficult to explain the anomalous responses of the two patients in Cohen and Gala's study who had substantial PRL secretion but not in response to hypoglycemia; no similar occurrence was observed in the present study. Although Cohen and Gala agree with the results of Wilson et. al.[81] and Noel et. al.[82] who showed that significant PRL responses could be obtained consistently when the blood glucose level was decreased to 9 mg/dl. and 15 mg/dl. respectively, they maintain that this degree of hypoglycemia is too extreme to make insulin hypoglycemia a safe and practical test of PRL secretion. Nevertheless, the results of the present study and of Copinschi et. al.[83] indicate that a decrease in the blood glucose to the relatively safe level of 25 mg/dl. is quite effective in stimulating PRL and it appears that insulin hypoglycemia is a valuable tool in the evaluation of PRL secretion.

As both TRH stimulation and insulin tolerance tests were performed on all thirteen patients, it is possible to compare the usefulness of both tests in evaluating PRL secretion. As presented in Figure 7 (p35), all patients had adequate PRL responses to TRH. As shown in Figure 5(p33), nine of thirteen patients had adequate PRL responses to hypoglycemia. The mean PRL baselines for all thirteen patients were 9.7 ng/ml. in the TRH test and 9.0 ng/ml in the insulin tolerance test; the mean PRL peaks for all thirteen patients were 27 ng/ml in the TRH test and 27.4 ng/ml. in the insulin

tolerance test. It therefore appears that both tests are useful in evaluating PRL secretion and that on the average, they yield remarkably similar results. However, not all patients responded to hypoglycemia and therefore it may be prudent to perform both tests. Furthermore, if, as discussed above (p 43), it can be shown that TRH affects PRL secretion solely at the pituitary level, performing both tests may allow localization of defects in PRL secretion to the pituitary or the hypothalamus. It would be useful to know how these two methods of PRL stimulation compare to a third method, phenothiazine stimulation[84].

The failure to observe a TSH response to hypoglycemia in any of the thirteen patients in this study is consistent with the reports of Guansing et. al.[85] and Copinschi et. al.[86] that normal patients have no TSH response to hypoglycemia. Elevated TSH levels are found only in patients with pituitary disease[87]. It would be of interest to know whether dopamine plays a role in the inhibition of TSH response to hypoglycemia. It is known that dopamine blocks TRH stimulation of TSH[88]. If pimozide, an effective dopaminergic blocking agent[89], could prevent the inhibition of TSH response to hypoglycemia, this would support a dopaminergic role in the failure of TSH response.

The effect of estrogen-containing compounds on the outcome of these hormonal stimulation tests was insignificant except in the case of hypoglycemic stimulation of cortisol. The

failure of estrogen to augment the TSH response to TRH is in conflict with the report of Ramey et.al.[90] that oral contraceptives in normal euthyroid females caused a significant increase in TSH response to TRH. As Ramey presents only mean values, it is possible that there were a small number of patients among his group of fourteen who had responses that were significantly below the mean response and were comparable to those of the three patients in the present study. Thus, it may be that the failure of estrogen to affect the mean TSH response to TRH in the present study may be due to the small number of women receiving estrogen. Indeed, one of the three women did have a response significantly above the mean for all 13 patients (patient 5) as well as the highest response in the study. Although it is known that estrogen causes increased PRL response to perphenazine stimulation in both men and women[91], and that the PRL response to TRH is significantly higher in females than in males[92], the effect of estrogens on PRL response to TRH in normal females has not bee assessed. In the present study, the effect of estrogen on PRL response to TRH was not significant. Estrogen had no significant effect on the response of GH in this study. There are no reports in the literature on the effect of estrogens on the GH response to hypoglycemia. Merimee and Fineberg have shown that when the fall in glucose exceeds 40 mg/dl., there is no significant variation within the phases of the menstrual cycle of GH response to hypoglycemia, indicating the negligible effect of physiologic increases of

estrogen. The effect of estrogen on hypoglycemic stimulation of cortisol was significant with a mean peak for patients receiving estrogen of 58.0 micrograms/ml. in contrast to a mean peak of 30.1 micrograms/ml. for those patients not receiving estrogen (P less than .0001-paired "t" test). Although it is known that pretreatment with diethylstilbestrol in normal children gives significantly higher peak cortisol responses to hypoglycemic stimulation[93], and that oral contraceptives augment the peak 17-hydroxycorticosteroid response to Piromen stimulation[94], a substance which stimulates pituitary release of ACTH[95-97], there is no report in the literature of the effect of oral contraceptives on cortisol response to insulin hypoglycemia. No significant effect of estrogen on PRL and TSH responses to hypoglycemia was found and there are no reports in the literature on the effect of estrogen in these circumstances.

APPENDIX I

TRH test for TSH(microunits/ml)

time	-15	0	15	30	45	60	90	120
Patient								
1	0	0	6	7	7	5	1	0
2	0	0	13	15	15	12	6	3
3	0	0	13	21	16	15	9	7
4	2	2	2	11	11	8	9	6
5	1	1	24	34	23	23	13	10
6	4	7	19	32	27	20	15	10
7	0	0	11	9	8	6	5	3
8	0	0	7	7	3	4	2	.7
9	0	0	10	13	9	7	5	4
10	0	0	9	11	10	9	6	2
11	0	0	30	26	25	22	13	12
12	0	0	5	6	5	4	.5	2
13	0	0	3	10	9	7	6	2
mean	.5	.8	11.7	15.5	12.9	10.9	7.0	4.7
SEM*	.3	.5	2.3	2.7	2.2	1.9	1.3	1.1
2 SD*	2.4	4.0	16.6	19.2	15.6	13.8	9.2	7.8
Patients receiving estrogen(3)								
mean	.3	.3	11.7	15.7	11.7	10.7	4.8	4.0
SEM*	.3	.3	6.2	9.2	5.7	6.2	4.1	3.1
2 SD*	1.2	1.2	21.4	31.8	19.8	21.4	14.2	10.6
Patients not receiving estrogen(10)								
mean	.6	.9	11.7	15.5	13.3	11.0	7.6	4.7
SEM*	.4	.7	2.6	2.6	2.4	1.9	1.2	1.3
2 SD*	2.6	4.4	16.2	16.4	15.2	12.2	7.8	8.0

SEM=standard error of the mean SD=standard deviation

TRH Test for PRL(ng/ml.)

time	-15	0	15	30	45	60	90	120
Patient								
1	14	12	30	26	20	15	17	12
2	8	7	20	19	19	13	12	10
3	17	16	52	52	51	43	29	20
4	12	9	15	13	14	7	10	9
5	9	6	22	18	17	13	11	8
6	11	11	37	35	28	20	11	9
7	13	12	28	22	20	17	25	12
8	7	7	10	14	15	6	8	8
9	9	7	16	12	18	10	7	9
10	14	14	43	50	45	33	20	20
11	13	14	20	29	21	23	19	16
12	5	7	12	13	15	17	8	9
13	7	8	11	17	15	12	14	10
mean	10.7	10.0	24.3	24.6	22.9	17.6	14.7	11.7
SEM	1.0	.9	3.6	3.8	3.3	2.9	1.9	1.2
2 SD	7.0	6.6	26.2	27.2	23.6	20.8	13.8	8.6
Patients receiving estrogen (3)								
mean	9.3	8.3	21.3	19.0	17.3	15.0	12.0	9.7
SEM	2.6	1.9	5.2	3.8	1.5	1.2	2.6	1.2
2 SD	9.0	6.4	18.0	13.2	5.0	4.0	9.2	4.2
Patients not receiving estrogen(10)								
mean	11.1	10.5	25.2	22.6	24.6	18.4	17.2	12.3
SEM	1.0	1.1	4.5	3.9	4.1	3.8	3.0	1.5
2 SD	6.6	6.8	28.8	24.6	26.0	23.8	18.8	9.2

Insulin tolerance test for glucose (mg/dl.)

time	-30	0	30	45	60	90	120
Patient							
1	90	85	20	25	20	20	15
2	83	82	20	34	35	38	47
3	87	87	53	41	39	43	--
4	86	84	20	47	55	59	64
5	85	83	25	31	35	44	57
6	89	84	22	35	34	39	50
7	80	79	34	61	64	78	79
8	87	84	21	41	36	46	56
9	80	80	25	50	50	54	66
10	74	74	21	41	37	55	59
11	77	78	25	30	28	42	48
12	92	89	35	51	54	72	67
13	80	78	24	38	43	51	60
mean	83.8	82.1	26.5	40.4	39.8	49.3	55.7
SEM	1.5	1.1	2.6	2.8	3.6	4.2	4.5
2 SD	10.8	8.2	18.8	19.8	26.0	30.0	31.4
Patients receiving estrogen(3)							
mean	89.0	89.0	26.7	35.6	36.3	45.3	46.3
SEM	2.1	2.1	4.4	7.9	9.8	15.0	15.9
2 SD	7.2	7.2	15.2	27.2	34.0	52.0	55.6
Patients not receiving estrogen(10)							
mean	82.3	81.0	26.5	41.8	42.1	50.5	60.3
SEM	1.5	1.2	3.2	2.8	3.5	3.8	3.2
2 SD	9.8	7.8	20.4	18.0	22.0	24.0	19.4

Insulin tolerance test for cortisol(micrograms/ml.)

time	-30	0	30	45	60	90	120
Patient							
1	8	16	16	39	47	53	60
2	11	10	12	27	27	35	34
3	15	19	18	26	36	34	--
4	16	11	9	24	36	31	26
5	27	21	20	27	43	43	48
6	10	8	11	26	31	23	29
7	10	13	8	12	14	7	6
8	13	11	10	21	31	35	32
9	18	14	14	27	30	26	27
10	10	10	8	17	23	24	23
11	11	9	7	20	25	31	28
12	27	18	30	46	50	66	43
13	6	7	14	24	29	25	20
mean	14	12.8	13.6	25.8	32.5	33.3	31.3
SEM	1.8	1.2	1.8	2.4	2.8	4.1	4.0
2 SD	13.2	9.0	12.8	17.6	20.0	29.2	28.0
Patients receiving estrogen(3)							
mean	20.7	18.3	22.0	37.3	46.7	54.0	50.3
SEM	6.3	1.5	4.2	5.5	2.0	6.7	5.0
2 SD	22.0	5.0	14.4	19.2	7.0	23.0	17.6
Patients not receiving estrogen(10)							
mean	12.0	11.2	11.1	22.4	28.2	27.1	25.0
SEM	1.1	1.1	1.1	1.6	2.1	2.7	2.8
2 SD	7.0	7.0	6.8	9.8	13.0	16.8	16.6

Insulin tolerance test for growth hormone(ng/ml.)

time	-30	0	30	45	60	90	120
Patient							
1	2	1	1	45	60	70	60
2	1	1	3	4	1	1	1
3	1	1	1	4	28	64	--
4	5	12	8	8	28	52	10
5	2	2	1	2	16	24	16
6	1	1	1	12	40	60	64
7	6	2	0	1	12	7	3
8	5	2	1	4	40	40	45
9	7	3	12	30	40	40	15
10	10	2	1	5	20	24	12
11	5	6	1	9	24	60	60
12	1	1	1	44	65	40	16
13	1	1	1	14	36	44	20
mean	3.6	2.7	2.5	14	31.5	40.5	26.8
SEM	.8	.9	1.0	4.3	5.0	6.0	6.8
2 SD	5.8	6.2	7.0	31.0	36.2	43.0	47.0
Patients receiving estrogen(3)							
mean	1.7	1.3	1.0	30.3	47.0	44.7	30.7
SEM	.3	.3	0	14.2	15.6	13.5	14.7
2 SD	1.2	1.2	0	49.0	54.0	46.8	50.8
Patients not receiving estrogen(10)							
mean	4.2	3.1	2.9	9.1	26.9	39.2	25.6
SEM	1.0	1.1	1.2	2.6	4.1	7.0	8.1
2 SD	6.2	7.0	7.8	16.8	26.2	44.2	48.6

Insulin tolerance test for prolactin(ng/ml.)

time	-30	0	30	45	60	90	120
Patient							
1	10	7	10	30	28	43	22
2	10	11	6	11	18	20	14
3	17	15	15	15	25	35	--
4	9	8	11	30	27	19	16
5	7	8	9	23	43	36	30
6	11	9	10	34	39	41	35
7	12	12	12	7	11	12	14
8	9	7	7	11	8	9	10
9	5	5	6	9	10	10	6
10	11	10	9	33	31	19	17
11	13	12	12	18	38	47	45
12	7	7	6	20	11	9	15
13	8	9	9	7	6	10	9
mean	9.9	9.2	9.4	19.1	22.7	23.8	19.4
SEM	.9	.8	.8	2.8	3.6	4.0	3.4
2 SD	6.2	5.4	5.4	20.2	25.8	28.8	23.2
Patiente receiving estrogen(3)							
mean	8	7.3	8.3	24.3	27.3	29.3	22.3
SEM	1.0	.3	1.2	3.0	9.2	10.4	4.3
2 SD	3.4	1.2	4.2	10.2	32.0	36.0	15.0
Patients not receiving estrogen(10)							
mean	10.5	9.8	9.7	17.5	21.3	22.2	18.4
SEM	1.0	.9	.9	3.4	3.9	4.4	4.3
2 SD	6.4	5.8	5.8	21.6	24.8	27.8	26.0

Insulin tolerance test for thyrotropin(microunits/ml.)

time	-30	0	30	45	60	90	120
Patient							
1	0	0	.8	.6	0	.4	.5
2	0	0	0	0	0	0	0
3	1	0	0	1	0	0	--
4	0	0	0	0	0	0	0
5	3	2	0	0	0	0	0
6	8	7	4	4	3	2	2
7	3	3	4	0	0	1	4
8	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0
11	6	4	2	1	1	1	1
12	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0
mean	1.6	1.2	.8	.5	.3	.3	.6
SEM	.7	.6	.4	.3	.2	.2	.4
2 SD	5.4	4.4	3.0	2.2	1.8	1.2	2.4
Patients receiving estrogen(3)							
mean	1.0	.7	.3	.2	0	.1	.2
SEM	1.0	.7	.3	.2	0	.1	.2
2 SD	3.4	2.4	1.0	.6	0	.4	.6
Patients not receiving estrogen(10)							
mean	1.8	1.4	1.0	.6	.4	.4	.4
SEM	.9	.8	.5	.4	.3	.2	.2
2 SD	5.8	5.0	3.4	2.6	2.0	1.4	1.4

APPENDIX II

Explanation of Selection of Normal Control Groups from the Literature

A. Normal controls for TRH stimulation of TSH

Source 1: Journal of Clinical Endocrinology and Metabolism, vol. 34,1972,p.1076. Presents reponses of 12 normal females to 200 micrograms of TRH. Although only 100 micrograms of TRH was used in the present study, it is well known that the two doses are almost equivalent[96].

Source 2: Journal of Clinical Endocrinology and Metabolism, vol. 40,1975,p.712. Presents responses of 15 normal females to 100 micrograms of TRH.

Pooled results for the grand mean (GM), standard error of the grand mean(SEGM), and 2 standard deviations (2 SD), equivalent to a confidence limit of 95%.

time	0	15	30	45	60	90	120
GM	2.6	15	16.8	14.2	11.6	8.3	6.2
SEGM	.7	2.5	1.6	1.5	1.5	1.1	.9
2 SD	7.1	9.7	16	15.5	15.2	11.0	9.3

B. Normal controls for TRH stimulation of PRL

Source 1: Journal of Clinical Endocrinology and Metabolism, vol. 41,1975,p.985. Presents responses of 10 normal males to 100 micrograms of TRH.

Source 2: unpublished data from Dr. Gerard N. Burrow.

Pooled results for the grand mean (GM), standard error of the

grand mean (SEGM), and 2 standard deviation (2 SD), equivalent to a confidence limit of 95%.

time	0	15	30	45	60	90	120
GM	19.8	38.4	36.8	34.7	28.9	24.1	20.2
SEGM	.9	3.1	1.7	2.3	1.9	1.4	1.2
2 SD	8.2	16.7	14.7	19.6	16.2	12.6	10.7

C. Normal controls for insulin hypoglycemia stimulation of cortisol

Source 1: Journal of Clinical Endocrinology and Metabolism, vol 40,1975,p.442. Presents the responses of cortisol to a mean hypoglycemia of 28 mg/dl. in 16 normal males.

Source 2: Journal of Clinical Endocrinology and Metabolism, vol. 34, 1972,p. 895. Presents the responses of cortisol to a mean hypoglycemia of 30 mg/dl. in five normal patients.

Source 3: Journal of Clinical Endocrinology and Metabolism, vol. 38,1974,p.836. Presents the responses of cortisol to a mean hypoglycemia of 25 mg/dl. in 13 normal patients, 8 males and 5 females.

Pooled results for the grand mean (GM), the standard error of the grand mean (SEGM), and 2 standard deviations(2 SD), equivalent to a confidence limit of 95%.

time	0	30	45	60	90	120
GM	11	13.5	18.8	21.3	19.1	15.9
SEGM	.7	.8	.7	1.1	1.1	1.0
2 SD	8.2	8.7	8.4	13.2	13.3	11.6

D. Normal controls for insulin hypoglycemia stimulation of GH

Source 1: New England Journal of Medicine, vol. 289,1973,p.236. Presents the responses of GH to a mean hypoglycemia of 40 mg/dl. in 8 normal patients, 4 females and 4 males.

Source 2: Journal of Clinical Endocrinology and Metabolism, vol 40,1975,p.442. Presents the responses of GH to a mean hypoglycemia of 28 mg/dl. in 16 normal males.

Source 3: American Journal of Obstetrics and Gynecology, April 15, 1975,p.1103. Presents the responses of GH to a mean hypoglycemia of 25 mg/dl. in five normal patients, 3 males and 2 females.

Source 4: Journal of Clinical Endocrinology and Metabolism, vol. 34,1972,p.895. Presents the responses of GH to a mean hypoglycemia of 32 mg/dl. in five normal patients.

Pooled results for the grand mean (GM), standard error of the grand mean (SEGM), and 2 standard deviations (2 SD), equivalent to a confidence limit of 95%.

time	0	30	45	60	90	120
GM	1.9	10.7	25.2	30.1	28.4	22.3
SEGM	.5	5.8	2.4	3.6	3.7	3.2
2 SD	6.3	25.8	28.5	42.4	43.4	36.8

E. Normal controls for insulin hypoglycemia stimulation of PRL

Source 1: Journal of Clinical Endocrinology and Metabolism, vol. 40,1975,p.442. Presents the responses of PRL to a mean hypoglycemia of 28 mg/dl. in 16 normal males. Results are presented in milliunits/ml. and have been expressed as percentage increase above baseline for comparison with patients in present study.

Results for mean and SEM expressed as percentage increase above baseline.

time	0	30	45	60	90	120
mean % increase	0	33	133	112	100	67
SEM % increase	20	30	50	30	45	30

The baseline for the 13 patients in this study is then used as a comparative baseline for Figure 5 and Figure 6.

F. Normal controls for insulin hypoglycemia stimulation of TSH

No data available.

Formulae for calculations of the grand mean (GM), standard error of the grand mean (SEGM), and standard deviation of a single observation (SD). NB: E= sum (equivalent to sigma)

n=number of items in sample $\bar{x}$=mean of items in sample

$S_{\bar{x}}$= SEM for items in sample

Samples

1	n_1	$\bar{x}_1$	$S_{\bar{x}_1}$
2	n_2	$\bar{x}_2$	$S_{\bar{x}_2}$
3	n_3	$\bar{x}_3$	$S_{\bar{x}_3}$
4	n_4	$\bar{x}_4$	$S_{\bar{x}_4}$

Calculation of GM($\bar{\bar{x}}$)

$$\bar{\bar{x}} = \frac{\overset{4}{\underset{i=1}{E}} n_i \bar{x}_i}{E\ n_i}$$

Calculation of SEGM and SD

$$S^2_{x_i} = \frac{\overset{n_i}{\underset{j=1}{E}} (x_{ij} - \bar{x}_i)^2}{n_i - 1}$$

$$S^2_{\bar{x}} = \frac{S^2_{x_i}}{n_i} \longrightarrow S^2_{x_i} = n_i\, S^2_{\bar{x}_i} \quad i=1,2,3,4$$

$$\text{pooled } S^2 \text{ or } S^2_p = \frac{(n_1-1)\, S^2_{x_1} + (n_2-1)\, S^2_{x_2} + (n_3-1)\, S^2_{x_3} + (n_4-1) S^2_{x_4}}{(n_1-1) + (n_2-1) + (n_3-1) + (n_4-1)}$$

$$\text{SEGM} = \sqrt{\frac{S^2_p}{n_1 + n_2 + n_3 + n_4}} \qquad \text{SD} = \sqrt{S^2_p}$$

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bibliography acronyms:

AIM=Annals of Internal Medicine

JAMA=Journal of the American Medical Association

JCI=Journal of Clinical Investigation

JCEM=Journal of Clinical Endocrinology and Metabolism

NEJM=New England Journal of Medicine

SUMMARY

Thirteen asymptomatic women with postpartum blood loss of 500 to 2000 ccs within the first ten days after delivery underwent evaluation of endocrine function of the anterior pituitary gland. Insulin tolerance tests and TRH stimulation tests for measurement of serum levels of growth hormone, cortisol, prolactin, and thyrotropin were performed. There was no laboratory evidence of pituitary dysfunction in this group of thirteen patients. It appears that anterior hypopituitarism secondary to postpartum hemorrhage is uncommon in women with minimal blood loss.

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