

# Growth Hormone Secretion during Sleep

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**ABSTRACT** Plasma growth hormone (GH), insulin, cortisol, and glucose were measured during sleep on 38 nights in eight young adults. Blood was drawn from an indwelling catheter at 30-min intervals; EEG and electrooculogram were recorded throughout the night. In seven subjects, a plasma GH peak (13–72 m $\mu$ g/ml) lasting 1.5–3.5 hr appeared with the onset of deep sleep. Smaller GH peaks (6–14 m $\mu$ g/ml) occasionally appeared during subsequent deep sleep phases. Peak GH secretion was delayed if the onset of sleep was delayed. Subjects who were awakened for 2–3 hr and allowed to return to sleep exhibited another peak of GH secretion (14–46 m $\mu$ g/ml). Peak GH secretion was not correlated with changes in plasma glucose, insulin, and cortisol. The effects of 6-CNS-active drugs on sleep-related GH secretion were investigated. Imipramine (50 mg) completely abolished GH peaks in two of four subjects, whereas chlorpromazine (30 mg), phenobarbital (97 mg), diphenylhydantoin (90 mg), chlorthalidone (20 mg), and isocarboxazid (30 mg) did not inhibit GH peaks. Altered hypothalamic activity associated with initiation of sleep results in a major peak of growth hormone secretion unrelated to hypoglycemia or changes in cortisol and insulin secretion.

## INTRODUCTION

The factors which influence the concentration of growth hormone (GH) in human plasma during the waking hours have received great attention. The rise in plasma growth hormone which occurs

with lowering the blood sugar (1), the infusion of certain amino acids (2), and exercise (3), is well recognized. In addition, secretion of growth hormone can be stimulated by certain pathological or nonphysiological stimuli such as operative stress (3, 4) and the administration of pyrogens (5) or large doses of vasopressin (6).

Despite intense interest in the study of plasma growth hormone levels in man, observations of the plasma growth hormone concentration during sleep have been limited. Hunter, Friend, and Strong (7) made hourly measurements of growth hormone in the plasma of nine normal subjects during the day and from 1–3 measurements during the night. In eight of nine subjects, they observed an elevated level of plasma GH during the night. They speculated that since the longest interval between meals occurred at night, the increased secretion of growth hormone was a response to fasting and the associated need for an accelerated mobilization of free fatty acids. Similar observations were made also in children by Hunter and Rigal (8).

A more detailed study of plasma GH concentrations in sleep was carried out by Quabbe, Schilling, and Helge (9) in six normal adult subjects. Plasma GH was low for several hours after the evening meal, but intermittent peaks of GH secretion were observed during the night. Although objective measurements of the depth of sleep were not made, these authors reported that plasma GH was usually low during light sleep and peaks of GH secretion were most commonly observed during deep sleep. The number of GH peaks found in two women was greater than in four men. Concomitant measurements of plasma glucose failed to demonstrate any significant correlation between the blood glucose and GH levels. In addition, the

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TABLE I  
CNS-Active Drugs Used in Study

Generic name	Trade name	Dosage	
		mg	mg/kg body weight
Chlorpromazine	Thorazine spansule	30	0.44–0.55
Imipramine	Tofranil	50	0.88–1.10
Phenobarbital	Eskabarb spansule	100	1.43–1.76
Chlordiazepoxide	Librium	20	0.35–0.43
Isocarboxazid	Marplan	30	0.44–0.55
Diphenylhydantoin	Dilantin	90	1.32–1.91

peaks of GH secretion did not induce detectable changes in the plasma free fatty acids during the nighttime hours, although the expected progressive rise of the plasma free fatty acids during sleep did occur. These observations have been confirmed by Glick and Goldsmith in their report to the International Symposium on Growth Hormone in Milan (10).

We performed the present investigations to determine the pattern of GH secretion during sleep and to correlate the changes in plasma GH with the electroencephalographic-determined stages of sleep and concomitant measurements of plasma insulin, glucose, and cortisol. After a reproducible pattern of GH secretion was observed during the early hours of sleep, a variety of pharmacological agents active on the central nervous system (CNS) were tested for their ability to modify this pattern of GH secretion.

## METHODS

Four men and four women between the ages of 20 and 30 yr, of normal weight and without evidence of nervous or mental disorders, served as subjects for this study. No subjects were reported to have insomnia or other sleep difficulties and all exhibited normal EEG activity during sleep. The women gave a history of menstrual regularity, and none was ingesting contraceptive or other hormonal medications.

All medications and alcoholic drinks were prohibited for at least 3 days before the sleep study. The subjects were requested to have a normal sleep during the night immediately preceding the day of the experiment and were not allowed to take a nap in the daytime preceding the sleep study. On the night of the study, the subjects ate a normal dinner between 5:00 and 6:00 p.m. and were then admitted to the Clinical Research Center. They were allowed no additional food but were permitted to drink water as desired. At 8:00 p.m. they went to bed in a quiet room.

An indwelling catheter ("Intracath" needle gauge 17, catheter 12 inches) was inserted into an antecubital vein under local anesthesia and filled with 0.9% NaCl solution containing 10 U of heparin per ml. The end of the catheter was capped and the exposed portion of the catheter was fixed to the forearm with tape and gauze pads so that blood drawing could be done without touching the subject's arm. Catheterization was generally performed 60–90 min before the onset of sleep and blood samples (2–4 ml) were collected usually at 30-min intervals throughout the night. During the early hours of deep sleep, blood was drawn every 20 min. Samples were collected in heparinized tubes, centrifuged within 30 min, and the plasma stored at  $-20^{\circ}\text{C}$  until analysis. The subjects were awakened between 6:30 and 8:30 a.m. but remained in bed for 1 hr. After the subjects awoke in the morning, 20 ml of blood was drawn for routine laboratory tests. A total of 20–25 plasma samples were thus

TABLE II  
Peak Growth Hormone Levels Observed in 38 Sleep Studies on Eight Normal Individuals

Subject	Sex	Age	Height	Weight	Plasma growth hormone ( $\mu\text{g/ml}$ )									
					Control sleep		Delayed sleep	Interrupted sleep*	CP	PB	CD	IP	IC	DH
					No. 1	No. 2								
		yr	cm	kg	$\mu\text{g/ml}$									
L. S.	M	30	165	67	33(1)†									
S. G.	M	23	178	77	72(1)									
T. F.	M	27	168	57	18(2)	44(1)	12(1)		17(1)	24(3)	60(1)			
B. O.	M	22	183	68	17(1)	24(1)		64,46(2)	10(1)	16(1)		15(1)	18(1)	42(2)
B. B.	F	20	155	47	40(2)		24(2)	48,24(2)			14(3)	NP(0)		46(3)
D. G.	F	22	160	57	34(3)		22(2)				16(2)	NP(1)	20(2)	
F. R.	F	20	170	65	NP(1)	NP	NP(2)							
M. K.	F	24	173	54	42(2)	13(3)		24,14(2)	74(4)	30(5)		46(1)	43(3)	32(3)

CP, chlorpromazine; PB, phenobarbital; CD, chlordiazepoxide; IP, imipramine; IC, isocarboxazid; DH, diphenylhydantoin; NP, no peak.

\* GH values of the first and second peaks are shown.

† Numbers in parentheses indicate number of GH peaks appearing during a night's sleep.

TABLE III  
*Duration Spent in Various Stages of Sleep*

Condition	No. of expt.	Total sleep time	Waking	Per cent time spent in sleep stage					
				1-REM	1	2	3	4	
		<i>min</i>			<i>%</i>				
Normal control sleep	12	522 ± 22	5.5 ± 1.2	22.9 ± 1.8	9.1 ± 1.7	48.9 ± 2.5	9.7 ± 1.4	3.9 ± 0.8	
Delayed sleep	4	362 ± 20	4.5 ± 2.5	23.3 ± 3.7	8.4 ± 3.6	46.5 ± 1.2	13.6 ± 2.5	3.8 ± 1.7	
Interrupted sleep	3	422 ± 17	3.0 ± 2.1	27.5 ± 2.9	4.9 ± 2.0	46.6 ± 3.7	12.4 ± 1.3	5.7 ± 4.	
Medicated sleep									
Imipramine	4	533 ± 30	4.5 ± 0.6	7.9 ± 2.7	6.3 ± 1.8	64.3 ± 2.2	10.0 ± 2.6	6.0 ± 0.5	
Chlorpromazine	3	530 ± 54	1.1 ± 1.3	31.3 ± 5.0	3.4 ± 3.5	48.3 ± 2.1	13.7 ± 3.4	2.4 ± 2.0	
Phenobarbital	3	587 ± 23	1.6 ± 1.2	21.9 ± 5.3	6.8 ± 8.6	53.1 ± 2.0	11.4 ± 4.5	5.2 ± 2.4	
Diphenylhydantoin	3	586 ± 20	2.8 ± 1.2	23.7 ± 4.0	4.4 ± 1.2	56.2 ± 5.8	9.5 ± 1.4	3.5 ± 2.8	
Chlordiazepoxide	3	551 ± 33	5.5 ± 5.5	21.9 ± 4.9	5.0 ± 2.8	58.2 ± 2.2	7.9 ± 1.6	1.6 ± 1.8	
Isocarboxazid	3	572 ± 20	3.0 ± 1.9	29.4 ± 2.3	3.1 ± 1.1	50.2 ± 3.7	11.7 ± 1.3	6.0 ± 3.6	

All values represent mean ± SEM.

obtained in the 12 hr experimental period, representing a volume of approximately 100 ml of blood.

Electroencephalogram (EEG), electrocardiogram (ECG), and electrooculogram (EOG) were recorded by an 8 channel Grass Model III D electroencephalograph. An EEG recording was obtained from right ear to right frontal, vertex, occipital, and temporal regions (monopolar) and from the vertex to occipital areas (bipolar). Vertical and horizontal movements of the right eye were recorded with a 1.0 sec time constant and calibration of 50  $\mu$ v/10 mm. The polygraphic recording was made at a paper speed of 3 cm/sec throughout the night. The sleep EEG records, were scored into 5 stages according to the criteria of Dement and Kleitman (11): stage 1, low voltage, irregularly mixed, fast and slow pattern with complete absence of sleep spindles; stage 2, 12-14-cps sleep spindles with low voltage background; stage 3, an intermediate amount of high amplitude, slow waves with some spindling; stage 4, a predominance of high amplitude, slow waves; stage 1-REM, rapid eye movements in EOG and stage 1 EEG activity.

Great care was taken to keep the subjects comfortable and relaxed during the experiment. They slept well and felt little or no discomfort due to the indwelling catheter and scalp and facial leads. The blood drawing rarely awakened the subject, although the subject was disturbed occasionally by the necessity of repositioning the arm so that a blood sample could be obtained. These occasional arousals were only a few minutes in duration and were randomly dispersed over the sleep period.

Three of the eight subjects were studied during only 1 night of normal sleep. Three to eight sleep studies were carried out on each of the other five subjects. The time lapse between two sleep studies in the same subject ranged from 1 wk to 5 months.

The drugs acting on the central nervous system which were administered in this study were chlorpromazine, phenobarbital, imipramine, chlordiazepoxide, isocarboxa-

zid, and diphenylhydantoin. Each drug is representative of a type of CNS active pharmacological agent widely used in clinical medicine. The medications were administered by mouth in customary clinical dosage 30 min to 2 hr before sleep (Table I).

Plasma human growth hormone (HGH) and insulin levels were measured by the double antibody methods of Schalch and Parker (12) and Morgan and Lazarow (13), respectively. The GH standard was a highly purified preparation of HGH (HS 612A) kindly supplied by Dr. A. E. Wilhelmi. Plasma cortisol level was measured by the competitive protein-binding radioassay of Murphy using hydrocortisone-4-<sup>14</sup>C, human corticosteroid-binding globulin, and Sephadex columns (14) or Fuller's earth (15). Plasma glucose was measured by a ferricyanide reduction method using the Technicon AutoAnalyzer.

## RESULTS

### Normal control sleep

12 normal control experiments were carried out on eight subjects (Table II). Control experiments were repeated in two men and two women at intervals of 11 days to 6 months. Onset of sleep occurred between 10:00 and 11:00 p.m. in nine experiments and between 11:00 and 12:00 p.m. in three experiments. The distribution of the time which subjects spent in each stage of sleep during the night is shown in Table III. These results are comparable to those reported previously in normal young adults (16).

Blood samples drawn immediately after catheterization showed a GH level of less than 4  $\mu$ g/ml in eight experiments. In four experiments, all on women, elevated GH concentrations ranging

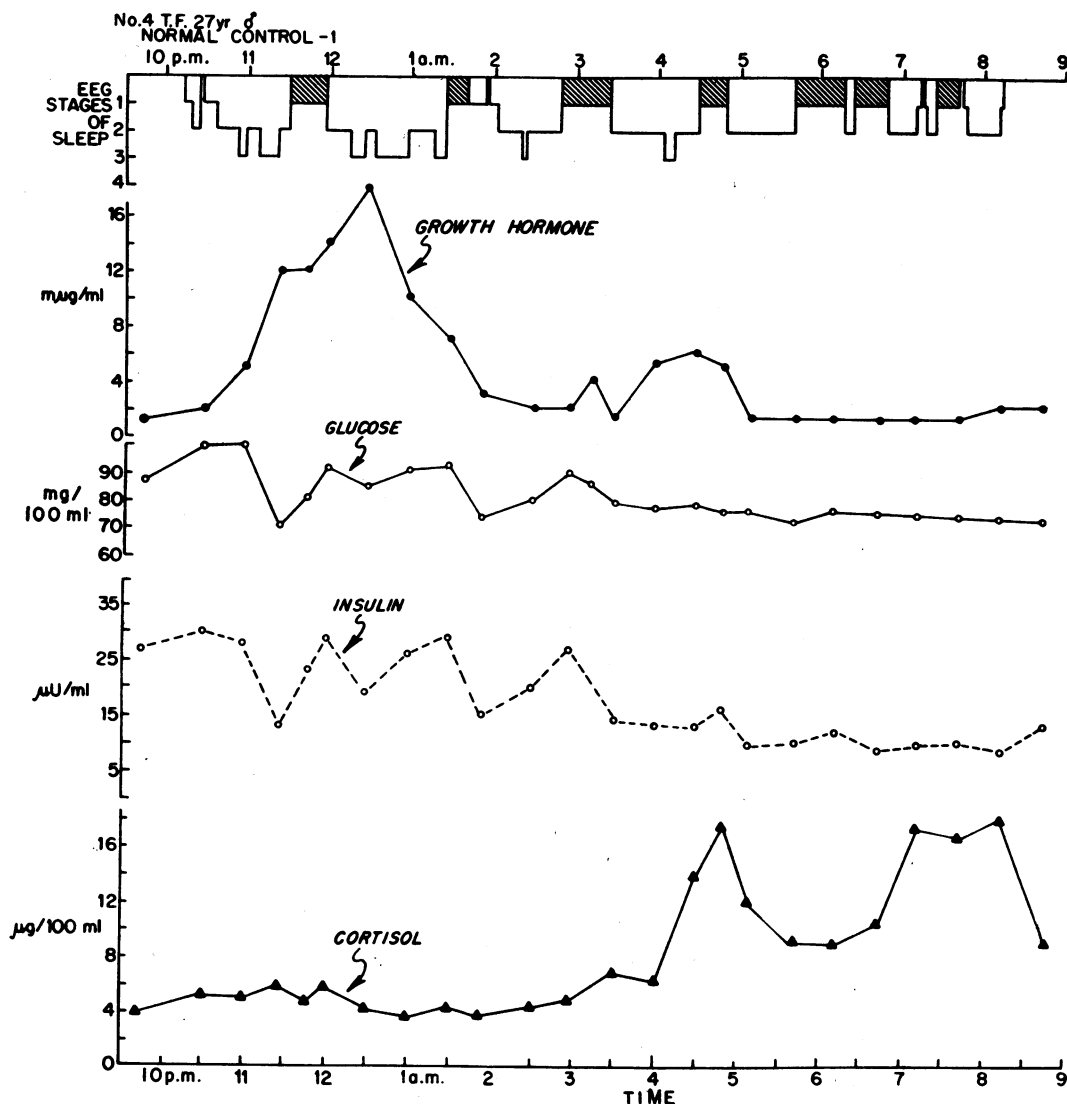


FIGURE 1 The plasma growth hormone, glucose, insulin, and cortisol levels and EEG-EOG monitored CNS activity during a normal night's sleep in a 27 yr old man (T. F.). In this and subsequent figures the levels of sleep are indicated at the top of the figure. Cross-hatched areas are periods of rapid eye movement.

from 8–22 m $\mu$ g/ml were observed and were considered to be due to the stress caused by catheterization. In each case, these initial high values returned to normal basal levels, e.g. < 5 m $\mu$ g/ml, within 30 min.

In 10 experiments performed on seven of the eight subjects, a significant rise in the plasma GH concentration, i.e. defined in this study as a level > 5 m $\mu$ g/ml, occurred within the first 90 min after the onset of sleep (Figs. 1, 2, and 6). The most characteristic pattern observed was a gradual in-

crease in the GH levels during this period with the first detectable rise noted 20–40 min after the initiation of sleep. Some individuals, however, exhibited abrupt increases with peak levels attained by 40 min. The time between the onset of sleep and the GH peak ranged from 39 to 165 min with a mean of 70 min. The GH level remained elevated for 1.5–3.5 hr and then gradually returned to the base line.

The pattern of GH secretion during sleep was very reproducible as demonstrated in control

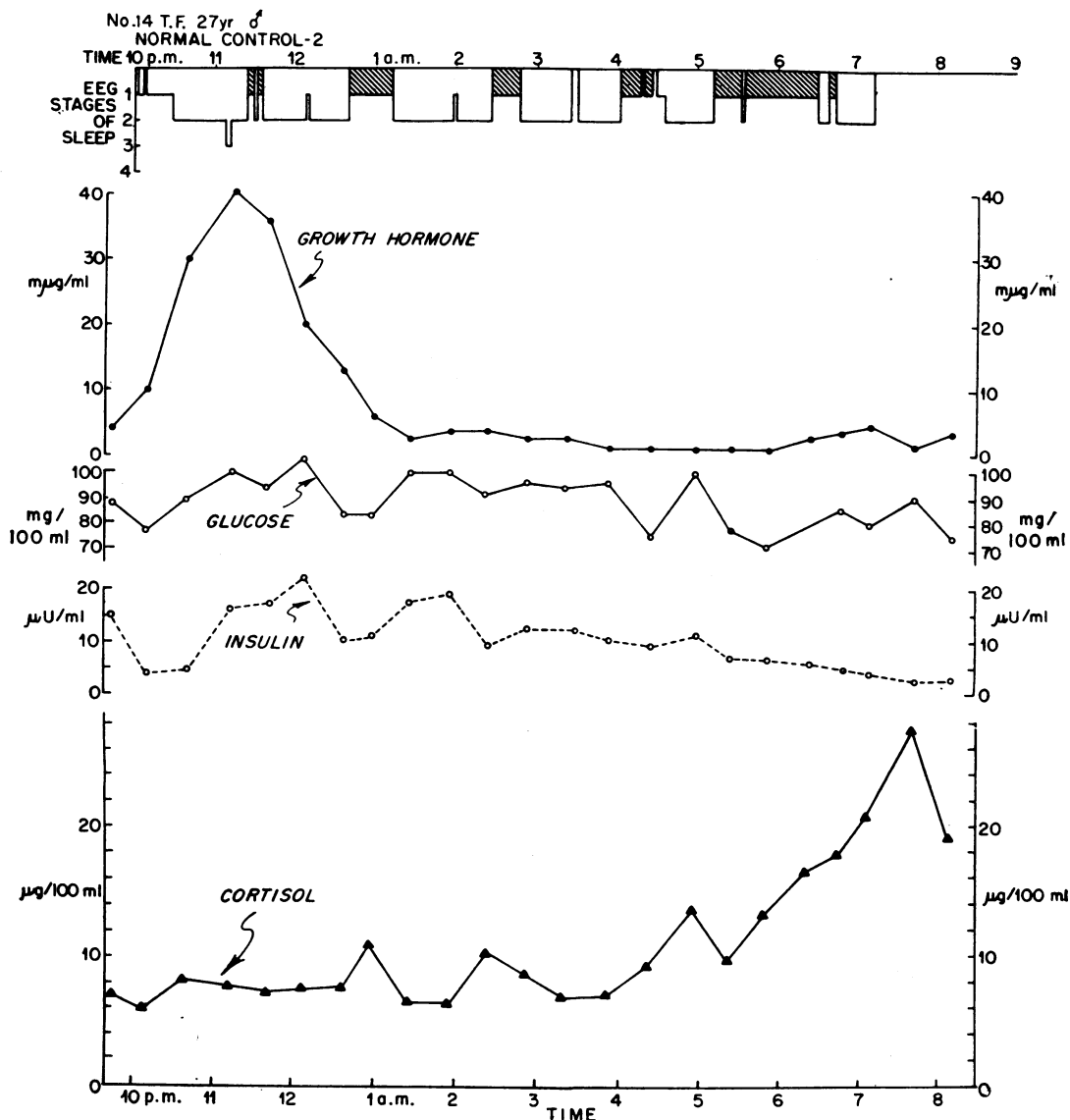


FIGURE 2 Reproducibility of plasma hormone responses during sleep. This control study was carried out on the same individual (T. F.) as shown in Fig. 1, 2.5 months later.

studies repeated on two or more occasions in four subjects. Typical examples are shown in Figs. 1 and 2.

The peak GH levels ranged from 13 to 72  $\mu\text{g}/\text{ml}$  with a mean of  $34 \mu\text{g}/\text{ml} \pm 5.8 \text{ se}$  (Table II). There was no significant sex difference in the peak levels of GH; males ranged 17–72  $\mu\text{g}/\text{ml}$  ( $35 \pm 9.4 \mu\text{g}/\text{ml}$ ); females ranged 13–42  $\mu\text{g}/\text{ml}$  ( $32 \pm 7.7 \mu\text{g}/\text{ml}$ ). In the six control studies carried out on the four male subjects, the plasma GH concentration,

after the initial GH peak, remained at 5  $\mu\text{g}/\text{ml}$  or less for the remainder of the night except for one study in subject T. F. in which a secondary rise to 6  $\mu\text{g}/\text{ml}$  was noted. In the female subjects, with the exception of subject F. R. noted below, at least one and in some instances two subsequent GH peaks ranging from 8–20  $\mu\text{g}/\text{ml}$  were regularly observed. The peaks were usually sharply defined and limited in duration with return to basal levels ( $< 5 \mu\text{g}/\text{ml}$ ) before subsequent rises. In each of these individuals, however,

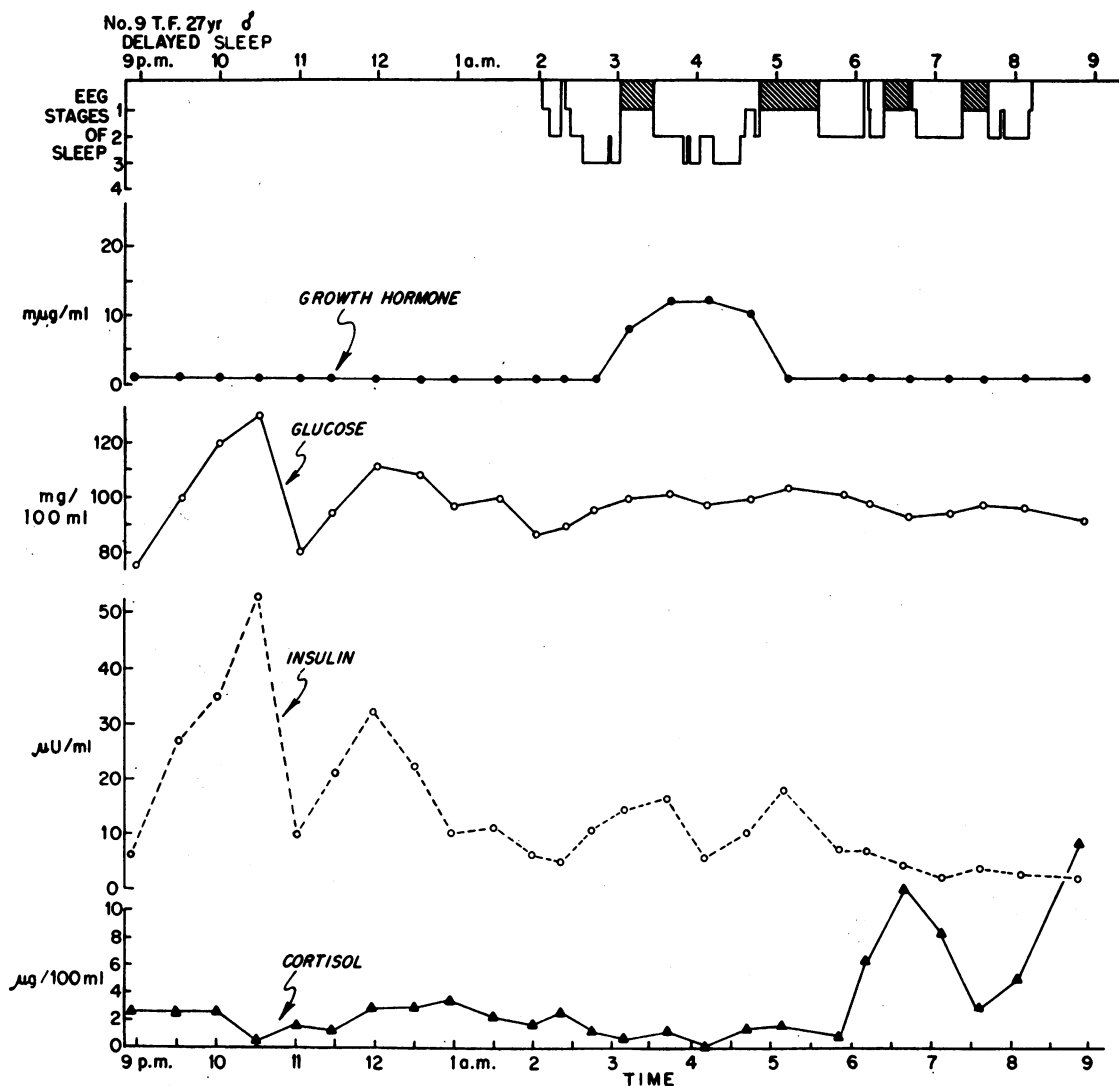


FIGURE 3 The effect of delaying the onset of sleep on the plasma growth hormone secretory pattern (T. F.).

the initial plasma GH peak was always considerably greater than the subsequent elevated level.

In two control studies on one woman (F. R.), which were carried out 11 days apart, GH levels did not rise at the onset of sleep. However, in each of these studies, minimal elevation to 7 and 9 mμg/ml were noted during the early morning hours (6–7 a.m.) just before arising.

The GH levels at the time of awakening between 6:00 and 8:30 a.m. were less than 3 mμg/ml in 10 experiments and 5–6 mμg/ml in 2 experiments with no sex difference noted. The GH values remained at this level for 1 hr after awakening in nine experiments, but increased slightly to levels

of 6–13 mμg/ml in three experiments performed on the female subjects. In each instance, the rise in plasma GH was attributed to either physical exercise, i.e. going to toilet, or the painful stress caused by removal of the scalp and facial electrodes.

#### Delayed sleep

In order to examine the relationship between initiation of sleep and the appearance of the peak elevation of plasma GH, we delayed the onset of sleep 3–3.5 hr (until 1:30–2:30 a.m.) in four subjects (one man and three women) who fell asleep between 10:00 and 11:00 p.m. in the control

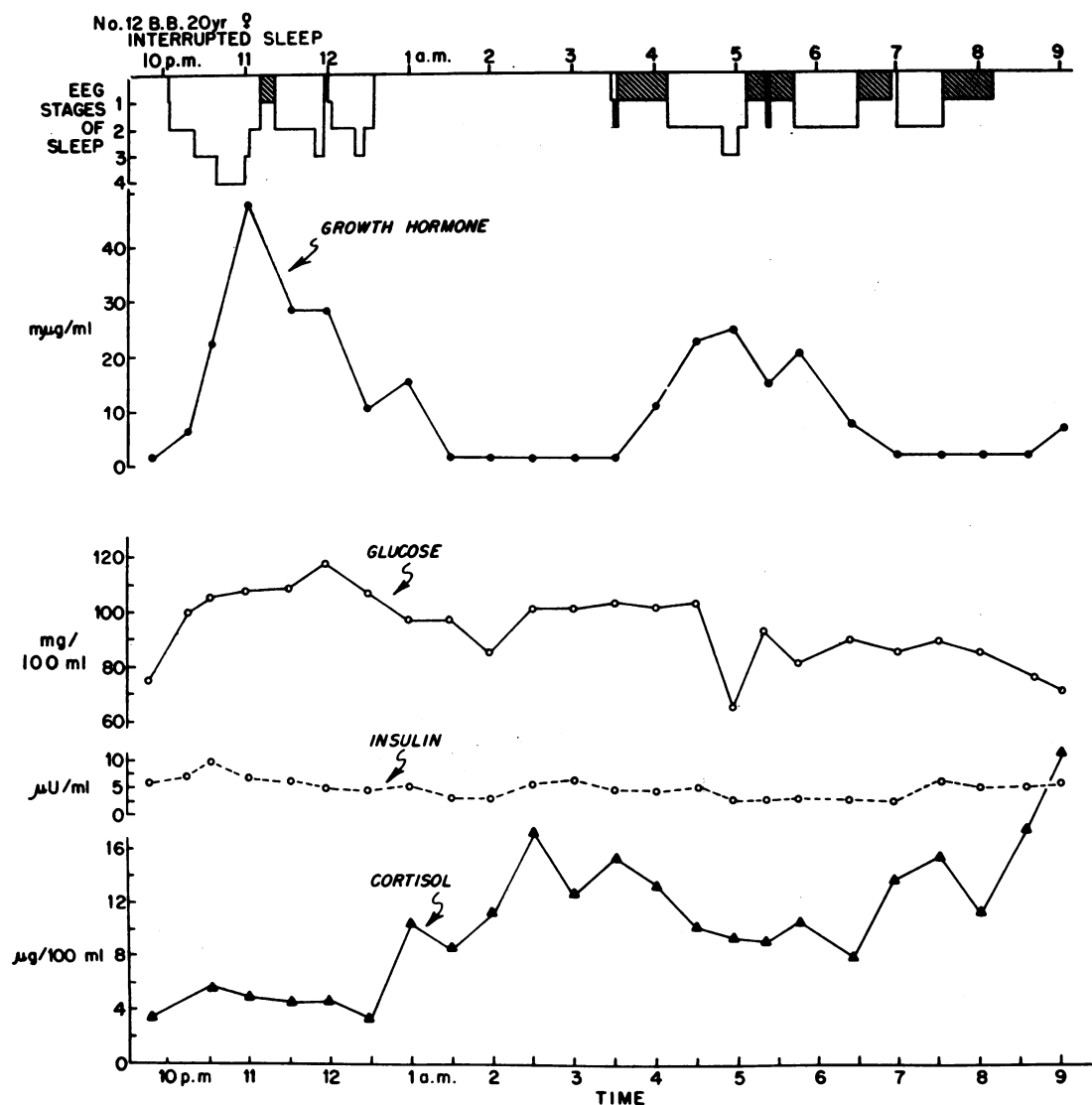


FIGURE 4 The effect of a prolonged interruption of sleep (3 hr) on the plasma growth hormone secretory pattern (B. B.).

experiments. In three subjects, GH levels remained less than 5  $\mu\text{g}/\text{ml}$  during the 4.5–5.5 hr preceding the delayed onset of sleep. When sleep was permitted, GH levels showed a peak elevation of 12–24  $\mu\text{g}/\text{ml}$ , 30–90 min after the onset of sleep (Fig. 3). The GH peak after the delayed onset of sleep appeared to be lower than the peak GH level attained after the onset of sleep in the control study.

The one subject, F. R., who exhibited no GH peaks after the onset of sleep in two control experiments, also had no peak GH elevation after the delayed onset of sleep.

### Interrupted sleep

Occasional arousals of a few minutes' duration were randomly dispersed over the sleep period in all control experiments. Awakenings of 5–26 min duration occurred once to five times in 8 of the 12 control experiments. However, no rise in GH levels was observed after resumption of sleep subsequent to these brief awakenings.

An attempt was made to examine the effect of awakening of longer duration on the pattern of GH secretion in one man and two women. The subjects fell asleep between 10:00 and 12:00 p.m.

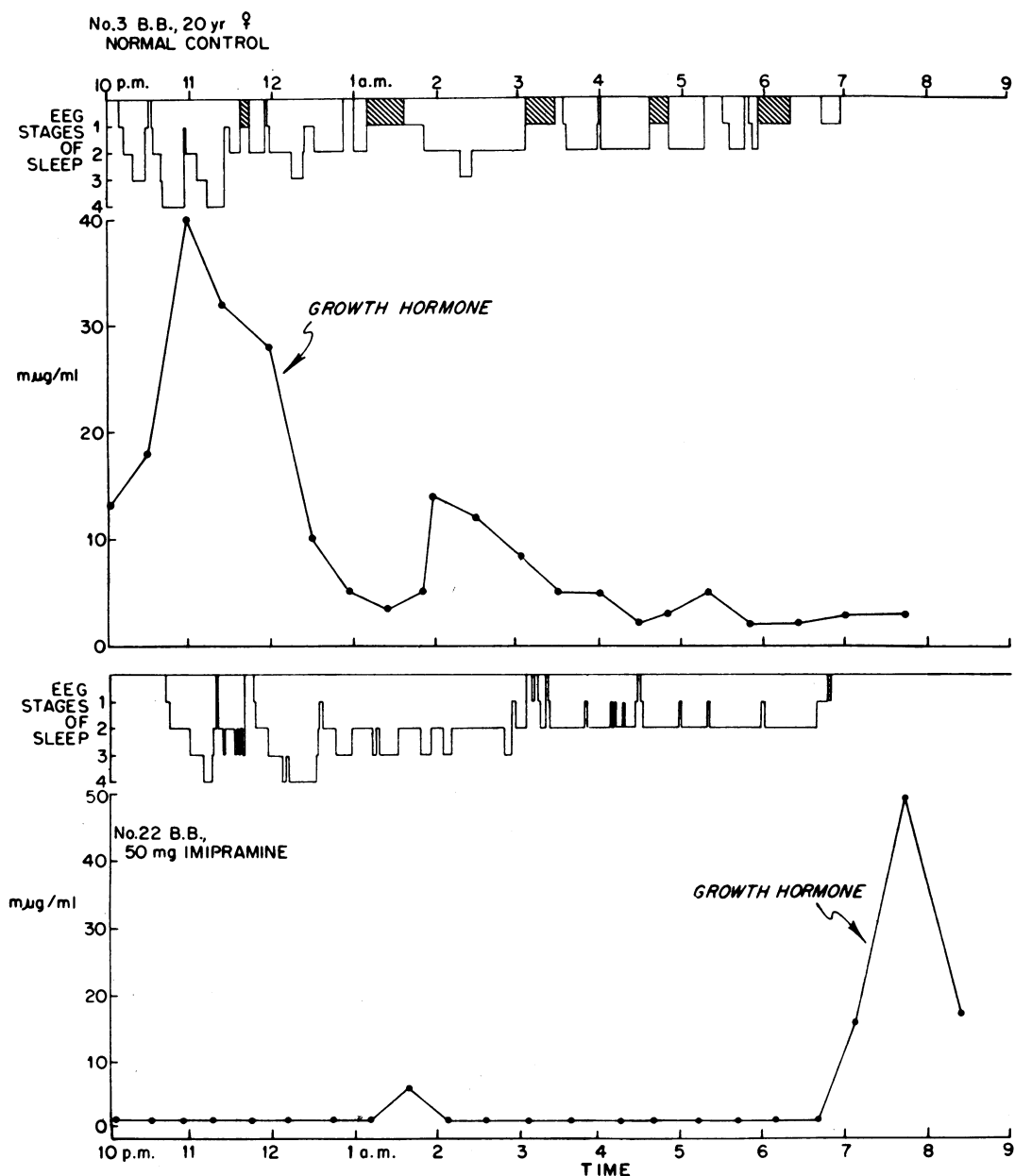


FIGURE 5 The suppressive effect of imipramine on the plasma growth hormone secretory response after the onset of sleep (B. B.).

and were awakened between 12:30 and 2:30 a.m. after they had slept for 2.5–3 hr. They were kept awake for 2–3 hr and then allowed to return to sleep. During the period of this prolonged awakening, they read books or listened to a radio while sitting in bed. In all three subjects, two peak elevations of plasma GH were observed; one occurred

soon after the initial onset of sleep and another peak appeared after the second onset of sleep (Fig. 4). The first peaks of GH were 64, 48, and 24 mμg/ml whereas the second peaks were 46, 24, and 14 mμg/ml, respectively. The first peak of GH was always higher than the second in the same subject.



## Effect of CNS active drugs

**Chlorpromazine.** In each of the three subjects treated with 30 mg of chlorpromazine, the time spent in stage 1-REM increased compared with that in the normal control study (Table III). The secretory pattern of GH was unaltered in two subjects, whereas another subject, M. K., who had 2-3 GH peaks during two control sleep studies, showed 4 peak elevations of 46, 30, 18, and 74  $\mu\text{g/ml}$  during sleep after chlorpromazine (Table II).

**Phenobarbital.** At the dosage used, phenobarbital did not alter significantly the sleep pattern of the three subjects studied (Table III). On the other hand, two of these individuals did show marked changes in their GH secretory pattern (Table I); T. F. exhibited 3 peaks (24, 11, and 6  $\mu\text{g/ml}$ ) and M. K. showed 5 peaks (30, 30, 32, 28, and 6  $\mu\text{g/ml}$ ). In one subject, B. O., the GH secretory pattern was unaltered. It is of interest that this individual was the heaviest of the three and consequently received the smallest dose of drug per kg body weight.

**Imipramine.** In each of the four subjects treated with imipramine, the total duration of stage 1-REM sleep was significantly suppressed whereas that of stage 2 sleep was increased (Table III). In three of the four subjects, stage 1-REM did not appear during the first half of a night's sleep, but deep sleep did occur as usual after the onset of sleep. In two subjects, D. G. and B. B. (Table II and Fig. 5), initial GH peaks were totally suppressed and only one elevated plasma GH level of 6  $\mu\text{g/ml}$  was noted in either subject throughout the night. In another subject, M. K., stage 1-REM was not suppressed during the initial hours of sleep, which suggested an inadequate drug effect at this time, and a GH peak of 46  $\mu\text{g/ml}$  appeared after the onset of sleep. However, only one GH peak occurred in this study, whereas 3-5 peak elevations of GH were observed in this subject during normal or medicated, e.g. phenobarbital, chlorpromazine, sleep studies. Again, the heaviest individual, B. O., failed to exhibit any alteration in his GH secretory pattern after drug ingestion.

**Diphenylhydantoin.** No significant change was observed in either the sleep pattern (Table III) or the secretory patterns of GH, insulin, and cor-

TABLE IV  
Correlation of Plasma GH Peak and Sleep Stage

Sleep stage	Duration of sleep stage	No. of GH peaks	Per cent GH peaks	Frequency*
	%			
1-REM	22.7	14	20.0	0.62
Waking	4.0	1	1.4	0.25
1	6.6	0	0.0	0.00
2	51.7	25	35.7	0.48
3	10.8	19	27.2	1.76
4	4.2	11	15.7	2.62

\*  $\frac{\text{No. of GH peaks}}{\text{duration sleep stage (\%)}}$ . This expression indicates the relative frequency of appearance of GH peaks with each stage of sleep.

tisol in the three subjects treated with diphenylhydantoin (Table II).

**Isocarboxazid (IC).** In the three subjects given IC, sleep patterns (Table III) and the plasma levels of GH (Table II), insulin, glucose, and cortisol were unaltered compared with those in the control study.

**Chlordiazepoxide.** In the three subjects treated with chlordiazepoxide (Table II) no significant change was observed in either the sleep pattern (Table III) or the secretory patterns of GH, insulin, glucose, and cortisol.

### Correlation of sleep pattern and GH level

In order to investigate the relationship between GH peaks and the stages of sleep, we determined a predominant stage of sleep during 10 min preceding the rising phase of each of 70 GH peaks occurring in 38 normal and medicated sleep studies. As shown in Table IV, 30 (43%) of the 70 GH peaks occurred during deep sleep, i.e. stages 3 and 4, which represented only 15% of the total duration of sleep time.

## DISCUSSION

These investigations have uncovered a greater uniformity in the pattern of secretion of GH during sleep than has previously been recognized. This is best demonstrated in Fig. 6 where mean plasma GH in the 12 control studies on normal adult subjects has been plotted as a function of time before and after the initiation of sleep. There is a clearly defined peak plasma GH which

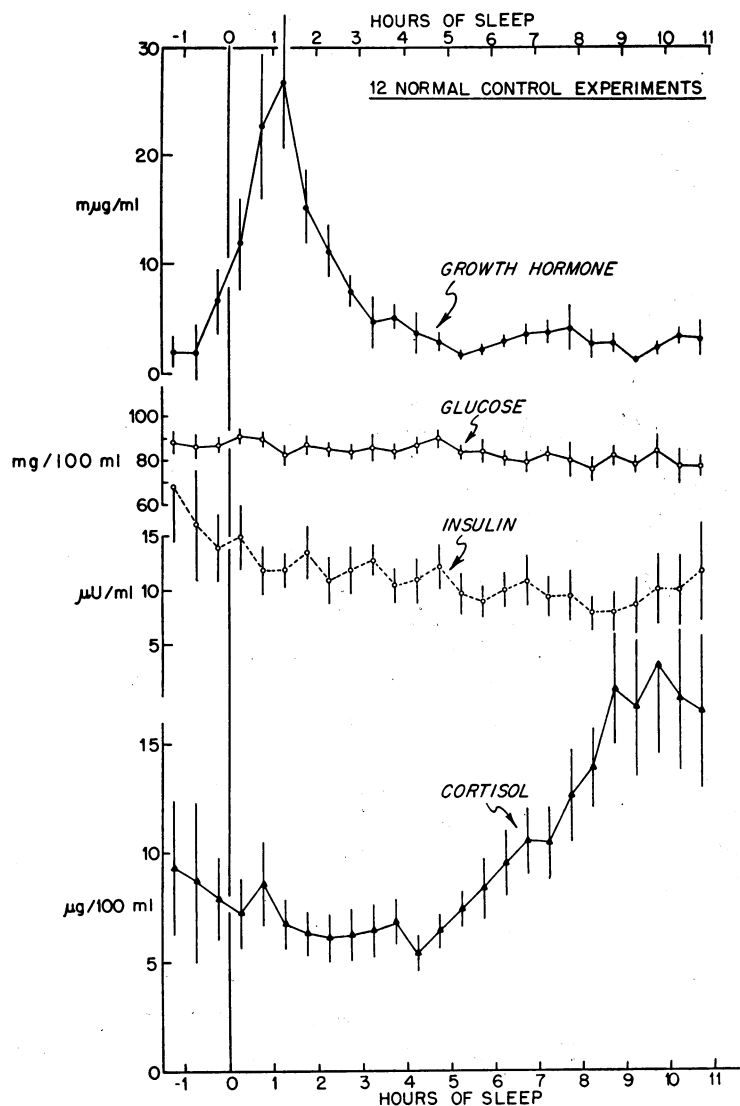


FIGURE 6 The plasma growth hormone, glucose, insulin, and cortisol levels during 12 normal control sleep studies. All values represent mean  $\pm$  SEM.

reached its highest value about 70 min after onset of sleep. The degree of rise in plasma GH is remarkable and is entirely comparable to that observed in our laboratory after such potent stimuli of GH secretion as insulin-induced hypoglycemia or arginine infusion (17). It is also remarkable that in this limited adult population, there was no indication that the initial sleep related GH peak in women was higher than that in men, and that the only subject who failed to exhibit a sleep related GH peak was a woman. These observations are in striking contrast to the GH secretory responses to other stimuli (18).

The experiments in which sleep was delayed or

interrupted provide strong evidence that the GH peaks which we have observed are related to the onset of sleep and do not reflect a true circadian rhythm in GH secretion. This pattern of response is in contrast to nighttime secretion of cortisol which is not immediately altered by changing the hours of sleep and wakefulness (19). In our experiments, the expected rise in cortisol during the early morning hours was readily demonstrated. However, unlike Weitzman, Schaumburg, and Fishbein (20) we were unable to correlate periods of REM sleep with peaks of plasma cortisol. It is noteworthy that during the later hours of sleep when cortisol secretion was increasing, the

likelihood of GH peaks decreased. Thus, upon awakening, at a time when cortisol levels were highest, plasma GH levels were uniformly low. The lack of a positive correlation between cortisol and GH secretion is evidence that GH secretion is not in response to nonspecific stress. Support for the notion that there may be a relative inhibition of the GH secretory mechanism during the period of adrenocorticotropin (ACTH)-adrenal cortical activation is provided by the experiment with delayed sleep. In these subjects, the peak of plasma GH which followed the delayed onset of sleep was lower than that which occurred after the onset of sleep earlier in the night. While the evidence is compatible with an inhibition of sleep-related GH secretion by the circadian activation of the adrenal cortex, this is probably not caused by a direct effect of corticosteroids on GH secretory mechanism. In the experiment of Frantz and Rabkin (21), large doses of corticosteroids were ineffective in blocking the insulin induced secretion of GH when administered immediately before challenge. At present it would appear more likely that the basic circadian rhythm in hypothalamic function which results in adrenal activation is in some way inhibitory to the secretion of the growth hormone-releasing factor. Other equally plausible interpretations are possible.

The electrocephalographic and oculomyographic monitoring of these patients was performed in an attempt to correlate hypothalamic endocrine activities of the brain with the electrical manifestations of sleep. No correlation could be demonstrated between the GH peaks and periods of rapid eye movement sleep. These sleep intervals are associated with dreaming and circulatory changes (22). It is also characteristic of rapid eye movement intervals to occur more frequently later in the sleep period. The correlation of onset of GH peaks with the level of sleep appeared to favor an association of GH peaks with the deeper encephalographic stages of sleep (stages 3 and 4). This correlation, however, may be fortuitous since the early hours of sleep are more commonly characterized by periods of the deeper stages of sleep which become less common as the period of sleep continues.

Blood glucose and insulin concentrations fell in an irregular pattern during the night and were lowest at a time when GH peaks rarely occurred.

These findings confirm similar findings by Quabbe et al. (9), and provide additional evidence against the view of Hunter, Friend, and Strong (7) that the secretion of GH during sleep is primarily determined by the need to mobilize stored nutrients during night fasting. Likewise, we have also failed to observe acute changes in plasma free fatty acids which correlated with the major peaks of GH secretion during sleep (unpublished observations).

The appearance of a plasma GH peak associated with the onset of sleep was not influenced by most of the medications administered. Chlorpromazine and phenobarbital seem to permit the secretion of more GH peaks in certain subjects. The only drug which appeared to have an inhibitory effect on GH secretion during sleep was imipramine. This agent completely abolished the sleep related peak of growth hormone in two subjects. In one other subject, inhibition of secondary GH peaks was readily demonstrated. In only one of the four subjects was no effect observed. The mechanisms by which imipramine might affect GH secretory mechanisms are not clear. The drug is known to produce anticholinergic effects within the central nervous system (23), and it is possible that such an action might be significant in blocking hypothalamic secretion of growth hormone-releasing factors. Experiments are underway in our laboratory to establish the suppressive effect of imipramine on sleep induced GH secretion.

While these experiments were in progress, we learned of similar observations of Honda et al., described in abstract form (24). The pattern of GH secretion during sleep which has been described in this paper was also found by these workers. In addition, they also found that a delay in the onset of sleep for 3 or more hr was associated with a delay in the appearance of the initial GH peak until after the onset of sleep was permitted. It would appear that in every way these observations are in agreement with ours.

#### ACKNOWLEDGMENTS

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