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ENDOCRINE AND PHYSIOLOGICAL CHANGES DURING "SPONTANEOUS" PANIC ATTACKS*

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SUMMARY

Eight patients with DSM-III-defined panic attacks were compared to four normal subjects on hormonal and physiological variables measured at six predetermined times through 24 hr and also during nine "spontaneous" attacks. Levels at predetermined times were not different, other than a *reduction* of urinary unconjugated epinephrine in patients. Plasma prolactin was elevated at the peak of most of the attacks and correlated with attack severity. Plasma cortisol and growth hormone, and heart rate, were elevated during some attacks, and plasma norepinephrine showed small increases. Significant plasma epinephrine and MHPG changes were not observed.

INTRODUCTION

HORMONAL CHANGES are associated with stress in normal subjects (Rose, 1980) and in people with mixed depression/anxiety (Wyatt *et al.*, 1971) and primary anxiety disorders including phobias (Chosy *et al.*, 1970; Nesse *et al.*, 1985a), generalized anxiety (Mathew *et al.*, 1982; Rosenbaum *et al.*, 1983) and panic anxiety. Studies in panic have included resting conditions (Nesse *et al.*, 1984), normal activity (Hamlin *et al.*, 1983; Ballenger *et al.*, 1984; Nesse *et al.*, 1985b) and pharmacologically (Appleby *et al.*, 1981; Charney *et al.*, 1984, 1985; Liebowitz *et al.*, 1985, 1986; Carr *et al.*, 1986) and situationally induced (Ko *et al.*, 1983) panic attacks. Challenge tests in panic patients which did not produce panic attacks have also been studied (Grunhaus *et al.*, 1983; Nesse *et al.*, 1984; Charney and Heninger, 1986; Roy-Byrne *et al.*, 1986a,b). However, despite the presence of at least some spontaneous panic attacks as a *sine qua non* for the DSM-III-defined diagnosis of panic disorder (American Psychiatric Association, 1980), no studies of endocrine changes associated with spontaneous panic attacks have been reported. Therefore, hormonal as well as physiological changes were monitored during nine spontaneous attacks in patients with this disorder, and the same variables were also studied in panic patients and normal subjects at six predetermined times over 24 hr.

MATERIALS AND METHODS

Subjects

Eight patients with DSM-III-defined panic attacks (six women, mean age = 33 years) and four normal subjects (two women, mean age = 29 years) were studied. The mean duration of illness was 6.6 years (range: 1.5–19 years), and the self-reported mean duration of panic attacks was 35 min (range 1 min to 1 hr). Four patients reached criteria for a diagnosis of agoraphobia; five had other phobias as well, including heights, elevators, flying, driving and being alone.

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All patients reported an average occurrence of at least one panic attack per day for the previous several weeks.

All subjects were screened with a psychiatric evaluation, medical history, physical examination and laboratory studies including complete blood count, blood chemistries, thyroid function tests and electrocardiograms; all were normal, other than the panic diagnosis in patients. All subjects were on a normal daytime waking–night-time sleep cycle, and there were no differences between patients and normals in average daily exercise level. This research was approved by the University of Michigan Institutional Review Board for Human Use in Research, and all subjects gave informed consent.

Procedure

Subsequent to the evaluation, patients on any medication were gradually withdrawn; all subjects were drug-free for at least 1 week prior to study. Subjects followed a low monoamine diet (Maas, 1983) and avoided caffeinated beverages for 3 days prior to and during the study. Subjects stayed at bedrest throughout the study period, with an indwelling venous catheter for sampling of blood ("heparin lock"). Subjects were studied for approximately 36 hr in the University of Michigan Clinical Research Center.

All urine, collected in 6-hr aliquots (0100–0700 hr, 0700–1300 hr, 1300–1900 hr and 1900–0100 hr), was acidified and refrigerated during collection, and frozen immediately after completion of collection. Blood specimens were collected under two different circumstances. First, blood was drawn at 4-hr intervals (0300 hr, 0700 hr, 1100 hr, 1500 hr, 1900 hr and 2300 hr) for 24 hr. Second, blood was drawn at four times in association with each panic attack — at the peak and end of each attack, and 10 and 60 min after the end of each attack. The occurrence of a panic attack, including the peak and end of each attack, was defined subjectively by each patient. Patients were instructed to report an attack whenever they experienced the onset of any of those symptoms which were identified during the diagnostic evaluation as associated with DSM-III-defined panic attacks, as long as the attack also involved a feeling of fear. Subjects were allowed to identify "limited symptom attacks" (i.e. less than four symptoms) as well as "full" panic attacks, but to consider number and intensity of symptoms as well as duration in the severity ratings.

Urine and blood specimens not associated with attacks were obtained from both patients and normal subjects. For blood specimens, tubes were spun in a refrigerated centrifuge and plasma was separated and frozen until assay. Blood pressure, pulse and oral temperature were also determined at the time of each blood draw. Rating scales, composed of 100-mm lines, were rated at the time of each blood draw; ratings were done for "sad, blue, depressed", "confused", "worried, anxious, nervous", "tense, irritable", "tired, low energy", "feeling good" and "panic severity". Also, at the end of each attack, overall attack severity was rated 0–10 (none = 0, most ever = 10). Finally, all subjects wore Holter monitors (recorders of each heart beat) throughout the study period.

Urine was assayed for unconjugated epinephrine and norepinephrine. Blood for plasma epinephrine and norepinephrine was collected into tubes containing reduced glutathione and EGTA. Catecholamines were assayed with a radioenzymatic technique. Blood for the other plasma hormones (cortisol, human growth hormone and prolactin) and MHPG (3-methoxy-4-hydroxy-phenethyleneglycol, a metabolite of central and peripheral nervous system catecholamines) was collected into heparinized tubes. MHPG was assayed with a liquid chromatographic method, cortisol with a competitive-protein binding technique, and growth hormone and prolactin with radioimmunoassays.

RESULTS

Of the eight patients studied, four had no attacks during the study period, one had one, two had two each and one had four. For the nine attacks, the mean time of attack onset was approximately 1000 hr, and the mean subjective severity rating was 6.22/10 (SD = 1.92, range = 4–9).

Hormonal and physiological data obtained at predetermined times are presented for patients who had at least one attack ($n = 4$), patients who had none ($n = 4$) and normal subjects ($n = 4$) (Fig. 1). A significant difference (repeated-measures ANOVA, two-tailed $p = 0.02$) was observed between these three groups for urinary epinephrine; normal subjects were highest and patients who did not have attacks were lowest. There was also a trend for differences in urinary norepinephrine (repeated-measures ANOVA, two-tailed, $p = 0.06$), again with normal subjects the highest. For the six plasma hormones, no significant differences among groups were observed, and the actual levels were within the expected ranges for normal subjects (Krieger, 1979; Maas, 1983; Ziegler and Lake, 1984; Cameron *et al.*, 1987).

There was a trend for patients who had attacks to have lower heart rates than the other two groups (repeated-measures ANOVA, two-tailed, $p = 0.07$); however, this was due to one patient

who had an average 24-hr heart rate, by Holter monitoring, of 55.8 beats per min. Without this patient, the average Holter-determined rates were 72.3, 75.2 and 78.5 beats per min for patients with attacks, normal subjects and patients without attacks, respectively. There were no differences among the groups for the other three physiological variables. Variability of these data is indicated by the standard deviations (Table I).

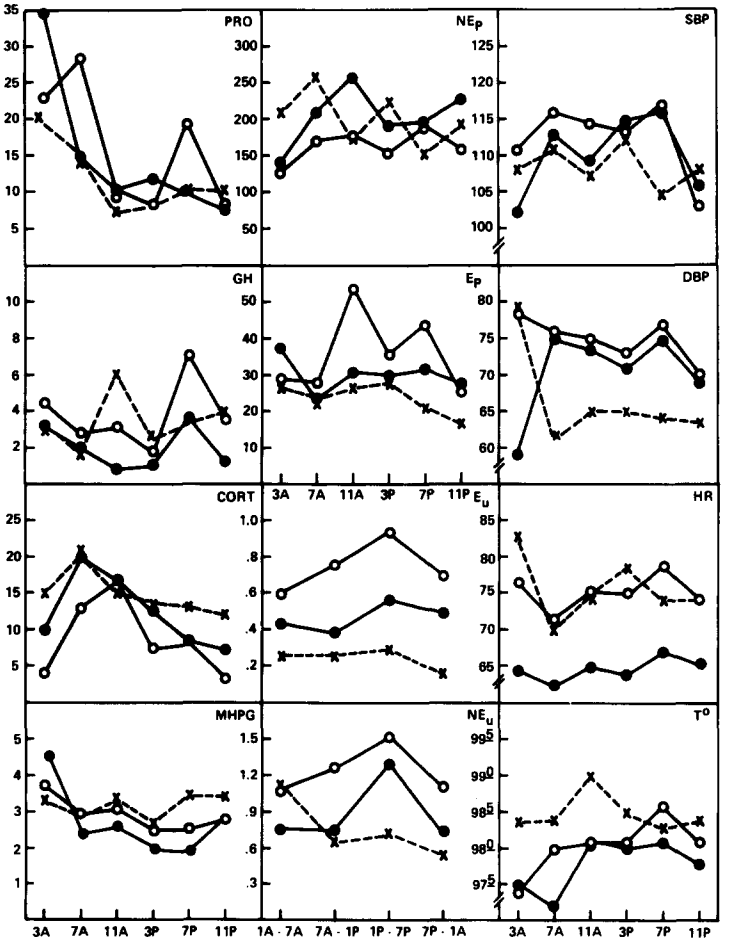

FIG. 1. Hormone and physiological variables measured at predetermined times. Plasma variables—prolactin (pro) (ng/ml), growth hormone (GH) (ng/ml), cortisol (cort) (μg/dl), 3-methyl-4-hydroxy-phenethyleneglycol (MHPG) (ng/ml), norepinephrine (NEp) (pg/ml) and epinephrine (Ep) (pg/ml)—and physiological variables—systolic blood pressure (SBP) (mm Hg), diastolic blood pressure (DBP) (mm Hg), heart rate (HR) (beats per min) and oral body temperature (T°) (degrees Fahrenheit) were measured at 0300 hr (3A), 0700 hr (7A), 1100 hr (11A), 1500 hr (3P), 1900 hr (7P) and 2300 hr (11P). Urinary variables—unconjugated epinephrine (Eu) (μg/collection) and norepinephrine (NEu) (μg/collection)—were measured in 6-hr aliquots [0100−0700 hr (1A−7A), 0700−1300 hr (7A−1P), 1300−1900 hr (1P−7P) and 1900−0100 hr (7P−1A)]. Measurements were made for patients who had at least one panic attack during the study (●—●) (n = 4), patients who did not have any attacks during the study (×----×) (n = 4) and normal subjects (○—○) (n = 4). Units of measurement are on the left-hand ordinate and measured variables are indicated in the upper right-hand corner of each frame.

TABLE I. STANDARD DEVIATIONS FOR ALL VARIABLES AT PREDETERMINED TIMES

	Code	0300 hr	0700 hr	1100 hr	1500 hr	1900 hr	2300 hr
Plasma prolactin	1	29.5	3.4	4.7	5.0	0.81	0.97
	2	6.8	7.9	2.9	3.5	2.3	5.2
	3	5.0	26.3	3.6	2.2	17.1	1.4
Plasma growth hormone	1	4.9	3.0	0.69	0.92	4.7	1.7
	2	2.8	55.6	6.4	1.4	4.7	3.7
	3	5.6	4.3	3.0	0.91	8.8	1.8
Plasma cortisol	1	9.4	9.0	6.2	2.3	2.7	4.2
	2	14.9	11.5	9.9	10.4	14.9	7.4
	3	4.3	3.1	12.3	3.5	5.0	3.5
Plasma MHPG	1	3.5	0.58	0.86	1.1	0.31	1.1
	2	0.26	0.27	0.44	1.2	0.29	1.1
	3	0.73	0.43	1.0	0.26	0.22	0.48
Plasma norepinephrine	1	45.2	91.1	103.7	41.0	32.7	48.0
	2	53.0	77.3	26.2	84.9	22.6	73.5
	3	12.2	38.8	53.3	17.5	92.9	55.1
Plasma epinephrine	1	4.2	5.7	14.8	12.7	17.1	17.2
	2	2.8	15.7	21.2	24.4	5.7	7.1
	3	14.1	8.5	59.4	12.0	14.8	12.0
Systolic blood pressure	1	7.6	5.9	2.9	11.3	12.7	12.4
	2	11.9	7.2	12.2	3.2	3.1	12.9
	3	11.3	14.7	10.3	12.8	16.9	8.7
Diastolic blood pressure	1	9.4	14.8	11.4	7.2	11.2	6.5
	2	11.0	10.0	14.8	15.5	7.4	17.7
	3	7.5	12.4	8.4	10.5	6.8	4.9
Heart rate	1	5.7	8.6	11.3	8.0	14.0	14.2
	2	8.7	7.9	7.6	8.5	5.1	10.3
	3	7.0	3.2	5.0	7.6	9.6	5.2
Body temperature	1	0.39	0.67	0.31	0.31	0.37	0.49
	2	0.55	1.1	0.85	0.61	0.90	0.55
	3	0.28	0.55	0.72	0.24	0.62	0.50

		0100–0700 hr	0700–1300 hr	1300–1900 hr	1900–0100 hr
Urine norepinephrine	1	0.08	0.19	0.42	0.41
	2	0.85	0.37	0.12	0.10
	3	0.19	0.43	0.60	0.44
Urine epinephrine	1	0.24	0.10	0.21	0.49
	2	0.40	0.21	0.19	0.51
	3	0.20	0.37	0.13	0.26

Values are standard deviations at six predetermined times (hr) for plasma variables, and four 6-hr intervals for urinary variables. Codes are: 1 = patients who had attacks; 2 = patients who did not have attacks; 3 = normal subjects.

All of the plasma hormone and physiological variables were also studied during each of the nine panic attacks. "Pre" and "post" baselines were determined by using the temporally closest measurements of the six predetermined times before and after each attack. Visual inspection of the aggregate data (Fig. 2) suggests increases in prolactin, growth hormone and cortisol at the peak of the attacks; small increases for norepinephrine and heart rate also occurred. None of the other variables showed obvious changes at the times of attack peaks and none of the changes

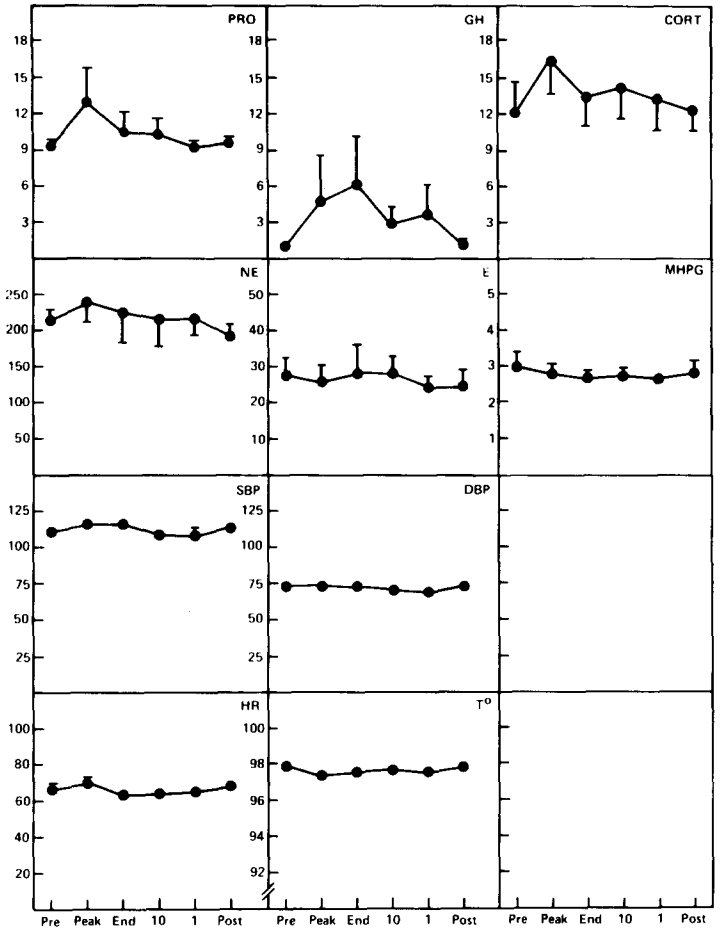

FIG. 2. Hormone and physiological variables measured during nine "spontaneous" panic attacks in four panic patients. Plasma variables—prolactin (pro) (ng/ml), growth hormone (GH) (ng/ml), cortisol (cort) (μg/dl), norepinephrine (NE) (pg/ml), epinephrine (E) (pg/ml) and 3-methoxy-4-hydroxyphenethyleneglycol (MHPG) (ng/ml)—and physiological variables—systolic blood pressure (SBP) (mm Hg), diastolic blood pressure (DBP) (mm Hg), heart rate (HR) (beats per minute) and oral body temperature (T°) (degrees Fahrenheit)—were measured prior to attack ("pre"), at the peak and end of the attack as defined subjectively by the patient, at 10 min and 1 hr after the end of the attack, and after the attack had ended at the next of the predetermined times ("post"). Units of measurement are on the left-hand ordinate and measured variables are indicated in the upper right-hand corner of each frame. Mean ± SEM for each variable is represented; no error bar is visible when the standard error fell within the dot representing the mean. Standard errors are sometimes small for "pre" and "post" times because the same values are sometimes represented more than once.

at the peaks of the attacks were statistically significantly higher than the "pre" baseline. Somatostatin concentrations, determined during attacks for two of the patients (not shown), were in the normal range.

Prolactin concentrations at the peak of attack were significantly correlated with subjective attack severity ($r = +0.70$, $p = 0.05$). No sex difference in mean baseline 24-hr prolactin

was observed (M: 14.07 ng/ml; F: 14.30 ng/ml). All similar correlations for the other variables ranged between −0.25 and +0.19; none approached statistical significance. When the level of the "pre" baseline level was included (regression analysis), the multiple-*R* for prolactin remained significant (0.72); furthermore, the values for epinephrine (0.94) and cortisol (0.75) were also significant, and the value for heart rate (0.67) approached significance. While the significant multiple-*R* for epinephrine does not appear to have physiological importance, because of the lack of a physiologically meaningful change in epinephrine levels during the attacks, the results for cortisol, and possibly heart rate, suggest that increases are occurring in association with the more severe attacks, but that variations in baseline values sometimes tend to obscure them.

The individual panic attack data (Table II) showed consistencies between subjects as well as individual differences. All attacks but two showed higher peak prolactin than baseline, and for all but one, peak prolactin was higher than after the attack was over. Growth hormone showed no changes except in one patient; in both of the attacks of this patient substantial increases (to 8.91 ng/ml at the end of one attack, and 36.30 ng/ml at the peak of the other) occurred. Cortisol showed increases in seven attacks and decreases in two; norepinephrine showed increases in six attacks; MHPG showed mixed changes across subjects; and epinephrine showed no changes of physiological significance. All hormone changes except the growth hormone changes in one patient were small to moderate in magnitude.

Six of the attacks were associated with a decrease in oral temperature (possibly due to hyperventilation); heart rate rose during five attacks but did not clearly rise in the others; and blood pressure showed primarily increases but also decreases in both systolic and diastolic pressure, with no consistent pattern between or within patients. Results from the Holter monitors indicated heart rate increases during some attacks, to a maximum of 150 beats per min during one, but no obvious increases in other attacks. By Holter monitoring, two patients who had attacks and two who did not had rare atrial premature beats and/or rare to frequent ventricular premature beats. Normal subjects had no dysrhythmias.

Three of the four patients who had attacks had more than one (four, two and two). The data were inspected to determine if any consistencies of response pattern for the variables within each subject across attacks could be discerned. Although the numbers were small, a few patterns are suggested. Prolactin showed consistent increases in two of these subjects. One subject with two attacks had substantial rises in growth hormone during both attacks (above), while for the other subjects, growth hormone was consistently unchanged; this was the only patient who did not show prolactin increases. Norepinephrine showed increases during both attacks in both of the patients who had two attacks, but inconsistent changes during the four attacks in the other subject. As noted above, epinephrine did not show significant changes in any subject. The other six variables (cortisol, MHPG, heart rate, oral temperature and systolic and diastolic blood pressure) showed inconsistent variations within and between subjects.

At the six predetermined times and during each panic attack, 100 mm line analog scales were completed for the seven symptom complexes. Inspection of the results indicated that, as expected, patients were higher than normal subjects, and increases from baseline values during attacks were greatest and most consistent for "panic", "worried . . ." and "confused", in that order. "Tense . . .", "sad . . ." and "tired" showed less consistent changes and "feeling good" was least. As noted above, the ratings of attack severity from 0 (none) to 10 (most ever) averaged 6.22 for all nine attacks.

DISCUSSION

This is the first study of hormonal changes during "spontaneous" panic attacks. Plasma growth hormone, cortisol and especially prolactin increases appeared to occur during at least some attacks, with definite individual differences in the patterns of endocrine response. Plasma epinephrine and the catechol metabolite MHPG did not show consistent increases during attacks, and there

TABLE II. VALUES BEFORE, DURING AND AFTER ATTACKS

No.	Time	Severity	Plasma prolactin (ng/ml)	Plasma growth hormone (ng/ml)	Plasma cortisol (μg/dl)	Plasma norepi-nephrine (pg/ml)	Plasma epi-nephrine (pg/ml)	Plasma MHPG (ng/ml)	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Heart rate (beats/ min)	Body temperature (°F)
2		7	8.95	0.17	6.82	212	27	2.20	117	78	61	98.2
	2000 hr		9.84	0.18	1.68	264	18	3.01	124	80	64	97.8
			–	–	–	–	–	–	–	–	–	–
			11.11	2.93	1.48	202	29	2.60	116	80	60	98.4
			8.75	0.96	2.42	198	13	2.60	–	–	80	97.6
			9.04	0.33	2.58	274	14	4.51	109	75	60	97.2
2		9	9.04	0.33	2.58	274	14	4.51	109	75	60	97.2
	0100 hr		15.91	0.20	16.32	162	14	2.50	104	70	60	97.7
			15.38	0.17	13.32	127	11	2.90	112	70	64	96.9
			12.77	0.17	12.36	133	20	2.30	110	74	60	97.5
			9.71	0.17	12.84	163	25	2.60	114	70	60	97.2
			8.98	1.33	15.26	–	–	–	112	72	66	97.3
2		4	9.04	0.33	2.58	274	14	4.51	109	75	60	97.2
	0200 hr		10.22	0.18	9.56	140	18	2.40	120	80	60	97.0
			–	0.26	9.24	176	13	3.10	106	70	60	96.9
			11.18	0.24	13.12	136	18	2.50	110	76	68	97.2
			8.98	1.32	15.26	160	18	2.90	110	80	68	97.1
			–	–	–	–	–	–	112	72	66	97.3
2		9	8.98	1.32	15.26	160	18	2.90	112	72	66	97.3
	0600 hr		29.95	1.20	24.78	226	24	2.70	120	74	64	97.5
			12.66	0.45	18.22	196	20	2.90	120	80	60	97.4
			12.58	0.33	18.94	146	10	3.30	114	70	68	98.1
			8.17	0.33	22.04	320	22	3.20	110	60	69	97.7
			11.37	0.22	19.02	178	29	2.90	118	72	73	97.9
3		5	8.78	1.73	19.58	185	24	2.44	108	69	55	97.8
	1200 hr		11.09	0.51	24.28	208	19	2.99	–	–	–	–
			–	–	–	–	–	–	110	72	64	97.9
			8.25	0.63	16.20	267	41	3.58	122	70	60	97.8
			10.30	0.56	19.26	218	33	2.08	100	64	56	97.8
			9.05	1.25	11.74	149	16	1.98	103	60	55	98.1
3		5	8.78	1.73	19.58	185	24	2.44	108	69	55	97.8
	1300 hr		11.12	0.58	26.30	238	25	2.63	114	60	64	97.6
			–	–	–	–	–	–	–	–	–	–
			13.37	0.64	24.26	235	34	2.88	94	64	64	–
			10.15	0.60	15.76	183	23	2.67	112	70	64	97.9
			9.05	1.25	11.74	149	16	1.98	103	60	55	98.1
4		6	–	0.71	11.00	–	–	1.94	90	60	76	97.7
	0300 hr		–	0.53	15.66	–	–	4.68	110	80	96	96.4
			–	–	–	–	–	–	–	–	–	–
			–	1.56	25.16	–	–	2.11	92	66	56	97.0
			–	3.64	15.36	–	–	2.65	86	60	64	97.0
			–	6.41	18.70	–	–	1.91	114	97	64	97.6

Table II continued on p. 328

TABLE II CONTINUED. VALUES BEFORE, DURING AND AFTER ATTACKS

No.	Time	Severity	Plasma prolactin (ng/ml)	Plasma growth hormone (ng/ml)	Plasma cortisol (μg/dl)	Plasma norepi-nephrine (pg/ml)	Plasma epi-nephrine (pg/ml)	Plasma MHPG (ng/ml)	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Heart rate (beats/min)	Body temperature (°F)
6		4	10.38	3.59	6.90	222	51	–	133	74	87	98.6
	2100 hr		9.36	2.53	9.52	354	45	1.68	120	84	72	97.7
			8.65	8.91	6.48	319	45	2.09	120	84	64	98.6
			8.20	9.10	4.76	381	45	2.88	104	72	68	97.7
			7.90	21.80	3.16	290	37	2.64	130	84	64	97.7
			7.82	0.41	4.70	235	46	–	120	72	78	98.4
6		7	11.00	0.42	23.90	213	48	–	112	72	78	99.2
	1300 hr		5.57	36.30	20.58	327	46	2.35	126	78	84	96.6
			6.47	21.10	13.98	307	52	2.28	122	70	72	97.5
			5.29	11.10	11.84	–	–	–	112	70	76	98.0
			–	–	–	–	–	–	–	–	–	–
			9.16	2.24	15.70	230	40	–	129	65	73	98.0

Missing values were due to (a) time points being too close together to collect two specimens or make two measurements, (b) loss of specimen or (c) inability of assay to detect levels of substance in specimen (norepinephrine and epinephrine No. 4). Pre-baseline, attack peak, end of attack, 10 min post-attack, 1 hr post-attack and post-baseline values are listed for each variable for each attack.

was actually a tendency for urinary excretion of unconjugated epinephrine and norepinephrine to be lower in patients who did not have attacks than in normal subjects; plasma levels of all substances measured at predetermined times were normal. Physiological measurements showed no changes during attacks, except for variable increases in heart rate and decreases in oral temperature (which might not reflect decreases in core temperature); all physiological variables were normal at the predetermined times of measurement. No abnormality of circadian patterns was observed.

Cardiac symptoms are usually associated with anxiety and panic attacks, and attacks are often associated with discernible increases in heart rate (Lader and Mathews, 1970; Taylor *et al.*, 1982, 1986; Freedman *et al.*, 1985; Shear, 1986). However, of a total of 49 attacks studied in ambulatory panic patients (including Taylor *et al.*, 1982, 1986; Freedman *et al.*, 1985), 20 (41%) were not associated with identifiable increases, as determined by Holter monitoring. The present study suggests that heart rate increases may be even less common in supine subjects. Also, heart rate may not be elevated in panic patients at times when attacks are not actually occurring (Freedman *et al.*, 1985). Thus, the occasional lack of heart rate change we observed is not necessarily an anomalous finding. Furthermore, subjective reports of increased heart rate might reflect as much an increased awareness of heart action as an actual rate increase (Tyrer *et al.*, 1980; Pyke and Greenberg, 1986), especially since there may be an association between heart rate increase and attack severity as suggested by our regression analysis. Finally, similar to Shear (1986), but not Taylor *et al.* (1986), we observed cardiac rhythm disturbances in some patients.

Based on prior studies of pharmacologically or situationally precipitated panic attacks (Appleby *et al.*, 1981; Ko *et al.*, 1983; Charney *et al.*, 1984), increases in catecholamines and MHPG during attacks were expected, but they were not observed. Other research (Liebowitz *et al.*, 1985, 1986; Carr *et al.*, 1986) has indicated no differential change between patients and normal subjects in epinephrine or norepinephrine during lactate infusions. Decreases in urinary

epinephrine contrast with increases in a prior study (Nesse *et al.*, 1985b); however, that study was in ambulatory patients and, similar to heart rate response, posture and activity may be an important difference. Effects of lactate on cortisol are minimal (Appleby *et al.*, 1981; Liebowitz *et al.*, 1985, 1986; Carr *et al.*, 1986) and caffeine stimulates cortisol release equally in patients and normal controls (Charney *et al.*, 1985). Growth hormone has not shown any difference between patients and normals in response to lactate (Carr *et al.*, 1986). Thus, lack of consistent change in epinephrine and MHPG and variable increases in cortisol and growth hormone during "spontaneous" panic attacks (in supine otherwise-resting individuals) are not unexpected findings.

Similar to several prior studies of panic patients (Appleby *et al.*, 1981; Grunhaus *et al.*, 1983; Liebowitz *et al.*, 1985, 1986; Carr *et al.*, 1986; Charney and Heninger, 1986; Roy-Byrne *et al.*, 1986a), baseline prolactin levels in our study were normal. Although prior studies (Appleby *et al.*, 1981; Liebowitz *et al.*, 1985, 1986; Charney and Heninger, 1986) found sex differences, with prolactin in women higher than in men, we found no sex difference. Lactate produced a rise in prolactin (Appleby *et al.*, 1981; Liebowitz *et al.*, 1985, 1986; Carr *et al.*, 1986). Male patients who had attacks may have had a more vigorous prolactin response to lactate than male patients who did not, although this was not reported as significant (Appleby *et al.*, 1981; Liebowitz *et al.*, 1985, 1986); female patients did not show this effect. Patients and normals had equal magnitude increases in prolactin after tryptophan administration (Charney and Heninger, 1986). Finally, patients showed a normal response to the cold pressor test (Graunhaus *et al.*, 1983), but a reduced prolactin response to TRH, only in female patients (Roy-Byrne *et al.*, 1986a). Thus, our study is in agreement with prior studies of baseline prolactin levels. The prolactin response to TRH is subsensitive, but prolactin rises during "spontaneous" panic, and it may increase somewhat during lactate-induced panic as well, at least in men. Prolactin increases thus might serve as a marker of the occurrence of a panic attack.

The association of prolactin with CNS neurotransmission has been studied. Rises in prolactin suggest reduced dopaminergic and/or possibly cholinergic input during an attack, and/or an increase in serotonergic, opioid, GABAergic, and/or histaminergic influences (Checkley, 1980; Reichlin, 1985; Tuomisto and Mannisto, 1985); noradrenergic effects are mixed, and other neurotransmitters are also likely to be involved. The only neurotransmitter among those listed above which is associated with a rise in prolactin but with no rise in growth hormone, ACTH (and, therefore, cortisol), and somatostatin may be GABA (Tuomisto and Mannisto, 1985), although not all reviewers have indicated this exact pattern (Checkley, 1980; Elias *et al.*, 1982; Reichlin, 1985). Thus, the endocrine results of our study seem to be most consistent with a GABA effect, and GABA neurotransmission has been implicated in anxiety, due to the effects of benzodiazepines on the GABA receptor (Paul *et al.*, 1981). It is not clear which neurotransmitters are involved in the prolactin response to TRH; this response may be mediated at the pituitary level directly.

McIntyre *et al.* (1986) reported lower plasma melatonin at midnight in 13 panic patients than in normal subjects; however, only one of their patients was drug-free. Three of our patients had panic attacks in the evening or night, when melatonin would be expected to be relatively high (Lewy, 1983). Melatonin concentrations were determined in two of our patients (Nos 2 and 6). Concentrations in these patients were substantially lower than expected at the peaks of the three attacks studied (3.5, 4.6 and 1.7 pg/ml), which occurred while subjects were in the dark or modest room light. Thus, these very preliminary results support the earlier findings of a melatonin reduction in panic patients at night.

More attacks, including a range of severity, must be studied to determine if our results are consistent, including any between-patient variability and/or within-patient consistency of pattern of endocrine changes. Also, since some prior studies reported endocrine and physiological abnormalities in panic patients when attacks were not occurring and under different conditions from those of our study (i.e. ambulatory or resting for a shorter period of time), replication of our baseline results is necessary. Only when consistent patterns are identified will it be possible to make confident inferences about the neurotransmitters involved. In the meantime, these and prior results indicate that systemic increases in catecholamines, especially epinephrine, are minimal or non-existent in association with panic and therefore are not making any significant contribution to adrenergic symptom production during panic attacks and that the psychobiology of panic attacks in people with panic disorder is probably different from the psychobiology of stress in normal subjects.

Note added in proof: Woods *et al.* (1987) recently reported some similar and some divergent physiologic and biochemical effects during *situational* panic attacks.

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