Anxiety and Plasma Cortisol at the Crest of the Circadian Cycle: Reappraisal of a Classical Hypothesis

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Near-maximal anxiety by subjective and behavioral criteria was evoked and terminated in phobic patients by initiation and termination of rapid live confrontation ("flooding *in vivo*") with the specific stimulus that each avoided, at a time approximating the crest of the circadian cycle of adrenal cortical function. The procedure was associated with moderate, but not marked, elevations of plasma cortisol above control levels in some, but not all, subjects. Differences in anxiety levels as self-rated by the patients did not account for differences in cortisol response. The findings should stimulate further reevaluation of the hypothesis that affective arousal is the key psychological determinant of adrenal cortical function. Dissociation between subjective-behavioral arousal and plasma cortisol during flooding may be a manifestation of what behavior therapists call "desynchrony of fear."

INTRODUCTION

It is well established that the hypothalamic-pituitary-adrenal (H-P-A) system is sensitive to psychological stimuli. The main psychological correlate of H-P-A activity is thought to be an undifferentiated state of emotional arousal or involvement, especially with novelty, uncertainty, unpredictability, anticipation, or intense disorganizing experiences and behavioral breakdown (1). However, in comparison to findings in animals, the findings in human subjects have been unimpressive, disappointing, and subject to great individual variability. This is usually attributed to the fact that many subjects do not become upset in apparently upsetting circumstances, perhaps in part because of psychological defenses (1).

Other interacting factors which might cause variability of response are the ultradian pulse pattern of cortisol secretion (2), the effect of novel experiences (1), or psychological effects operating selectively at particular circadian phases. Prolonged distress in psychiatric patients was previously reported to act selectively on adrenal function at different circadian phases, but this effect in turn differed between men and women and between urine and plasma measures (3). More recently (4), we demonstrated unresponsiveness of plasma cortisol levels during the "trough" of the circadian cortisol cycle to an acute dramatic anxiety

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stimulus: the treatment of severely phobic patients by *in vivo* confrontation ("flooding") with their particular phobic stimuli. There was, however, a definite plasma cortisol response at the same circadian phase to a situation combining novelty and anticipation of flooding, even though the subjective and behavioral manifestations of anxiety were much greater during flooding itself.

In order to evaluate further this unexpected finding, we now report an identical study with an additional set of subjects carried out at the opposite circadian phase, i.e., near the crest of the circadian cycle of plasma cortisol levels.

SUBJECTS AND METHODS

Subjects were six medically healthy, medication-free persons (five women, one man) with phobias for physical objects, manifested by panic on encountering the phobic stimulus and a fixed pattern of irrational, life-restricting maneuvers to avoid encountering it, often even including avoidance of photographs or motion pictures of the object. The ages of the women were 23, 26, 30, 31, and 52. The younger women were menstruating normally. The 52-year-old woman had stopped menstruating 2 years previously. She denied hot flashes or other menopausal symptoms. The age of the man was 42.

The design, outlined in Table 1, was disclosed to each subject in advance, and informed consent was obtained. Each subject spent five 3-hour sessions in the laboratory, on separate days, beginning at the same time of day for a given subject, usually around 7:00 a.m. The individual starting time for each subject was determined by recording the sleep schedule for 2 weeks, computing his or her midpoint of sleep, and adding 3 hours. This method provides greater uniformity of circadian phase across subjects than if all subjects were studied at the same clock time, since it adjusts for individual differences in sleep schedule. The intervals between sessions varied, but was most often about a week. Every 20 min during each 3-hour session a blood sample was taken through an indwelling needle, and Subjective Units of Distress (SUD) were self-rated on a scale of 0 (no distress) to 100 (maximum distress possible). No treatment was carried out during the first, second, and fifth sessions, which were used for adaptation to the laboratory and collection of control data. On these mornings the subjects sat quietly and read, studied, or engaged in other nonarousing activities. Treatment by *in vivo* flooding was carried out during the second hour of the third and fourth session. During treatment the SUD ratings are made almost minute-to-minute as a guide for the therapist and patient. The level fluctuates a great deal, and drops to near zero if the treatment is interrupted while the subject fills out a mood checklist or is interviewed. Therefore, as a measure of overall anxiety during each 20 min of treatment, all of the ratings during each interval were recorded and averaged.

TABLE 1. Design of Flooding Experiments

Session 1	Novelty session. No treatment
Session 2	Adaptation session. No treatment
Session 3	1st hour: pretreatment 2nd hour: treatment by flooding 3rd hours: posttreatment
Session 4	1st hour: pretreatment 2nd hour: treatment by flooding 3rd hour: posttreatment
Session 5	Control session. No treatment
Session 5+ (if needed)	No blood or urine samples 1 or 2 hours of treatment

After completion of the fifth and final session, if additional treatment was needed and desired, it was given at a later date without any further research procedures. In the previously reported study (4) symptom removal was accomplished within the 2 hours of treatment time included in the experimental design, or within a maximum of 1 additional hour. In the present study, no subject completed treatment within the initial 2 hours. Two did not accept the offer of additional treatment, and the remainder required 2 to 4 additional hours before symptom removal was judged complete.

Blood samples were assayed for cortisol content by competitive protein binding (5).

RESULTS

Although not entirely uniform across subjects or across time, the affective re-

sponse to flooding *in vivo* was regularly intense, often including weeping, screaming, attempts to get away, gross tremors, startling at slight sounds, chattering teeth, gooseflesh, and rapid labile heartbeat. As these manifestations subsided at one level of exposure, the therapist pushed rapidly ahead to more intense exposure. The overall effect is a gruelling experience, often described as the most frightening of the patient's life.

The mean self-ratings of distress averaged across subjects for each time point within each session are plotted in Fig. 1. They were in general agreement with the observable behavior of the subjects, showing moderate elevations prior to, and marked elevations during, the two treatment hours. Subjects usually attributed the pretreatment anxiety to anticipation of confronting the phobic object. A moderate elevation was also present at the beginning of the initial adaptation session. With a specific exception noted below, subjects usually attributed this to uneasiness about the treatment or the experimental procedure, especially the anticipated discomfort of blood sampling, and a few mentioned the possibility of being confronted with the phobic stimulus, even though they had been assured that this would not happen until the third session. During the times of moderate self-reported uneasiness, subjects did not appear intensely disturbed, as they did during actual treatment.

In a three-way analysis of variance (sessions × subjects × time-within-sessions) of the SUD data all main effects and double interactions were significant: time-within-sessions at $p<0.05$ and the remainder at p values ranging from 0.025 to 0.001. The significant sessions by time-within-sessions interaction indicated effects operating selectively at particular times within particular sessions, mainly the treatment in the middle of Sessions 3 and 4. The significant subjects by sessions interaction signifies that among different subjects the patterns of session means diverged in a nonrandom manner. The significant effect of subjects

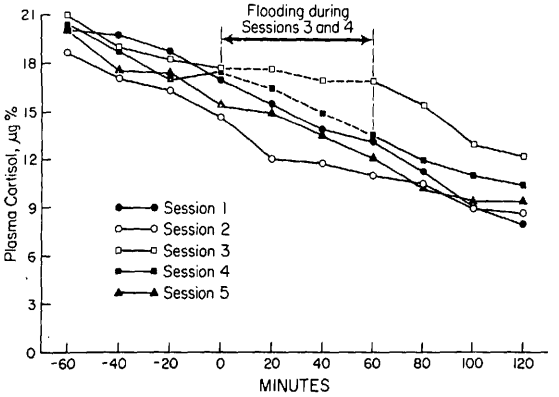

Fig. 1. Plasma cortisol in flooding. Subjective Units of Distress (SUD) averaged across subjects at each session. Morning experiments ($N = 6$).

signifies that there was greater variation among subject means than could be accounted for by the divergent patterns of session means. The import of these findings is conveyed by Table 2, which presents all SUD data, session means, and Scheffe numbers (6) for each subject, indicating which session means differ significantly. For a given subject, any two session means which differ by an amount equal to or greater than the Scheffé number are significantly different from each other at $p<0.05$ or better. In Table 2 a superscript above a session mean within a subject indicates the session means within that subject that differ from it at the 5% level of significance or better. The use of the Scheffé numbers is further explained in the legend of Table 2. Subject means are also presented.

The most divergent individual pattern was that of Subject 6, who had near-maximal anxiety during the initial no-treatment sessions, declining steadily to near 0 at the end of the fifth session. At the beginning of the experiment he was nearly panicked with fear of exsanguination, even though the amount of blood taken (about 100 cc) in each session, and the negligible risk, had been carefully discussed in advance. This concern diminished with each succeeding session. Apparently he was unexpectedly treated for two phobias instead of one, an exsanguination phobia mainly in Sessions 1 and 2 and a caterpiller phobia in Sessions 3 and 4.

Subject 3 had her final no-treatment session in a different laboratory and after a delay of over a year, which may have accounted for her maximal anxiety report at the beginning of that session.

Plasma cortisol levels, averaged across subjects for each time point within each session, are plotted in Fig. 2. There was a suggestion of an effect of flooding in that the usual diurnal decline was interrupted during flooding but at no other time. However, on statistical analysis there was not a significant difference between sessions, and the sessions by time-within-sessions interaction was not significant, indicating that there was no selective effect operating in any particular session or at any particular time segments during any particular sessions, i.e., no statically significant effect of flooding, either at the particular time of flooding or over the session as a whole, was demonstrated by this analysis. The significant effects were time-within-sessions ($p<0.001$), due to the usual diurnal decline during the morning hours, the subjects by sessions interaction ($p<0.001$), and the subjects by time-within-sessions interaction ($p<0.05$).

For examination of the subjects by sessions interaction, Table 3 presents all of the plasma cortisol data from each subject together with session means, Scheffé numbers for each subject, and subject means. Use of Scheffé numbers was the same as in the analysis of SUD data and is explained further in the legend of Table 3. Onset and termination of cortisol secretory episodes, by the criteria of Weitzman et al. (2), are also indicated in the table. Criteria for onset are three successive samples in which the second is at least 2 μg% higher than the first, and the third is also higher than the first. Criteria for termination of an episode are a fall of 1 μg% or more followed by a continuing decline. With blood samples at 20-min intervals, identification of secretory episodes is only approximate. With a 5-min schedule, what appear to be single large episodes may resolve into several smaller ones (7).

Secretory episode criteria indicated a

TABLE 2. Time-Within-Session (Minutes)[a]

Subj.	Age	Sex	Session	−60	−40	−20	0	+20	+40	+60	+80	+100	+120	Session mean	Scheffé number	Subj. mean
1	31	F	1	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	$1.0^{3,4}$	32.7	18.4
			2	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	$1.0^{3,4}$		
			3	50.0	50.0	30.0	30.0	100.0	94.0	90.0	1.0	1.0	1.0	$44.7^{1,2,5}$		
			4	50.0	20.0	20.0	50.0	94.0	90.0	100.0	1.0	1.0	1.0	$42.7^{1,2,5}$		
			5	0.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	20.0	1.0	$2.8^{3,4}$		
2	23	F	1	20.0	40.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	6.8^{3}	28.1	13.3
			2	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0^{3}		
			3	1.0	10.0	30.0	50.0	75.0	73.0	74.0	54.0	10.0	1.0	$37.8^{1,2,5}$		
			4	20.0	10.0	1.0	10.0	73.0	73.0	1.0	1.0	1.0	1.0	19.1		
			5	10.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.9^{3}		
3	26	F	1	20.0	20.0	35.0	50.0	40.0	30.0	20.0	30.0	20.0	10.0	27.5^{3}	25.0	38.4
			2	30.0	30.0	30.0	30.0	30.0	30.0	20.0	20.0	20.0	20.0	26.0^{3}		
			3	65.0	60.0	60.0	60.0	95.0	95.0	97.0	45.0	40.0	35.0	$65.2^{1,2,4,5}$		
			4	30.0	30.0	30.0	30.0	70.0	65.0	45.0	30.0	30.0	30.0	39.0^{3}		
			5	100.0	60.0	40.0	30.0	25.0	15.0	20.0	20.0	15.0	20.0	34.5^{3}		
4	30	F	1	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	$1.0^{3,4}$	25.1	21.9
			2	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	$1.0^{3,4}$		
			3	70.0	70.0	70.0	90.0	80.0	63.0	47.0	1.0	1.0	1.0	$49.3^{1,2,5}$		
			4	50.0	50.0	50.0	80.0	70.0	80.0	50.0	20.0	20.0	1.0	$47.1^{1,2,5}$		
			5	30.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	11.0	$11.1^{3,4}$		
5	52	F	1	30.0	40.0	10.0	10.0	20.0	30.0	20.0	30.0	20.0	30.0	24.0	24.7	30.6
			2	30.0	50.0	50.0	50.0	30.0	30.0	30.0	20.0	30.0	30.0	35.0		
			3	30.0	30.0	30.0	40.0	72.0	80.0	80.0	40.0	30.0	30.0	46.2^{5}		
			4	20.0	20.0	20.0	20.0	84.0	81.0	72.0	10.0	10.0	10.0	34.7		
			5	1.0	1.0	20.0	30.0	20.0	30.0	10.0	10.0	10.0	1.0	13.3^{3}		
6	42	M	1	95.0	75.0	75.0	75.0	75.0	95.0	95.0	99.0	99.0	99.0	$88.2^{2,4,5}$	25.8	50.3
			2	80.0	80.0	70.0	60.0	60.0	50.0	50.0	50.0	40.0	40.0	$58.0^{1,5}$		
			3	90.0	80.0	70.0	60.0	95.0	85.0	57.0	40.0	30.0	30.0	$63.7^{4,5}$		
			4	80.0	60.0	60.0	70.0	66.0	25.0	1.0	1.0	1.0	1.0	$36.5^{1,3,5}$		
			5	25.0	15.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	$5.2^{1,2,3,4}$		

[a] Raw data of Subjective Units of Distress (SUD) with subject means, session means within subjects, and Scheffé numbers for session means within subjects. For computation purposes zero ratings are converted to 1.0. The time immediately before flooding began in Sessions 3 and 4 for any subject was set at 0 min for all sessions for that subject. Underscored data are those taken during flooding. For a given subject, any session means which differ by an amount equal to or greater than the corresponding Scheffé number are significantly at $p > 0.05$. Notations for session means: ^{1} = significantly different from Session 1 at $p < 0.05$; ^{2} = ditto for Session 2, etc.

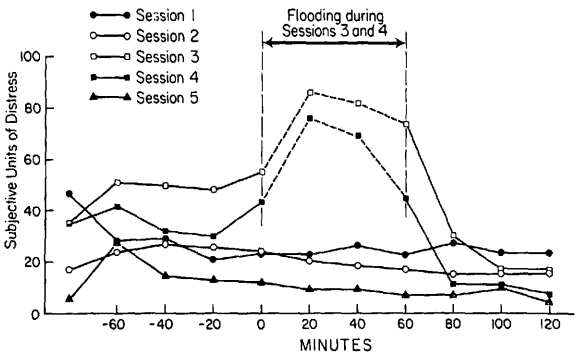

Fig. 2. Self-ratings of distress. Plasma cortisol levels averaged across subjects at each time point of each person. Morning experiments (N = 6).

fair degree of synchronization between subjects, in that termination criteria usually were met either at the beginning or shortly after the beginning of each session.

Three of the six patients did not meet onset criteria for secretory episodes during any treatment session. Out of a total of 12 sessions containing a treatment hour, onset criteria were met at some point during only 5. A not unusual finding was a generally higher cortisol level before, during, and after the treatment hour but without an identifiable secretory episode at or near the time of treatment.

Subject 6, who had the intense exsanguination fear, showed a significant sessions effect on plasma cortisol levels. Session 1 was significantly higher than all other sessions and Session 2 was significantly higher than 3, 4, and 5, which did not differ from each other. His distress levels could account for the elevations in Sessions 1 and 2, but not for the failure of Sessions 3 and 4 to be elevated. Although "elevated" by his own standard, the cortisol values in his higher sessions were unremarkable when compared with control values of other subjects.

Only Subject 2 failed to show a significant sessions effect, even though she was one of the subjects with a distinct secretory episode coinciding with a first flooding experience. However, she also had active secretion during Sessions 1, 4, and 5. The episode in Session 1 coincided with a brief surge of anxiety when a silverfish, resembling a spider, for which she was phobic, emerged from the woodwork of the laboratory. The secretory episode in Session 4 began and ended before treatment was under way. There was no apparent psychological explanation for the slightly unusual continuation of secretion throughout the first hour of Session 5.

TABLE 3. Time-Within-Session (Minutes) [a]

Subj.	Age	Sex	Session	−60	−40	−20	0	+20	+40	+60	+80	+100	+120	Session mean	Scheffé number	Subj. mean
1	31	F	1	23.4	21.6[b]	19.4	19.1	19.2	16.9	14.8	14.2	11.4	10.5	17.0[2]	3.61	16.6
			2	22.2	19.1[b]	17.3	15.7	11.9	13.0	10.6	7.6	5.8	4.2	12.8[1,3,4]		
			3	27.3	24.1[b]	25.0	24.0	23.6	20.2	17.1	16.2	12.6	11.1	20.1[2,5]		
			4	23.7	18.6[b]	11.5	19.1[c]	17.7	18.5	20.6	16.7[b]	15.0	13.9	17.5[2]		
			5	20.9	20.8[b]	20.0	18.8	21.8	16.3	14.3	10.7	7.0	8.1	15.9[3]		
2	23	F	1	17.6	22.6[c]	22.6	22.3	15.7[b]	12.6	12.4	9	7.3	7.2	15.0	5.16	15.2
			2	21.5	20.4[b]	20.8	17.6	14.4	11.1	10.4	9.7	8.0	7.0	14.7		
			3	14.5	13.4[b]	12.9	17.9[b]	18.4	18.8	22.3	21.7	14.6	13.4	16.8		
			4	13.8	19.5[c]	20.9	18.4[b]	13.9	12.4	10.8	8.6	6.4	7.0	13.2		
			5	18.1	15.8	23.8[c]	21.6[b]	19.7	18.6	16.8	12.2	11.3	9.4	16.7		
3	26	F	1	14.4	12.7[b]	11.4	11.0	8.7	6.8	7.2	5.9	6.0	3.2	8.7[2,3,4,5]	2.30	13.5
			2	17.6	16.1[b]	14.9	14.8	11.2	10.4	10.6	9.6	8.5	7.4	12.1[1,3,4]		
			3	21.8	21.4	19.0[b]	18.4	19.1	18.6	17.0	15.6	13.1	12.7	17.7[1,2,5]		
			4	27.4	20.8[b]	18.6	18.6	17.5	17.9	12.6	12.3	9.9	7.9	16.3[1,2,5]		
			5	22.4	18.9[b]	14.7	14.9	13.7	9.8	9.9	8.7	6.8	7.4	12.7[1,3,4]		
4	30	F	1	22.3	21.3[b]	20.0	15.7	15.2	12.5	12.3	9.2	6.1	5.6	14.0[4]	3.78	15.0
			2	16.4	13.1[b]	12.1	9.5	9.5	7.8	8.4	11.0	13.0	11.1	11.2[3,4]		
			3	23.4	21.1[b]	20.9	18.6	18.3	17.4	17.2	14.1	11.6	10.9	17.3[2]		
			4	20.6	20.8	21.0	18.7[b]	19.5	16.7	14.8	15.9	17.7	18.0	18.4[1,2,5]		
			5	21.6	16.1[b]	14.0	13.3	11.2	12.9	12.7	9.8	14.0	13.4	13.9[4]		
5	52	F	1	26.9	23.0[b]	20.0	16.2	21.3[c]	19.6[b]	17.6	15.4	12.9	11.3	18.4[2,5]	3.57	16.0
			2	15.1	15.7	15.5	15.2	11.0[b]	14.0	10.0	13.0	9.0	12.0	13.0[1,3]		
			3	25.7	20.4[b]	18.8	15.3	14.7	14.8	18.3[c]	18.3	20.4	19.2[b]	18.6[2,5]		
			4	22.7	18.6[b]	14.0	17.3[c]	18.5	15.4[b]	12.9	11.6	10.8	9.3	15.1		
			5	21.6	19.6	17.5	12.7	12.8	13.9	12.9	12.6	10.8	11.4	14.6[1,3]		
6	42	M	1	16.0	18.0[c]	19.2	18.8	14.3[b]	14.9	15.5	13.2	11.4	10.7	15.2[3,4,5]	1.58	12.7
			2	19.2	18.3	17.3[b]	15.4	15.1	14.4	16.1	12.3	10.3	10.7	14.9[3,4,5]		
			3	14.3	14.0	13.9	12.6[b]	12.3	11.9	10.6	8.1	6.9	6.5	11.1[1,2]		
			4	14.7	15.3	16.6	13.4[b]	11.5	9.7	9.1	7.2	7.0	6.7	11.1[1,2]		
			5	16.6	14.2[b]	14.1	12.3	10.3	9.8	9.0	8.3	7.4	7.5	11.0[1,2]		

[a] Raw data of plasma cortisol with subject means, session means within subjects, and Scheefé numbers for session means within subjects. The clock time immediately before flooding began in Sessions 3 and 4 for any subject was set as 0 for all sessions for that subject. Underscored data were taken during flooding. Any two session means within subject are significantly different at $p < 0.05$ if they differ by an amount equal to or greater than the corresponding Scheffé number. Notations for raw data: [b] termination of secretory episode by Weitzman et al. criteria; [c] = onset of cortisol secretory episode by criteria of Weitzman et al. (2). Notation for session means: [1]= significantly different from Session 1 at $p < 0.05$ or less; [2]= significantly different from Session 2 at same level, etc.

The remaining four subjects all showed significant differences between sessions. In all of these subjects one of the sessions containing flooding had the highest mean cortisol level for that subject. Usually this was the session with the first treatment hour. In two of these four subjects the mean plasma cortisol of the initial adaptation session was significantly higher than one or both of the other no-treatment sessions and approximated the means of the treatment sessions. Two subjects had no evidence of increased cortisol during the initial adaptation session. Subjective distress ratings do not account for the presence or absence of a "first session effect" in these subjects.

The role of the pain of venipuncture is difficult to evaluate. There were no apparent marked differences in patients' reactions, and concern, when expressed, was usually mild. The design was intended to place a considerable time interval between venipuncture and experimental manipulations. Replacement of nonfunctioning needles was too infrequent to permit systematic evaluation of its effect. Inspection of data surrounding needle replacement episodes suggested that there was usually no effect on plasma cortisol.

DISCUSSION

In the present study, and in the previous one of the same phenomenon (4), anxiety and distress account for considerably less variation in plasma cortisol levels than current concepts lead one to expect from a powerful emotional stimulus. The observed dissociations between subjective-behavioral and endocrine aspects of anxiety may be due to a slight extent to inaccuracies in the identification of anxiety or even to false displays of pseudoaffect. There are, after all, no ideal methods for the psychological assessment of affect. In the present context, however, self-ratings offer as few disadvantages and as many advantages as any available method, and their basic validity is attested by the striking congruence between the stimulus situation, the expected reaction, the self-report, and the observed behavior. With this strong a case for validity and with the magnitude of the observed dissociations, there is little reason to believe that the conclusions are fundamentally misleading. Furthermore, for any who may insist on using physiological measures as ultimate validity criteria, flooding is not physiologically inert. Elsewhere (8) we have reported growth hormone responses to flooding by some, but not all, of these same patients, including some who did not respond with cortisol. Autonomic responses also occur during flooding, although not always in synchrony with other anxiety indicators (9, 10). As was noted above, autonomic responses were apparent in our patients, although we did not study them systematically.

Recent evidence that cortisol secretion may be partly independent of ACTH (11, 12) warrants further investigation by measuring ACTH in patients undergoing flooding.

The findings could be unique to phobic anxiety. There is not enough empirical evidence to assess this possibility adequately, but what there is raises little need to invoke it. The human literature has long been characterized by weak and variable associations between hormonal and psychological measures (1). The animal literature contains some stronger findings, but when behavioral arousal has been directly observed or quantified,

it has not been a strong correlate of pituitary-adrenal measures (13–15).

Although the present study and the previous one (4) share one common finding (an individually variable, and on the whole, unimpressive association between plasma cortisol and strong anxiety), there are also differences. In the present study 3 of the 6 subjects showed elevations during novelty-adaptation sessions, and 4 of the 6 showed elevations during flooding sessions. In the previous report (4), individual differences in response patterns were not examined in detail. We have now carried out similar analyses of the earlier data on 7 subjects. These show evidence of statistically significant *suppression* of plasma cortisol levels during flooding sessions in 3 subjects, and no evidence of statistically significant elevation in *any* subject. On the other hand, 5 of the 7 subjects of the previous study showed statistically significant elevation during novelty-adaptation sessions. Taken together these findings suggest (1) a slight but detectable tendency to elevation of plasma cortisol during flooding sessions in some subjects in the present study; (2) no tendency to elevation and a detectable tendency to suppression of plasma cortisol levels in some subjects during flooding sessions in the previous study; and (3) roughly equivalent frequency of elevation of plasma cortisol levels during novelty-adaptation sessions in the two studies. Restating these differences in a slightly different way, the previous study showed cortisol elevations which clearly outweighed any elevation by flooding; the present study shows novelty and flooding effects that are about equal. The differences in findings could be due to (1) intended differences in the study conditions, i.e., different circadian phases; (2) unintended differences in subjects or study conditions, most likely due to nonrandomization of subjects. If (1) were the case, different circadian phase, then novelty responses and flooding might involve separate mechanisms, where novelty might tend to elevate plasma cortisol at both circadian phases and flooding might tend to elevate cortisol at the crest and depress it at the trough of the circadian cycle. If (2) were the case, nonrandomization, many factors could be involved, the most obvious one at present being that the morning subjects required more treatment to achieve final symptom relief. However, this too could be due to either (1) or (2). In order to choose between (1) and (2) randomized assignment will be necessary.

Psychophysiological dissociation of the type described here may be an example of what behavior therapy researchers call "desynchrony of fear" (9, 10). This means that during desensitization procedures, the subjective, behavioral, and autonomic components of anxiety drop out at different rates. The rates and sequences vary with the individual. If the pituitary-adrenal system follows the desynchrony principle, then increased cortisol levels during the novelty-adaptation sessions may represent for the patient a stage of the treatment in the sense that cortisol responses may occur and begin to extinguish in the anticipatory period before formal treatment has begun. In order to evaluate these possibilities, multivariate studies, including endocrine measures, would have to be carried out over the entire course of treatment.

SUMMARY

Six patients with severe phobias for physical objects spent five 3-hour ses-

sions in the laboratory, timed to coincide approximately with the crest of the circadian cycle of plasma cortisol. At 20-min intervals blood was sampled through an indwelling needle for cortisol assay, and subjective distress was self-rated on a scale of 0 to 100. During the second hour of the third and fourth sessions strong anxiety was evoked by rapid live exposure ("flooding *in vivo*") to the specific stimulus that each patient feared.

The expectation that this strong anxiety would cause reliable and marked cortisol secretion was not borne out. Three of the six patients had no cortisol secretory episodes according to the criteria of Weitzman et al. (2) during any treatment sessions despite near-maximal anxiety. Out of the total of twelve 3-hour sessions containing a treatment hour, Weitzman et al. criteria for onset of secretory episodes were met during only 5. For the group as a whole there was no statistically significant difference between treatment and control sessions. Cortisol elevations were about equal in frequency and magnitude during adaptation sessions to the laboratory as during flooding sessions, even though subjective-behavioral arousal was much greater during flooding. There were marked individual differences in response, with individual subjects showing cortisol elevations during flooding sessions only, during novelty-adaptation sessions only, during both, or during neither. When cortisol elevations were associated with flooding, the level was usually elevated over the entire 3-hour session, before, during, and after the confrontation, rather than specifically during the confrontation itself.

The findings should stimulate reevaluation of the hypothesis that affective arousal is the key psychological determinant of adrenal cortical function. They may be a manifestation of what behavior therapists call "desynchrony of fear."

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