Endocrine and Cardiovascular Responses During Phobic Anxiety

RANDOLPH M. NESSE, MD, GEORGE C. CURTIS, MD, BRUCE A. THYER, PHD, DAISY S. MCCANN, PHD, MARLA J. HUBER-SMITH, BA, AND RALPH F. KNOPF, MD

In vivo exposure therapy for phobias is uniquely suited for controlled studies of endocrine and physiologic responses during psychologic stress. In this study, exposure therapy induced significant increases in subjective anxiety, pulse, blood pressure, plasma norepinephrine, epinephrine, insulin, cortisol, and growth hormone, but did not change plasma glucagon or pancreatic polypeptide. Although the subjective and behavioral manifestations of anxiety were consistent and intense, the magnitude, consistency, timing, and concordance of endocrine and cardiovascular responses showed considerable variation.

INTRODUCTION

Stress has been implicated in the etiology of many diseases, including myocardial infarction, cancer, and psychiatric conditions (1–3). With the advent of radioimmunoassay (RIA) and related techniques, reliable measurements of hormones in small samples have become practical, and endocrine research on the mechanisms of stress response has, in turn, been stimulated (4–9). Although many physiologic variables are now known to respond to psychologic stimuli, the principles that organize these responses have remained elusive. One view is that subjective, behavioral, and physiologic arousal are tightly linked. In some human studies, however, physiologic responses to psychologic stress have proved weak or unreliable. Research has been hampered by the difficulty of reliably inducing severe and sustained stress in human subjects in a laboratory setting. For this purpose, we have proposed exposure therapy for phobias as a research tool (10). In this procedure, the patient is confronted with the actual feared object (snake, spider, etc.) and is encouraged to approach and touch the object as rapidly as possible (11). The anxiety induced is very intense, but patients are motivated by the knowledge that relatively few sessions are usually necessary for the treatment to be effective.

In our initial work with this approach, plasma growth hormone was not changed during adaptation to the laboratory, but two thirds of subjects showed some increase during treatment (12). Plasma cortisol increased during laboratory adaptation but showed no statistically significant response to treatment (13, 14). When data from individual subjects were analyzed separately, a few subjects treated during

From the Departments of Psychiatry and Internal Medicine, The University of Michigan Medical School, Ann Arbor, MI.

Address reprint requests to: Randolph M. Nesse, M.D., Department of Psychiatry, The University of Michigan Medical School, B2917 C.F.O.B, Box 056, 1045 East Ann Street, Ann Arbor, MI 48109.

Presented in part at the American Psychosomatic Society Annual Meeting, March 11, 1984, on Hilton Head Island, SC.

Received for publication February 9, 1984; revision received July 30, 1984.

Published by Elsevier Science Publishing Co , Inc
52 Vanderbilt Ave , New York, NY 10017

0033-3174/85/$3.30

the early morning showed mild cortisol elevations, whereas subjects treated during the evening showed no increase at all. Plasma prolactin and thyroid stimulating hormone levels were not affected by exposure therapy (15, 16). These results suggested three possible explanations: 1) that the carefully controlled conditions eliminated confounding effects such as posture, exercise, diet, time of day, and novelty, which may have influenced previous studies; 2) that the anxiety induced by exposure therapy is fundamentally different from other kinds of psychologic stress; or 3) that the various aspects of the stress response are not, in fact, closely coupled.

The present study was designed to extend this inquiry by incorporating new variables and more stringent controls, by randomly assigning subjects to time of treatment, and by analyzing the data to take full advantage of the simultaneous frequent measurement of multiple variables. Pulse and blood pressure were measured because they are known to increase during anxiety (17, 18) and because they may mediate disease. Subjective anxiety was measured with two widely used scales. Plasma epinephrine (19–22), norepinephrine (19–22), growth hormone (12, 23), and cortisol (13, 24) were measured because they also are known to increase during stress. This protocol allows study of the intensity, timing, and coordination of their responses to acute psychologic stress under strictly controlled experimental conditions. The influence of stress on insulin has been uncertain (25) but of obvious importance for understanding glucose regulation. Glucagon and pancreatic polypeptide are the other two islet cell hormones whose plasma levels mainly reflect pancreatic secretion (26, 27). Both increase during hypoglycemia, and glucagon release might be adaptive during stress because it induces glycogenolysis and gluconeogenesis (26, 27). Repeated simultaneous measurements of these 12 variables during periods of rest and anxiety make possible a detailed and coordinated view of the responses to psychologic stress.

METHODS

Ten women requesting treatment from the University of Michigan Phobia Clinic were selected for study according to the following criteria. All had simple animal phobias rated 4 (severe) or 5 (very severe) on the 5-point Gelder and Marks Phobia Severity Scale (28) and had no other psychiatric disorders. They were 25–43 years old, took no medication, and reported good physical health and normal menstrual cycles. History, physical examination, and blood analyses (screening panel, CBC, T3, T4) confirmed their good health. All gave informed consent.

The research protocol included four 3-hr sessions for each subject. Sessions 1 and 4 were control periods in which subjects sat and read quietly. Sessions 2 and 3 were treatment sessions: during the middle hour of these sessions subjects received rapid in vivo exposure therapy for their phobias; during the first and third hours subjects again sat and read. Subjects understood this schedule before the protocol began. Individual sessions were scheduled at weekly intervals, always at the same time of day. Stage in the menstrual cycle was not a factor in session scheduling. Between-session variance may have been increased for this reason, but systematic bias is unlikely. To control for circadian effects, half of the subjects were randomly assigned to morning sessions, the other half to evening sessions. Research sessions started 3 or 15 hr after the individual subject's mean time of mid sleep. Starting times were approximately 6:00 A.M. or 6:00 P.M. Subjects were instructed not to eat, smoke, exercise, or drink caffeinated or alcoholic beverages for 7 hr before each session and they sat quietly for at least 20 min before the start of each session.

The 12 dependent variables chosen for study were Subjective Units of Distress (SUDS), state anxiety, pulse, systolic and diastolic blood pressure, plasma epinephrine, norepinephrine, growth hormone, cortisol, insulin, glucagon, and pancreatic polypeptide. The SUDS scale is a self-rating of subjective anxiety on a scale of 0 ("no anxiety") to 100 ("the most anxious it is possible to feel") (29). State anxiety was

measured using the Spielberger State Anxiety Inventory (30). Pulse was measured by palpating the radial artery for 1 min. Blood pressure was measured using a standard sphymomanometer. Data for all variables was obtained at the start of each session (time 1) and every 20 min thereafter, except for state anxiety, which was rated hourly.

Blood samples were taken via a needle inserted into an antecubital vein at the beginning of each session (time 1) and kept patent by a slow normal saline infusion. Blood samples were placed immediately into chilled tubes containing glutathione and ethylene glycol tetraacetic acid (for epinephrine and norepinephrine assay) or heparin (for other assays). Plasma was rapidly separated using a refrigerated centrifuge, and aliquots were frozen at −70°C. Norepinephrine and epinephrine concentrations were assayed by a modification of an enzymatic single-isotope derivative procedure that is accurate at concentrations greater than 20 pg/ml (31). For norepinephrine, the within-assay coefficient of variation (WACV) is 3.9% and the between-assay coefficient of variation (BACV) is 10.7%, at 300 pg/ml. For epinephrine, the WACV is 8.6% and the BACV is 17.9% at 85 pg/ml. Growth hormone was assayed by an RIA with a sensitivity of 17 pg/tube, a WACV of 8.1%, a BACV of 7.8%, and 50% inhibition at 393 pg. Insulin was assayed with an RIA sensitive to 0.1 μU/tube, with a WACV of 6.4%, a BACV of 8.4%, and 50% inhibition of 2.2 μU. The glucagon RIA was sensitive to 2 pg/tube, had a WACV of 7.5%, a BACV of 10.2%, and 50% inhibition at 59 pg. The pancreatic polypeptide RIA was sensitive to 2.9 pg/tube, had an WACV of 3.5%, a BACV of 9.1%, and 50% inhibition at 66 pg. The cortisol assay by competitive protein binding was sensitive to 1.0 mg/dl, with a WACV of 7.0%, a BACV of 10.0%, and 70%–80% binding of cortisol.

The data were transformed to standardized scores based on each individual subject's standard deviation from her median for all 40 measurements of each variable (standardized score = raw value − median ÷ SD). The median was chosen as the indicator of central tendency because some variables had skewed distributions, and because the median best reflected baseline levels for labile variables. This method of analysis minimizes the variance resulting from baseline differences between subjects, equalizes the contributions of subjects to the analysis for those variables where subjects show widely differing baseline levels or amounts of variation, allows morning and evening results to be conveniently analyzed both together and separately, and allows uniform graphic and statistical analysis of diverse variables and interactions between variables. For each variable, a one-way analysis of variance (ANOVA) was used to compare the mean of all standardized values obtained during treatment periods to the mean of all standardized values obtained during nontreatment periods. These analyses compared, for each variable, the mean of all values for all subjects during anxiety periods (six per subject; three values obtained in each of the two treatment hours) to the mean of all other values obtained (34 per subject).

RESULTS

During exposure therapy, all subjects manifested intense anxiety by their verbal reports, by our observation of their agitation, tremors, piloerection, and crying, and by their scores on the SUDS and State Anxiety scales. Ten of the 12 variables showed a treatment effect significant at $p < 0.0001$. Only glucagon and pancreatic polypeptide did not respond. Figure 1 illustrates the response for each variable. Table 1 summarizes the statistical analysis of these results.

All variables were compared on the strength of response to the anxiety-provoking stimulus. Strength of response can be calculated in three different ways; each has different implications (Table 2). First, response strength can be estimated by the correlation ratio (η^2, eta-squared), which estimates the percent of the total variance explained by the treatment effect. This ranking method incorporates four factors: the amount, the consistency, and the temporal specificity of a variable's response to treatment, and the relative stability of baseline levels. A second system ranks variables according to the percent of data points that are above that subject's overall median for that variable; here the order mainly reflects the reliability of response. A third perspective is provided by ranking the variables according to the mean percent-increase during anxiety, above mean

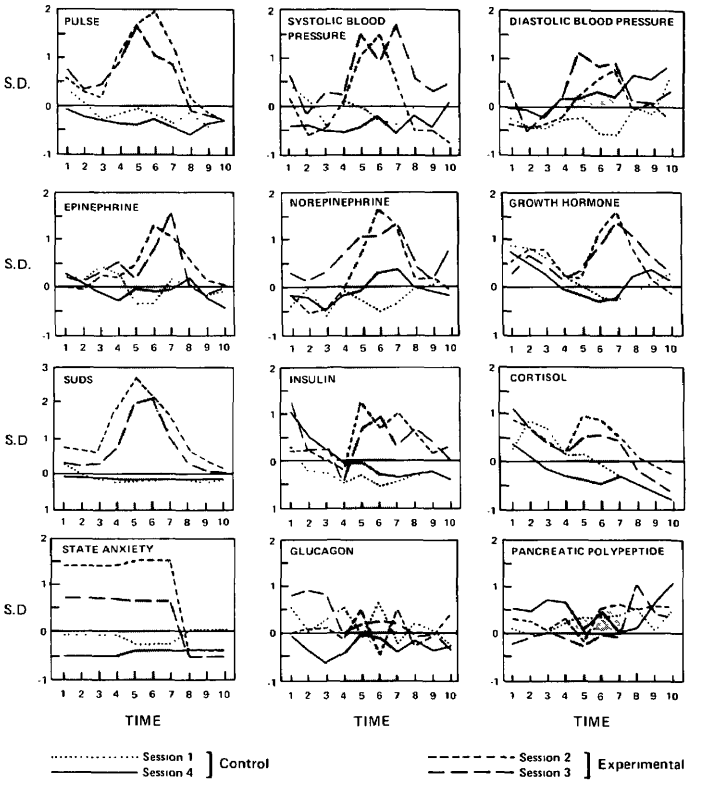

Fig. 1. Mean standardized scores for all subjects, at each time in each session. *Y* axis in all cases is scaled in standard deviation units. The *X* axis is divided into nine intervals of 20 min each. Anxiety-inducing treatment occurred during sessions 2 and 3 only, where it began at time 4 and ended at time 7, as indicated by the shading.

baseline levels. This widely used method reflects the absolute magnitude of the response but is relatively insensitive to the reliability of response and the stability of baseline levels. The relative ranking of each component of a stress response depends on how response strength is defined. This is best appreciated if multiple simultaneous samples for many variables are available for analysis.

Repeated simultaneous measurements of multiple variables also make it possible to compare the relative timing of various responses (see Fig. 1). Pulse and SUDS in-

TABLE 1. Summary of Means and ANOVAs[a]

	Experimental Times N = 6 per subject		Control Times N = 34 per subject				
	MEAN	SD	MEAN	SD	F	P	η^2
SUDS	1 944 (63.8)	1.196	0.122 (20.3)	0.698	189.09	<0.0001	0.405
Pulse	1 434 (85.4 bpm)	1.068	−0.005 (74.4 bpm)	0.831	131.41	<0.0001	0.264
Systolic BP	1.174 (115.6 mm Hg)	1.030	−0.116 (105.5 mm Hg)	0.858	91.12	<0.0001	0.218
Norepinephrine	1.190 (466.9 pg/ml)	1.190	−0.046 (336.2 pg/ml)	1.216	71 71	<0.0001	0.194
State anxiety	1.080 (46.9)	1.260	−0.010 (39.4)	0.0823	23.011	<0.0001	0.174
Epinephrine	0.898 (127.0 pg/ml)[b]	1.360	0.056 (107.9 pg/ml)[b]	0.864	29.86	<0.0001	0.091
Insulin	0.828 (12.2 mU/ml)	0.985	0.030 (11.5 mU/ml)	0.953	28.25	<0.0001	0.082
Diastolic BP	0.704 (73.2 mm Hg)	1.117	−0.058 (67.8 mm Hg)	0.942	26.45	<0.0001	0.075
Cortisol	0.664 (11 7 mg/dl)	1.041	−0.005 (9.4 mg/dl)	0.971	21.30	<0.0001	0.056
Growth hormone	0.922 (5.5 ng/ml)	1.323	0.310 (3.2 ng/ml)	0.897	19.19	<0.0001	0.048
Pancreatic polypeptide	0.128 (93 3 pg/ml)	1.010	0.349 (97.3 pg/ml)	0.998	2.12	ns	—
Glucagon	0.201 (43.5 pg/ml)	1.131	0.028 (39.7 pg/ml)	0.979	1.21	ns	—

[a]Mean of all experimental values (N = 6 per subject) versus mean of all control values (N = 34 per subject) expressed as standardized scores. Means for raw data are in parentheses. F ratio is from a one-way ANOVA comparing standardized values for all experimental times to those for all control times. Analyses are based on eight to ten subjects, except for SUDS (N = 7). η^2 is the correlation ratio

[b]When one subject with very high plasma epinephrine levels is excluded, these means become 69.7 and 37.3 pg/ml.

TABLE 2. Strength of Response During Anxiety for Each Variable

	η^2	Percent of Treatment Values Above Overall Median	Percent Increase Over Baseline
SUDS	0.40	100%	214%
Pulse	0.26	90	15
Systolic BP	0 22	87	10
Norepinephrine	0.19	87	46
Epinephrine	0.09	80	87
Insulin	0.08	84	6
Diastolic BP	0.08	76	8
Cortisol	0.06	74	24
Growth hormone	0.05	76	72

crease in anticipation of the treatment period, peak in mid-treatment, and begin decreasing before treatment ends. State anxiety increases markedly before and during treatment. The other variables, with the possible exception of norepinephrine in session 3, demonstrate a notable lack of response immediately before treatment. Blood pressure, norepinephrine, cortisol, and insulin increase promptly when phobic anxiety begins, and stay elevated during treatment. The rapid insulin increase, and the low or negative correlations of insulin values with values of other hormones during treatment suggest that insulin response is not secondary to other hormone response. More detailed work is needed, however, to better consider the relationships between insulin and other responses. Growth hormone remains at basal levels for at least 20 min after treatment begins and peaks only at the end of the hour of treatment, a finding that is consistent with the pattern of growth hormone response to other stimuli (33). At time 8, 20 min after treatment has ended, all variables except growth hormone and insulin have returned substantially toward baseline. Forty minutes after treatment, all variables are back to baseline levels.

The circadian effect on responses during treatment was assessed by comparing, for each variable, all standardized scores obtained during treatment times for morning subjects to those for evening subjects (see Fig. 2). Responses for the two groups

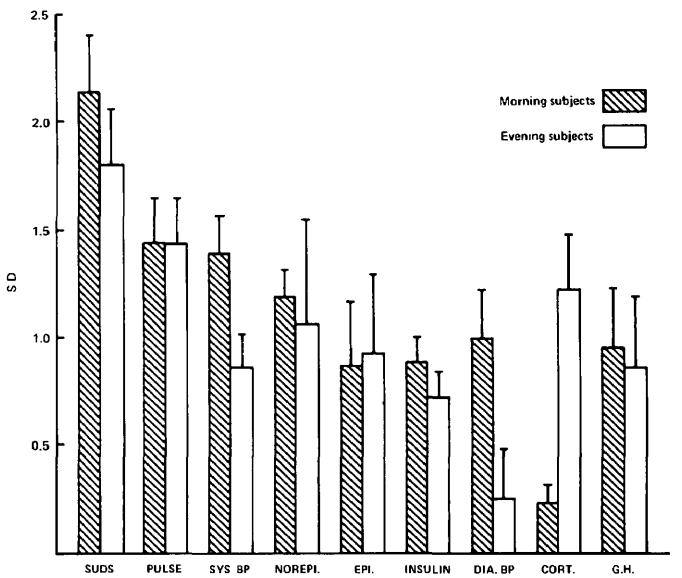

Fig. 2. Mean scores during treatment for morning subjects vs. evening subjects.

were comparable except that, when compared to evening subjects using a one-way ANOVA, morning subjects had, during treatment, higher blood pressure scores (systolic: $F = 3.32$, $p < 0.07$; diastolic: $F = 5.95$, $p < 0.02$) and much lower cortisol scores ($F = 15.39$, $p < 0.0003$). The response of cortisol to stress during the circadian period of maximal secretion is minimal ($F = 3.24$, $p < 0.07$) compared to the response in the evening ($F = 27.50$, $p < 0.0001$). The mean increase during stress for morning subjects was from 12.4 to 13.8 μg/dl, while evening subjects increased from 5.6 to 9.2 μg/dl.

A similar technique was used to compare anxiety responses in session 2 to those in session 3 (Fig. 3). Mean scores during treatment averaged 31% higher in session 2, except for systolic and diastolic blood pressure, which responded more in session 3. The difference in response between sessions 2 and 3 was not statistically significant for any variable (all $p > 0.10$). The general decline in response from session 2 to session 3 may reflect the rapid efficacy of flooding treatment, and suggests that pulse and hormone responses decrease concordantly with anxiety. The failure of blood pressure to follow this pattern is difficult to explain. Controlling for the menstrual cycle stage might have clarified these results.

Despite the clear effect of exposure therapy on 10 of the 12 dependent variables, it was *not* the case that all subjects showed a reliable and substantial increase in all variables during the entire treatment time.

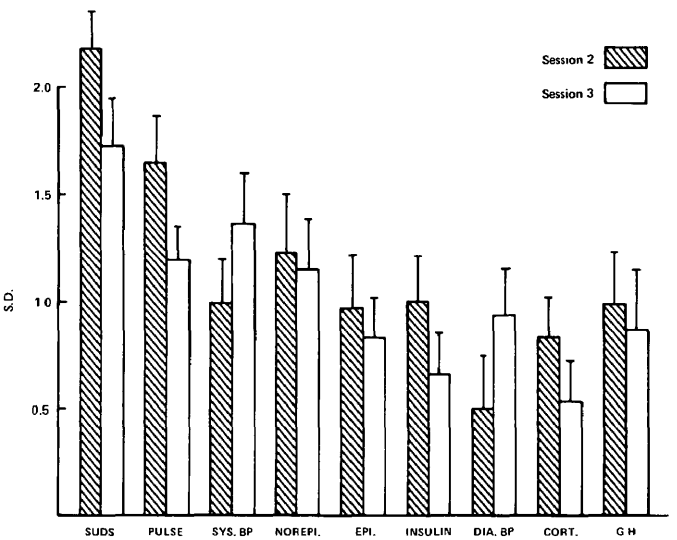

Fig. 3. Mean scores during treatment in session 2 vs. session 3.

Instead, examination of graphs of individual variables for individual subjects (for one example, see Figure 4) reveals relatively few instances of sustained elevations of multiple hormones throughout treatment. More often, a hormone peaks relatively sharply during some treatment times and is near baseline at other treatment times. The increased amplitude and frequency of these peaks, during treatment, averaged for many subjects, comprise the seemingly consistent elevations in Figure 1.

An individual subject's peaks for different variables sometimes concur, but very often do not. Confirming this relative lack of concordance are the generally low correlations between variables for all simultaneous values obtained during treatment periods (see Table 3). For example, epinephrine and growth hormone values during treatment are poorly correlated ($r = 0.043$), despite the fact that each strongly responds to phobic anxiety. The only variables whose values are significantly correlated during treatment ($p < 0.05$) are those of norepinephrine with growth hormone, epinephrine, and cortisol. If any hormone can be regarded as "central" to the stress response in this study, it is norepinephrine. Anxiety explains more of its variance than that of any other hormone, and it is the only hormone whose values during treatment are significantly correlated with more than one other hormone.

We examined the data to determine if those individuals who showed a particularly strong response in one hormone also tended to respond strongly in another hormone (Table 4). A response strength for each variable for each subject in both treatment sessions was estimated by the correlation ratio from a separate ANOVA that

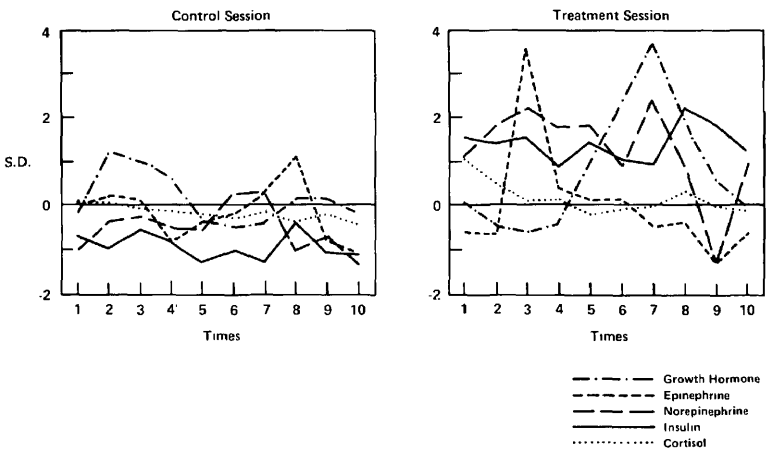

Fig. 4. Endocrine responses in a control and a treatment session for a single subject. Anxiety was induced during times 4–7 of sessions 2 and 3. *Y* axis is scaled in standard deviation units.

TABLE 3. Correlations Between Variables for Values During Anxiety Periods in Individual Subjects

Pulse	0.086	1.000						
Systolic BP	−0.115	0.311[a]	1.000					
Norepinephrine	0.054	0.027	−0.014	1.000				
Epinephrine	0.110	−0.002	0.000	0.396[b]	1.000			
Insulin	−0 203	0.022	−0.142	0.101	−0.310	1.000		
Diastolic BP	−0.162	0.073	0.311[b]	−0.405[a]	−0.196	−0.015	1.000	
Cortisol	−0 205	0.316[a]	0.008	0.319[a]	0.229	0.112	−0.228	1.000
Growth hormone	0.093	−0.187	0.160	0.398[b]	0.043	0.188	0.134	−0.138
	SUDS	Pulse	Systolic B.P.	Norepinephrine	Epinephrine	Insulin	Diastolic B.P.	Cortisol

[a]$p < 0.05$; [b]$p < 0.01$, uncorrected for the number of correlations performed.

TABLE 4. Correlations Between Response Strengths in Pairs of Variables in Individual Subjects

Pulse	0.395	1.000						
Systolic BP	0.031	0.434	1.000					
Norepinephrine	0.640	0.421	−0.203	1.000				
Epinephrine	0.279	−0.395	0.031	0.779[a]	1.000			
Insulin	−0.284	0.537	0.425	−0.585	−0.284	1.000		
Diastolic BP	−0.388	0.260	0.626	−0.720	−0.388	−0.541	1.000	
Cortisol	0.443	0.003	0.116	0.060	0.443	−0.127	−0.307	1.000
Growth hormone	−0.286	−0.390	−0.383	0.203	−0.286	−0.437	−0.186	−0.346
	SUDS	Pulse	Systolic B P.	Norepinephrine	Epinephrine	Insulin	Diastolic B.P.	Cortisol

[a]$p \leq 0.023$, uncorrected for the number of correlations performed.

compared the 6 treatment values to the 34 control values. These response strengths were then correlated. Only epinephrine and norepinephrine responses significantly predicted one another ($r = 0.779$, $p \leq 0.023$).

Correlations between the strengths of response for each individual in each variable in session 2 with that in session 3 (see Table 5) were performed to see if a subject's relative response strength in a variable in one session could predict the response in another session. The results suggest that subjects may have individually consistent patterns of response during separate episodes of stress a week apart, especially for cortisol, pulse, and insulin, but a stronger conclusion will require a study designed to answer this question.

TABLE 5. Correlations Between the Strength of a Subject's Response in Session 2 with that Subject's Response in Session 3

	N	*r*
Cortisol	9	0.44
Pulse	9	0.42
Insulin	8	0.35
SUDS	7	0.29
Diastolic BP	8	0.26
Epinephrine	7	0.14
Growth hormone	9	−0.02
Systolic BP	8	−0.18
Norepinephrine	7	−0.19

DISCUSSION

Some of these results directly confirm prior work whereas some are quite surprising. As expected, pulse, blood pres-

sure, epinephrine, norepinephrine, cortisol, and growth hormone all increased during anxiety, thus confirming much previous work (4–8, 17–24) in a setting that allows the rigorous control of experimental conditions during acute and intense psychologic anxiety. The definite increase of insulin deserves emphasis because previous studies have been inconclusive (25). The failure of glucagon and pancreatic polypeptide to respond is of interest because both increase during hypoglycemic stress (26, 27) and because their clear absence of response helps to validate the positive results for other variables. The definite responses of these ten variables to phobic anxiety increase confidence in our previous reports, based on a similar method, that plasma TSH and prolactin are not changed by phobic anxiety (15, 16).

These results help to explain why our previous work on cortisol and growth hormone showed weaker effects than some other studies. The reaction of both hormones during stress is particularly clear in the present study because of the controlled conditions, the large number of data points, and because the data transformation efficiently eliminated variance from subject's differences in baseline levels, so that even small individual responses are reflected in the analysis. When compared to other hormones, however, cortisol and growth hormone responses are relatively inconsistent, even though the magnitude of increase is substantial when peaks do occur.

The subjects were all women with severe, specific, simple phobias. Though they were in all other ways healthy and typical of the general population, the results cannot necessarily be generalized to men or to people without phobias. The stress employed was particularly acute and intense anxiety relatively uncontaminated by other emotions or physical factors. The body may well respond differently to stress that is chronic or induced by other emotions or situations.

Could anxiety-induced changes in glucagon and pancreatic polypeptide have been missed because their half-lives in plasma are only about 5 min (26, 27)? Although single brief peaks might escape detection, repeated peaks would have been reflected in the analysis, as they were for the catecholamines which have even shorter half-lives (33). Cortisol (34) and growth hormone (35) are cleared slowly enough from plasma that every substantial secretory burst should be observed with the 20-min sampling interval.

Not surprisingly, the SUD measure responded most strongly to exposure therapy, no matter how response strength was estimated. The ranking of other variables depended substantially on the measure of response strength used. The catecholamines consistently ranked high, whereas cortisol and growth hormone, traditional stress hormones, were the two lowest ranked variables in the analyses that emphasized reliability of response. Though growth hormone showed the third highest mean percent-increase during stress, data from any of the other responding variables would better predict treatment and nontreatment times.

The timing of various aspects of the response is relatively uncoordinated. Only pulse and anxiety levels were elevated in anticipation of treatment. Growth hormone showed a characteristic delayed response and, along with insulin, had elevations sustained past the end of treatment. It is clear, even from these group data, that the stress response is not a simple on–off phenomenon.

The rapid growth of knowledge about circadian effects (36) makes consideration

of their influence essential to stress research. The comparable responses of most variables at the circadian extremes was expected, but the minimal cortisol response in the morning conflicts with previous work (13, 14) and cannot be regarded as a firm conclusion, although blunted cortisol responses might be expected at times when levels are already high. Systolic and diastolic blood pressure were the only other divergent variables—both were more responsive in morning subjects. If confirmed, this finding has implications for studies involving blood pressure.

When responses in session 2 were compared to those in session 3 (Fig. 3), blood pressures again opposed the trend—they were the only variables that responded more in session 3 than in session 2. Though no firm conclusions can be drawn from the limited data available, the possibility that blood pressure may mediate stress-related disease draws attention to these divergent patterns.

Several interesting results emerge from the patterns of interactions between variables (Table 4). The strength of growth hormone response was negatively correlated with that of every other variable except norepinephrine. The strength of a subject's norepinephrine response predicts the strength of epinephrine response—this is not the case for any of the other 35 pairs of variables. This correlation suggests that linked mechanisms may control the release of norepinephrine and epinephrine during anxiety.

Subjects who had a cortisol, insulin, or pulse response during session 2 tended to show the same pattern in session 3. It would be possible to determine if individuals have characteristic patterns of response by expanding the same method to involve four or more episodes of treatment. This might begin to explain why different individuals develop different symptoms in response to stress.

Finally, subjects did not show reliable, substantial, and sustained increases in multiple variables during treatment. The endocrine responses to psychologic stress may be definite, but they are not reliable, sustained, and coordinated in the way that a simple theory of stress might predict. Instead, they consist of relatively inconsistent, brief and seemingly uncoordinated changes. The elegant analyses by Ward et al. (20) of individual subjects' variable catecholamine responses to a variety of stimuli point to the same conclusion. The concept of "stress" as a consistent pattern of response to a variety of stressors needs to be considered in the light of these findings.

SUMMARY

Endocrine, cardiovascular, and subjective responses during psychologic stress were studied by using exposure therapy for phobias to induce intense acute anxiety. This technique allowed rigorous control of confounding variables, and made possible the simultaneous measurement of 11 variables at 10 times during each of four 3-hr sessions. Ten healthy female subjects with severe simple phobias received rapid exposure treatment during the middle hours of sessions 2 and 3. All experienced severe anxiety during this treatment.

Results were transformed to standard scores. Scores during treatment were then compared to scores during control periods using one-way ANOVAs. Ten variables significantly increased ($F > 19.0$, $p < 0.0001$) during the anxiety periods. The design and analysis make it possible to compare and list these variables in order of response strength as measured by the

proportion of variance explained by the anxiety periods: subjective anxiety, pulse, systolic blood pressure, norepinephrine, state anxiety, epinephrine, insulin, diastolic blood pressure, cortisol, and growth hormone. The marked insulin response is of note because previous studies have been inconclusive on this point. Glucagon and pancreatic polypeptide did not respond. Compared to evening subjects, morning subjects showed much less cortisol response and somewhat more blood pressure response. Time of day did not affect other responses. Responses were decreased in session 3, compared to session 2, except for blood pressure. Graphs of mean values show the relative timing as well as the magnitude of responses in each variable. Graphs of individual's responses reveal that sustained substantial responses in multiple variables were the exception rather than the rule. For different variables, peaks very often did not concur. Response patterns were more complex and variable than expected. These results confirm and extend our knowledge of the endocrine and cardiovascular responses during psychologic stress, and they illustrate the advantages of a model that employs phobic anxiety as a stressor.

We thank the University of Michigan Clinical Research Center and its staff for their assistance, Dr. Daniel Rourke and the University of Michigan Statistical Research Laboratory for statistical consultation, Dr. Bernard J. Carroll and Dr. Oliver G. Cameron for support and advice, the staff of the Word Processing Center in the University of Michigan Department of Psychiatry, for manuscript preparation, and the proprietors of Ann Arbor Pet Supply for their indispensable assistance.

REFERENCES

1. Riley V: Psychoneuroendocrine influences on immunocompetence and neoplasia. Science 212: 1100–1109, 1981
2. Steptoe A: Psychological factors in cardiovascular research. New York, Academic, 1981
3. Anisman H, Zacharko RM: Depression: The predisposing influence of stress. Behav Brain Sci 5: 84–137, 1982
4. In Levi L (ed), Emotions—Their Parameters and Measurement. New York, Raven, 1975, pp 143–182
5. Selye H (ed): Selye's Guide to Stress Research. New York, Van Nostrand Reinhold, 1980
6. Rose RM, Jenkins CD, Hurst M: Air Traffic Controller Health Change Study. Galveston, Texas, University of Texas Medical Branch, 1978
7. Ursin H, Baade E, Levine S (eds): Psychobiology of Stress. New York, Academic, 1978
8. Mason JW, Maher JT, Harley LH, et al: Selectivity of corticosteroid and catecholamine responses to various natural stimuli. In Serban G (ed), Psychopathology of Human Adaptation. New York, Plenum, 1976, pp 147–172
9. Mason JW: A historical view of the stress field. J Hum Stress 1: 6–12, 22–36, 1975
10. Curtis GC, Nesse RM, Buxton M, et al: Flooding in-vivo as a research tool and treatment for phobias. Compr Psychiatry 17: 153–160, 1976
11. Marks I: Behavioral treatments of phobic and obsessive-compulsive disorders: a critical appraisal. In Hersen M, Eisler RM, Miller PM (eds), Progress in Behavior Modification. New York, Academic, 1975, Vol 1, pp 66–158
12. Curtis GC, Nesse RM, Buxton M, et al: Plasma growth hormone: Effect of anxiety during flooding-in-vivo. Am J Psychiatry 136: 410–414, 1979

13. Curtis GC, Nesse RM, Buxton M, et al: Anxiety and plasma cortisol at the crest of the circadian cycle: reappraisal of a classical hypothesis. Psychosom Med 40: 368–378, 1978
14. Curtis GC, Buxton M, Lippman D, et al: "Flooding in vivo" during the circadian phase of minimal cortisol section: Anxiety and therapeutic success through adrenal cortical activation. Biol Psychiatry 11: 101–107, 1976
15. Nesse RM, Curtis GC, Brown GM: Phobic anxiety does not affect plasma levels of thyroid stimulating hormone in man. Psychoneuroendocrinology 7: 69–74, 1982
16. Nesse RM, Curtis GC, Brown GM, et al: Anxiety induced by flooding therapy for phobias does not elicit prolactin secretory response. Psychosom Med 42: 25–31, 1980
17. Moss A, Wynar B: Tachycardia in house officers presenting cases at grand rounds. Ann Intern Med 72: 255–256, 1970
18. Bonelli J: Stress, catecholamines and beta-blockade. Acta Med Scand (Suppl) 660: 214–218, 1982
19. Dimsdale JE, Moss J: Plasma catecholamines in stress and exercise. JAMA 243: 340–342, 1980
20. Ward MM, Mefford IN, Parker SD, et al: Epinephrine and norepinephrine responses in continuously collected plasma to a series of stressors. Psychosom Med 45: 471–486, 1983
21. Frankenhauser M: Experimental approach to the study of catecholamines and emotion. In Levi L (ed), Emotions—Their Parameters and Measurement. New York, Raven, 1975, pp 209–234
22. Aslan S, Nelson L, Carruthers M, et al: Stress and age effects on catecholamines in normal subjects. J Psychosom Res 25: 33–41, 1981
23. Miyabo S, Asato T, Mizoshima N: Psychological correlates of stress-induced cortisol and growth hormone releases in neurotic patients. Psychosom Med 41: 515–523, 1979
24. Vernikos-Danellis J, Heybach JP: Psychophysiologic mechanisms regulating the hypothalamic–pituitary–adrenal response to stress. In Selye H (ed), Selye's Guide to Stress Research. New York, Van Nostrand Reinhold, 1980, pp 206–251
25. Lustman P, Carney R, Amado H: Acute stress and metabolism in diabetes. Diabetes Care 4: 658–659, 1981
26. Porte D, Halter J: The endocrine pancreas and diabetes mellitus. In Williams RH (ed), Textbook of Endocrinology, 6th ed. Philadelphia, Saunders, 1981, pp 716–843
27. Lonovics J, Devitt P, Watson LC: Pancreatic polypeptide. Arch Surg 116: 1256–1264, 1981
28. Gelder MG, Marks IM: Severe agoraphobia: a controlled prospective trial of behavior therapy. Br J Psychiatry 112: 309–319, 1966
29. Wolpe J: The Practice of Behavior Therapy, 2nd ed. New York, Pergamon, 1973
30. Spielberger CD: The measurement of state and trait anxiety; conceptual and methodological issues. In Levi L (ed), Emotions—Their Parameters and Measurement. New York, Raven, 1975, pp 713–725
31. McCann DS, Huber-Smith MJ: Plasma catecholamines. J Clin Immunoassay 6: 308–312, 1984
32. Hays WL: Statistics, 3rd ed. New York, Holt, Rinehart, and Winston, 1981, p 349
33. Cryer PE: Physiology and pathophysiology of the human sympathoadrenal neuroendocrine system. N Engl J Med 303: 436–444, 1980
34. Hellman L, Nakada F, Curtis J, et al: Cortisol is secreted episodically by normal man. J Clin Endocrinol 30: 411–422, 1970
35. Daughaday WH: The adrenohypophysis. In Williams RH (ed), Textbook of Endocrinology, 6th ed. Philadelphia, Saunders, 1981, pp 73–116
36. Moore-Ede MC: The Clocks That Time Us: Physiology of the Circadian Timing System. Cambridge, MA, Harvard University Press, 1982