

# Anxious and Depressive Disorders and Their Comorbidity: Effect on Central Nervous System Noradrenergic Function

Oliver G. Cameron, James L. Abelson, and Elizabeth A. Young

**Background:** Although comorbidity of anxiety with depression is common, investigations of physiologic abnormalities related specifically to comorbidity are rare. This study examined relationships of DSM-IV-defined depression, anxiety, and their comorbidity to noradrenergic function measured by blunting of the growth hormone (GH) response to the alpha2 adrenoceptor agonist (and imidazoline receptor agent) clonidine and by blood pressure and symptom responses.

**Methods:** Fifteen subjects with pure social anxiety or panic disorder, 15 with pure major depression, and 18 with both depression and anxiety were compared with healthy control subjects matched for age and gender. Other factors known to affect GH (weight, menstrual status, prior antidepressant, or other drug exposure) were controlled.

**Results:** Anxiety produced GH blunting, but depression was associated with normal GH responses. The comorbid state did not affect results beyond the impact of anxiety. Preclonidine stress-related GH elevations were observed, to the greatest degree in anxious subjects. Relevant symptom, but not blood pressure, changes were significantly associated with blunting.

**Conclusions:** With use of pure depression and anxiety groups and careful control of other factors known to affect GH, these results demonstrate central nervous system noradrenergic dysfunction in anxiety disorders. In contrast to less rigorously controlled studies, noradrenergic function in depression was normal.

**Key Words:** Anxiety, clonidine, comorbidity, depression, growth hormone, noradrenergic

Co-occurrence of psychiatric disorders (comorbidity) is common. In persons with depression or an anxiety disorder, comorbidity with the other disorder occurs in one-quarter to one-half of individuals (Kessler et al 1994, 1998, 1999) and is associated with increased severity (Barbee 1998; Lydiard 1991; Roy-Byrne et al 2000). Although there has been extensive interest in biological factors associated with depression and anxiety disorders, biological changes associated with the comorbid state, defined by diagnoses or symptoms, have been neglected. Individuals with comorbid diagnoses have either been excluded or have been treated as part of the group that has the same primary (occurring first) or predominant (more severe) diagnosis as the comorbid individuals.

One biological system of major interest in depressed and anxious individuals is brain noradrenergic function. One marker of this function is the growth hormone (GH) increase produced by stimulation with the alpha2 adrenoceptor agonist clonidine. Investigations of this marker in depression have reported blunted GH responses, implying reduced noradrenergic function, responsiveness, or both (e.g., Amsterdam and Maislin 1990; Ansseau et al 1988; Charney et al 1982b; Checkley et al 1981; Correa et al 2001; Horton et al 1986; Siever and Uhde 1984), including studies indicating blunting is a trait marker (Charney et al 1982a; Mitchell et al 1988; Siever et al 1992); however, a number of studies found no blunting (Fu et al 2001; Gann et al 1995; Katona et al 1993; Mitchell et al 1991; Schittecate et al 1989).

Single anxiety studies have reported blunting in generalized anxiety (Abelson et al 1991) and posttraumatic stress disorder

(Morris et al 2004). Blunting occurred in most (e.g., Abelson et al 1992; Brambilla et al 1995; Charney et al 1992) but not all (Schittecate et al 1992) panic studies, including one suggesting blunting is a trait marker (Coplan et al 1995). Limited results in social phobia (Tancer et al 1993, 1994/5) and obsessive-compulsive disorder (Hollander et al 1991; Lee et al 1990; Siever et al 1983) were inconsistent (blunted or normal).

Without drug administration, GH was abnormal during phobic exposure (Curtis et al 1979) and during "spontaneous" (Cameron et al 1987) and situationally induced (Woods et al 1987) panic attacks. It was also abnormal in response to isoproterenol-induced symptoms (Nesse et al 1984). In depression, GH abnormalities have been associated with other pharmacologic challenges (Anseau et al 1988; Hasey et al 1985; Matussek and Laakmann 1981) and under baseline conditions without drug (Mendlewicz et al 1985). Several factors (gender, age, weight, menstrual status and cycle phase, and prior antidepressant or other drug exposure) affect the GH response to clonidine (Altomonte et al 1988; Gil-Ad et al 1984; Kimber et al 2001; Tancer et al 1990).

Clonidine also binds to imidazoline receptors (Bousquet et al 1998; Regunathan and Reis 1996). Growth hormone release can result from either alpha2 adrenoceptors or imidazoline receptor stimulation (Ballidin et al 1993; Bamberger et al 1995). Sedative effects of clonidine seemingly are mediated by noradrenergic receptors, and the hypotensive effects by imidazoline receptors (Fornai et al 1990; Schafer et al 1995). Thus, these markers might be used to differentiate these receptor effects.

Blunted GH responses to clonidine in anxiety disorders, high comorbidity between depression and anxiety, and studies suggesting that, with careful experimental control, depressed individuals might be normal on this measure, all imply that past positive results in depression could be due to comorbid anxiety. Furthermore, the peripheral (Balon et al 1990; Cameron and Minoshima 2002; Nesse et al 1984; Shear 1986) or central nervous system (CNS; Cameron et al 2000; Charney et al 1984; Gurguis et al 1997) adrenergic activation producing anxietylike symptoms, similarity of some naturally occurring anxiety symptoms to adrenergic activation (Cameron 1994), reduction of such symp-

From the Department of Psychiatry (OGC, JLA, EAY) and Mental Health Research Institute (EAY), University of Michigan Medical Center, Ann Arbor, Michigan.

Address reprint requests to Oliver G. Cameron, M.D., Ph.D., 1215 Southwood Court, Ann Arbor, MI 48103-9735; E-mail: ocameron@umich.edu.

Received January 15, 2004; revised July 7, 2004; accepted August 19, 2004.

toms by adrenergic blockade (Lader 1988; Tyrer 1988), and the intimate involvement of CNS noradrenergic systems including the locus ceruleus in fear (Bremner et al 1996; Sullivan et al 1999; Tanaka et al 2000)—with none of these factors directly involved in depression—all suggest that adrenergic functions including that measured by GH responses to clonidine are directly related to anxiety but not depression. To test this hypothesis, individuals comorbid for major depression and an anxiety disorder were studied, along with individuals with pure major depression or a pure anxiety disorder. All were compared to specifically matched control subjects. Based on possible confoundings recognized in the GH depression literature, including comorbidity, as well as research documenting involvement of noradrenergic systems in anxiety (Cameron and Nesse 1988; Johnson and Lydiard 1995; Ressler and Nemeroff 2000; Sullivan et al 1999) and anxiety-associated functions (e.g., apprehension, arousal, attention, novelty, stress; Aston-Jones et al 1999; Koob 1999; Robbins 1984; Stanford 1995), we hypothesized that abnormal brain noradrenergic function, as indicated by GH blunting to clonidine, implying diminished postsynaptic  $\alpha_2$  adrenoreceptor effects, would be associated with anxiety but not depression. What roles symptom severity and the presence of comorbidity per se play in GH blunting were also investigated.

## Methods and Materials

### Subjects

Ninety-six subjects were recruited by advertisement, including 15 with an anxiety disorder without depression (anxiety group), 15 with major depression without an anxiety disorder (depression group), 18 with both disorders (comorbid group), and 48 individually age and gender matched control subjects. Diagnoses were made according to DSM-IV criteria with a Structured Clinical Interview (SCID) interview by an experienced research nurse. Subjects with pure disorders did not reach present or past criteria within 2 years for the other disorder, and the pure disorder was always primary, whereas comorbid individuals either met criteria for both disorders currently or within the past year. Control subjects never had any psychiatric disorders themselves or in any first-degree relatives. Subjects with pure or comorbid anxiety had predominant anxiety diagnoses of social phobia or panic disorder. Most were naive to psychotropic medications; five had received an selective serotonin reuptake inhibitor. All were medication free for at least 9 months. Obese subjects (body mass index  $\geq 30$ ) or those with any eating disorder or a recent weight loss averaging more than 1 kg/week were excluded, as was anyone under 18 or over 50. Female subjects were premenopausal and were studied within 10 days of the onset of menstruation. The University of Michigan Medical Center IRB approved the study. All subjects gave written informed consent.

### Procedures

Subjects were admitted to the Clinical Research Center at 7:30 AM. They were studied at bed rest with an intravenous catheter for clonidine infusion and blood sampling. Automated measurement of blood pressure (BP), blood sampling, and completion of self-rated visual analogue scales (VAS; “drowsy” rating) were performed before clonidine administration, and after 15, 30, 60, 90, and 120 min. Clonidine (Duraclon *R*), 2.0  $\mu\text{g}/\text{kg}$ , was administered intravenously over 5 min by infusion pump, starting at 9:00 AM. Preclonidine measurements were done for GH at 30, 15, and 1 min before clonidine, for BP at 60 and 10 min

before, and for VAS ratings at 10 min before. The State and Trait Anxiety Inventories (STAI) were completed at 8:50 AM and the Hamilton Depression and Anxiety Rating Scales and the Sheehan Disability Scale between 9:30 and 10:30 AM. Separated by at least 2 days before or after this study, each subject had a Trier Social Stress Test (TSST; Kirschbaum et al 1993), involving performance of a 5-min speech and a difficult mathematical subtraction task with time pressure in front of an audience of three “experts” (procedure detailed in Young et al 2004). Analyzed also were the STAI State and three VAS ratings (“nervous,” “anxious,” “fearful”) obtained during the TSST immediately before the social challenge. Order did not affect results of either study.

Blood samples for GH (ng/mL) and somatomedin-C (ng/mL) were stored on ice for a maximum of 30 min, then plasma was separated and frozen at  $-70^\circ\text{C}$ . Growth hormone was assayed by Nichols IRMA method (interassay coefficient of variation of 6.8%). Somatomedin-C was assayed locally by radioimmunoassay.

### Data Analyses

Area under the curve (AUC) was calculated by trapezoidal approximation for relevant data points. Distributions of untransformed data were approximately normal and log-transformation did not visibly affect normality, so raw data were used in all analyses except AUC. In addition to repeated-measures data, patients were compared with control subjects on GH peak change scores, calculated as highest GH level postclonidine (always either 9:30 or 10:00 AM) minus last GH level before clonidine administration (9:00 AM).

Hypotheses were tested using *t* tests and analyses of variance (ANOVA), including repeated measures (RM-ANOVA) with covariance (RM-ANCOVA). Because GH levels were measured both before and after clonidine and because GH measurements after clonidine were timed to start before a robust response and to end after the response was complete, interaction tests of each RM-ANOVA and RM-ANCOVA, testing for nonparallel levels between groups over time (e.g., a blunted GH clonidine response), were used as the main hypothesis tests. Because age and gender can affect GH levels and patient groups could not be closely matched on these variables, and because assay variability over time can affect results, analyses always compared patients with their individually matched control subjects, with subject and matched control always assayed in the same batch. Regressions were used to assess relationships of preclonidine to postclonidine GH levels, and relationships of age, weight, and symptom ratings to GH levels.

First, the hypothesis that patients (regardless of diagnosis) differed from control subjects was examined by comparing all patients combined with all control subjects. Then, to dissect the relative contributions of anxiety, depression, and the comorbid state to any GH blunting, two approaches were used. First, each of the DSM-IV-defined pure anxiety, pure depressed, and comorbid groups were compared with their respective control subjects. The comorbid patients were then subdivided into two groups, based on predominant symptoms, to identify the disorder more severely affecting the subject at time of study. All comorbid subjects except one could be assigned a predominant diagnosis, based on the more symptomatic or dysfunction-producing diagnosis, for the DSM-IV-defined qualifying duration of symptoms—for example, 2 weeks for a major depressive episode or 1 month for panic disorder. All patients with predominant anxiety ( $n = 23$ ) were compared with their control subjects and all with predominant depression ( $n = 24$ ) to theirs.

**Table 1.** Subject Characteristics of the Pure Depression, Pure Anxiety, Comorbid, and Control Groups (mean  $\pm$  SD, where applicable)

	Depression	Comorbid	Anxiety	All Control Subjects
<i>n</i>	15	18	15	48
Age (years)	28.7 $\pm$ 7.7	23.2 $\pm$ 5.5	25.4 $\pm$ 8.5	26.0 $\pm$ 7.1
Gender (F:M)	6:9	13:5	8:7	27:21
Weight (kg)	70.9 $\pm$ 13.4	67.1 $\pm$ 7.6	70.3 $\pm$ 13.9	68.7 $\pm$ 12.1
Anxiety Diagnoses	0	18	15	0
Panic disorder	0	5	3	0
Social phobia	0	13	12	0
Depression Diagnoses	15	18	0	0
Melancholic	7	4	0	0
Nonmelancholic	8	14	0	0
Hamilton Depression Rating <sup>a</sup>	19 $\pm$ 4.0	12.7 $\pm$ 6.7	3.3 $\pm$ 3.4	.5 $\pm$ .9
Hamilton Anxiety Rating <sup>b</sup>	13.8 $\pm$ 5.5	12.4 $\pm$ 7.0	5.8 $\pm$ 7.0	.7 $\pm$ .7
STAI-Trait <sup>c</sup>	50.4 $\pm$ 11.2	53.3 $\pm$ 8.3	40.1 $\pm$ 11.0	27.0 $\pm$ 5.2
STAI-State <sup>d</sup>	42.0 $\pm$ 14.1	50.3 $\pm$ 12.1	34.1 $\pm$ 7.4	25.0 $\pm$ 4.3
TSST STAI-State <sup>e</sup>	35.4 $\pm$ 9.3	45.6 $\pm$ 9.4	43.2 $\pm$ 11.1	28.6 $\pm$ 8.6
Sheehan Scale <sup>f</sup>	17.9 $\pm$ 5.7	20.6 $\pm$ 7.0	9.0 $\pm$ 6.5	1.4 $\pm$ 1.1

STAI, State and Trait Anxiety Inventory; TSST, Trier Social Stress Test.

<sup>a</sup>ANOVA:  $F = 137.9$ ,  $p < .0001$  for group; by Fisher protected least significant difference (PLSD),  $p < .05$  for all group contrasts.

<sup>b</sup>ANOVA:  $F = 46.3$ ,  $p < .001$  for group, by Fisher PLSD,  $p < .05$  for control subjects versus depression, anxiety, and comorbid groups; depression versus anxiety groups; and comorbid versus anxiety groups.

<sup>c</sup>ANOVA:  $F = 59.3$ ,  $p < .0001$  for group; by Fisher PLSD,  $p < .002$  for control groups versus depression, anxiety, and comorbid groups; depression versus anxiety groups; and comorbid versus anxiety groups.

<sup>d</sup>ANOVA:  $F = 40.9$ ,  $p < .0001$  for group; by Fisher PLSD,  $p < .05$  for all group contrasts.

<sup>e</sup>ANOVA:  $F = 19.7$ ,  $p < .0001$  for group; by Fisher PLSD,  $p < .05$  for all group contrasts except anxiety versus comorbid groups.

<sup>f</sup>ANOVA:  $F = 91.1$ ,  $p < .0001$  for group; by Fisher PLSD,  $p < .05$  for all contrasts except depression versus comorbid groups.

## Results

### Subject Characterization

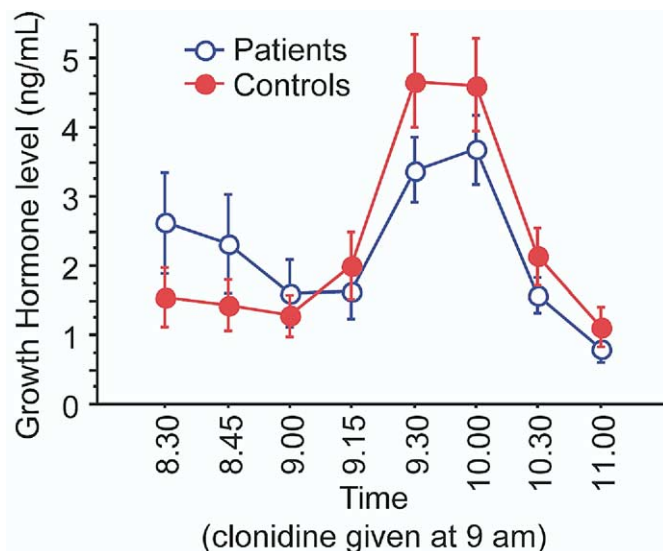
Table 1 contains age, gender, weight, diagnosis, and clinical rating scale scores, including ANOVA and post hoc comparison results. Matching ensured that all group comparisons included only groups that had matched age and gender distributions. There were no meaningful group differences in body weight. Social phobia was the predominant anxiety disorder diagnosis. Hamilton Depression, Hamilton Anxiety, STAI State, STAI Trait, TSST STAI-State, and Sheehan Disability scores all differed significantly across groups. Except for the TSST STAI-State, ratings for the depression and comorbid groups always exceeded the anxiety group. For all three, TSST VAS scores, anxious, comorbid, and depressed groups differed significantly from control subjects (range for overall  $F$  scores: 9.05–15.4, all  $p < .0001$ ), but not each other for “nervous” and “anxious,” whereas for “fearful,” the comorbid group differed from all others (which did not differ from each other).

### GH Response to Clonidine

The RM-ANOVA comparing all patients to all control subjects (Figure 1) showed a highly significant main effect of clonidine (i.e., repeated-measure:  $F = 19.11$ ,  $df = 7$ , 651,  $p < .0001$ ), reflecting robust GH release in response to clonidine. The clonidine-by-group interaction was significant ( $F = 2.48$ ,  $df = 7$ , 651,  $p = .016$ ) due to both some elevation in GH in patients at the first two of three baseline samples and their blunted GH responses following clonidine. (Immediately before clonidine, at 9:00 AM, GH levels for patients and control subjects were approximately equal.) The main effect of group was not significant in this or any subsequent GH RM-ANOVA comparing patient groups to control subjects.

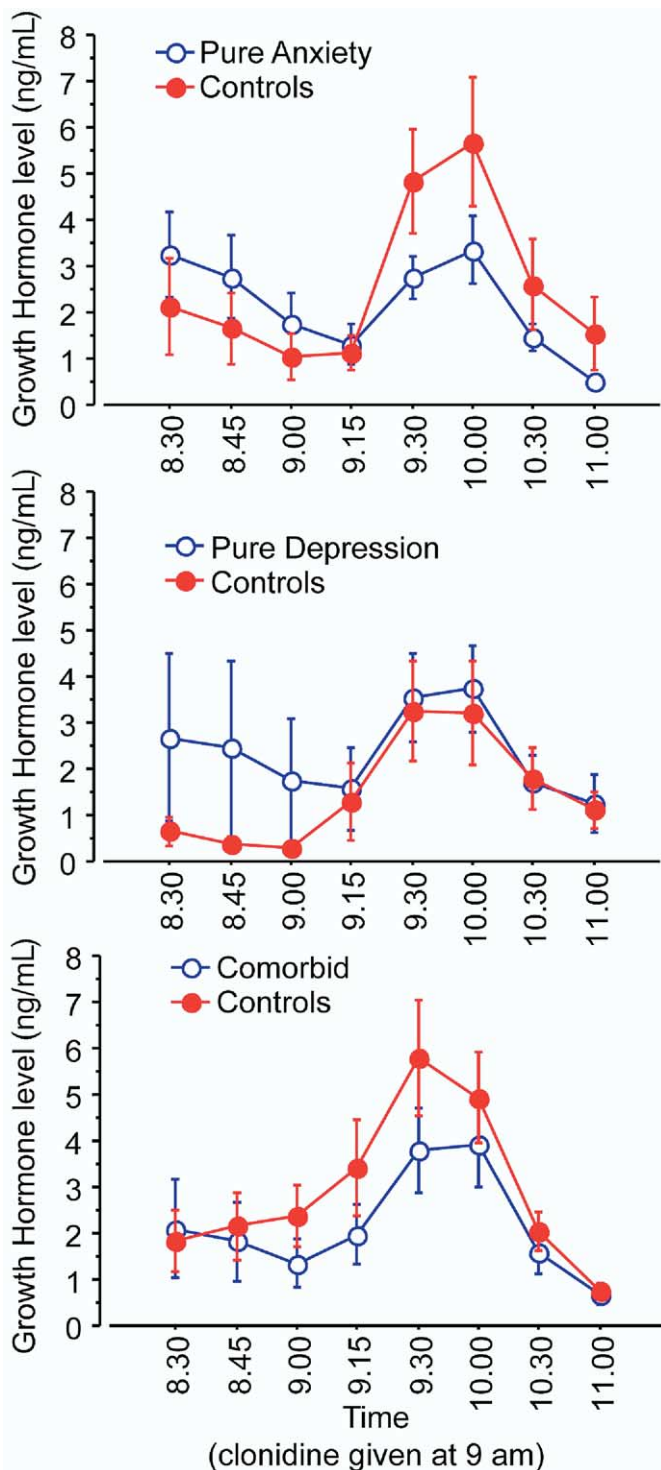
The three control groups for the three DSM-IV-defined diagnostic groups did not differ significantly from each other. The

RM-ANOVAs comparing each diagnostic group (pure anxiety, pure depression, comorbid) to respective control subjects showed the following (Figure 2): A clonidine effect on GH release was evident in all three analyses ( $F = 8.2$ ,  $df = 7$ , 196 for anxiety,  $F = 3.5$ ,  $df = 7$ , 196 for depression,  $F = 9.7$ ,  $df = 7$ , 231 for comorbid;  $p < .0001$  for anxiety and comorbid,  $p < .002$  for depression). The clonidine-by-group interaction was significant



**Figure 1.** Comparison of growth hormone (GH) levels (mean  $\pm$  SE) for all anxious, depressed, and comorbid subjects combined (“patients”:  $n = 48$ ) to all individually age- and gender-matched control subjects ( $n = 48$ ) before and after intravenous clonidine (2.0  $\mu$ g/kg) administration at 9:00 AM. x axis: discrete time points of GH sampling; y axis: GH levels (ng/mL). See Results for statistical analyses.



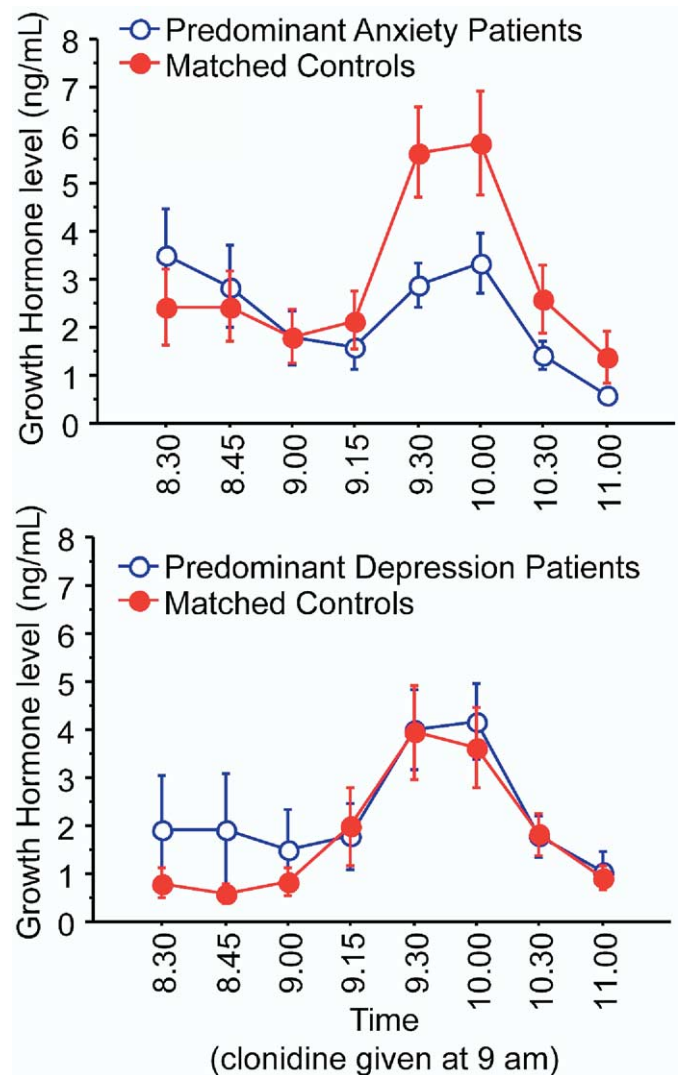


**Figure 2.** Comparison of growth hormone levels for anxious subjects (upper panel, "pure anxiety":  $n = 15$ ), depressed subjects (middle panel, "pure depression":  $n = 15$ ), and subjects comorbid for anxiety and depression (lower panel, "comorbid":  $n = 18$ ) to respective matched control subjects ( $n =$  that for patient group for each comparison). Other details same as Figure 1.

only in the pure anxiety group ( $F = 2.58, df = 7, 196, p = .015$ ), because only the pure anxiety group showed clearly blunted GH responses following clonidine compared with control subjects.

The pure depressed group had normal GH clonidine responses (interaction  $F = .71, df = 7, 196, p = .66$ ). The comorbid group, like pure depression, did not show significantly abnormal GH responses (interaction  $F = .70, df = 7, 231, p = .67$ ); however, in the comorbid group GH responses appear to be intermediate, between clear blunting seen in pure anxiety and normal responses seen in pure depression.

To further evaluate the source of blunting, patients in the comorbid group were divided according to predominant diagnosis. All patients with predominant anxiety (pure plus comorbid) were compared with their control subjects, and all with predominant depression (pure plus comorbid) were compared with theirs. The RM-ANOVA for predominant anxiety showed the robust effect of clonidine on GH ( $F = 11.20, df = 7, 301, p < .0001$ ). It also showed a significant clonidine-by-group interaction ( $F = 3.19, df = 7, 301, p = .003$ ), due to highly blunted GH responding in the anxious patients (Figure 3). The parallel



**Figure 3.** Comparison of growth hormone levels for predominantly anxious subjects (upper panel, "predominant anxiety patients":  $n = 23$ ) and predominantly depressed subjects (lower panel, "predominant depression patients":  $n = 24$ ) to respective matched control subjects ("matched control subjects":  $n =$  that for patient group for each comparison). Other details same as Figure 1.

RM-ANOVA comparing patients with predominant depression with their control subjects showed the clonidine effect ( $F = 9.34$ ,  $df = 7$ ,  $322$ ,  $p < .0001$ ), but the clonidine-by-group interaction was not significant ( $F = .49$ ,  $df = 7$ ,  $322$ ,  $p = .84$ ) because of very similar GH responses in depressed patients and control subjects. Interaction terms for RM-ANCOVAs, using the 8:30 AM pre-clonidine GH levels as covariates (time of maximum baseline difference across groups), remained significant for pure anxiety and predominant anxiety analyses ( $F = 2.13$  and  $2.98$ ,  $p = .042$  and  $.005$ , respectively), but not for the all-patient comparison ( $F = 1.42$ ,  $p = .19$ ). Anxious subjects were divided into social phobia and panic disorder subgroups. Inspection of results (not shown) indicated comparable blunting, but subgroups were too small to reach significance.

In summary, patients overall showed abnormal GH clonidine responses. Blunting was clearly associated with anxiety and not with depression. To verify results, paired  $t$  tests compared patient groups to matched control subjects on peak GH clonidine response (change scores). Comparison of predominant anxiety subjects to control subjects reached significance ( $t = 2.87$ ;  $df = 44$ ;  $p = .03$ ), and comparison of pure anxiety patients to control subjects showed a strong trend ( $t = 1.99$ ;  $df = 28$ ;  $p = .06$ ). In contrast, comparisons of predominantly depressed ( $t = .55$ ;  $df = 46$ ;  $p = .69$ ) and pure depressed ( $t = .52$ ;  $df = 28$ ;  $p = .61$ ) to their respective control groups did not approach significance.

Because blunting of GH clonidine responses in depression was reported in prior studies as specific to melancholia, effect of the presence or absence of melancholia on GH response was examined. All patients with depression were compared with their control subjects, dividing the depressed group into those with melancholia and those without. No significant group differences were detected (mean  $\pm$  SD, ng/mL, for postclonidine peak: melancholia =  $5.37 \pm 4.26$ ; nonmelancholia =  $3.97 \pm 4.20$ ; control subjects =  $5.27 \pm 4.97$ ).

Figures 2 and 3 suggest that GH levels declined across the baseline period in anxious patients, but considerably less so in nonanxious patients. Exploring this further, RM-ANOVAs were performed including the three samples before clonidine (8:30, 8:45, and 9:00 AM.). Over this baseline period, all comparisons with control subjects involving pure anxiety subjects (groupings: all patients; all anxiety, including all comorbid; predominant anxiety; and pure anxiety) showed significant time effects ( $F$  range: 4.18–9.82;  $df$  range: 2, 56–2, 188; all  $p \leq .02$ ) because of declining values in patients from 8:30 to 9:00 AM. None of the comparable comparisons that did not include pure anxiety subjects (groupings: pure depression; all depression, including all comorbid; predominant depression; comorbid only) showed similar statistically significant time effects. For the anxiety-predominant analysis, the interaction term was also significant ( $F = 3.09$ ;  $df = 4$ , 184;  $p < .02$ ), indicating that the GH level decline was significantly greater in predominantly anxious patients than in their control subjects.

To determine the relationship of GH levels before and after clonidine, regressions were performed for 8:30 AM and 9:00 AM GH levels with peak change score and with postclonidine AUCs. Of primary interest was the question of whether higher pre-clonidine levels predict reduced GH release following clonidine. In regressions including all 96 subjects, GH levels at 8:30 and 9:00 AM were significantly predictive of postclonidine GH secretion (AUC:  $R = .22$ ,  $p = .03$ ; and  $R = .36$ ,  $p = .0004$ , respectively); however, higher levels before clonidine were associated with

higher levels after. Baseline levels were also positively predictive of postclonidine peak GH, although this was only significant for 9:00 AM ( $R = .23$ ,  $p = .006$ ).

To determine whether blunted GH responses were due to persistently increased GH secretion, resulting in increased negative feedback, 8:30 AM somatomedin-C was measured. For pure depression and control subjects, results (mean  $\pm$  SD, ng/mL) were  $234 \pm 24$  and  $221 \pm 12$ ; for comorbid,  $283 \pm 35$  and  $342 \pm 42$ ; and for pure anxiety,  $292 \pm 24$  and  $273 \pm 21$ . All differences were nonsignificant.

Regression analyses confirmed that neither age nor weight had any impact on GH responses, using either AUC or peak change score results. Across all 96 subjects, a large gender effect was observed. In an RM-ANOVA with two independent variables, gender and diagnosis, the main effect of gender was highly significant ( $F = 17.5$ ,  $df = 1$ ,  $92$ ,  $p < .0001$ ), due to much higher overall GH levels in female subjects; however, the clonidine-by-diagnosis interaction effect was also significant ( $F = 2.17$ ,  $df = 7$ ,  $637$ ,  $p = .03$ ), due to reduced GH responses in both male and female patients relative to their same-gender control subjects. There were no other significant interactions. Thus, blunted GH responses seen in patients were independent of gender. Additionally, ANOVAs with gender and diagnosis, using GH peak change scores, found no gender effect, indicating that gender differences were due to group differences in GH baselines, not GH clonidine responses.

Regressions determined whether dimensional ratings of anxiety (STAI and Hamilton Anxiety Scores) on the same day as the clonidine study would predict GH results (8:30 and 9:00 AM levels, AUC, or peak change score). None significant. The pure anxiety group had the clearest GH blunting, but also significantly lower scores on anxiety rating scales. Examination of the relationship between depression severity (using Hamilton Depression scores) and GH measures showed no significant correlations, looking at all subjects together or patients alone (all  $R = .1$ ). In contrast, TSST STAI State regressions with GH AUC showed significant negative associations within the predominant anxiety group ( $R = .47$ ,  $p = .022$ ) and within the pure plus comorbid anxiety group ( $R = .42$ ,  $p = .014$ ), but not within the normal or depressed groups.

### BP and "Drowsy" Responses to Clonidine

Effects of clonidine on sedation (VAS "drowsy") and BP (systolic [SBP] and diastolic [DBP]) were assessed, with RM-ANOVAs comparable to those run on GH data. Predictably, both SBP and DBP fell significantly over time in response to clonidine ( $F = 27.7$  and  $48.5$ ,  $df = 9$ ,  $846$  for both, both  $ps < .0001$ , for main effect of time), but patients and control subjects did not differ in BP levels or clonidine responses. There were no significant interactions for either SBP or DBP in comparisons of all patients to all control subjects or any subgroup to matched control subjects.

There was the expected rise and then fall in drowsiness in all subjects in response to clonidine ( $F = 15.1$ ,  $df = 6$ ,  $552$ ,  $p < .0001$ ). All patients rated themselves as more drowsy, compared with all control subjects ( $F = 9.58$ ,  $df = 1$ ,  $94$ ,  $p < .003$ ); however, clonidine had similar (i.e., parallel) patterns of effect on drowsiness ratings in patients and control subjects (no significant interaction). There were no significant interactions for drowsiness for any patient subgroup compared with matched control subjects.

## Discussion

The primary goal of this study was to explore relative contributions of anxiety, depression, and their comorbidity to the blunted GH clonidine responses reported in previous research in patients with major depression and various anxiety disorders. Results support the hypothesis that the presence of anxiety *per se* (specifically, panic disorder and social phobia, of sufficient symptom number, severity, and chronicity to qualify for DSM-IV diagnoses) accounts for GH blunting. In this study, pure depression was associated with a normal GH response. The comorbid state did not affect results beyond the impact of anxiety. Thus, in past studies of depression, failure to exclude subjects with comorbid anxiety could have contributed to the blunting reported; however, lack of significant blunting in a sizeable group with documented depressive–anxious comorbidity in this study suggests that comorbidity alone probably does not fully explain past positive results reported in the depression literature. Many prior depression studies did not adequately control for gender, age, weight, menstrual phase, menopausal status, and prior recent tricyclic antidepressant exposure. This study indicates that with appropriate control subjects (as described in Methods) and exclusion of anxious comorbidity, depression itself is not associated with abnormal GH clonidine responses. Also, based on rating scales, overall syndrome severity (anxiety, depression, and disability scores on clonidine study day) was least among patient groups for anxious subjects, indicating that acute severity *per se* did not produce blunting. Furthermore, within the comorbid group, the observed nonsignificant blunting appeared to be due to individuals who were predominantly anxious, suggesting that these individuals might be different pathophysiologically from those with predominant depression.

Reports in the depression literature have suggested that GH blunting might be linked to melancholia (Amsterdam et al 1989b; Checkley et al 1984; Matussek et al 1980). In this study, individuals with melancholic depression showed no greater blunting than nonmelancholic patients. Using symptom ratings, despite several intervening days, TSST STAI State ratings for anxious subjects were negatively correlated with GH AUC. In contrast, anxiety ratings for the anxious subjects were lower during the clonidine procedure, and no relationships with any GH measures were seen. Furthermore, significant relationships were not observed for nonblunted depressed subjects with anxiety ratings, nor for any subjects with depression ratings, during clonidine. Thus, a measure that partly reflects depression severity—melancholia—is not associated with blunting, whereas elevated anxiety—produced here by the TSST—is negatively correlated with GH response to clonidine, but only in those individuals with chronic, impairing anxiety that passes the DSM-IV diagnostic threshold.

Blunted GH clonidine responses have traditionally been interpreted as reflecting abnormal alpha2 adrenoreceptor function (Siever et al 1981), but clonidine also binds to imidazoline receptors, which could be implicated in GH blunting. As expected, clonidine produced significant BP decreases, but no interaction effects were observed. Because hypotensive effects of clonidine are thought to be mediated by imidazoline receptors, lack of effects of diagnosis on BP response implies normal imidazoline receptor responsiveness to clonidine in all groups and lends support to the hypothesis of abnormality of alpha2 adrenoreceptors. One prior study (Piletz et al 1996) reported normal imidazoline binding in generalized anxiety.

Sedative effects of clonidine are believed to be mediated by

alpha2 adrenoreceptors. Drowsiness ratings demonstrated higher levels for all disorders combined than for control subjects. This pattern was true for individual patient groups as well; however, differences were as large before clonidine as after, indicating that the effect observed was not specifically differential sensitivity to the sedative effects of clonidine. Thus, in this study, sedative responses to clonidine do not provide evidence for or against any abnormality of alpha2 adrenoreceptor function.

Normal somatomedin-C levels indicate that a chronic abnormality of GH axis activity, leading to abnormal feedback effects, was not a mechanism responsible for the blunting observed. In contrast, a significant association between GH levels and elevated anxiety symptoms, in those with anxiety disorders only, indicates that chronic or recurrent anxiety symptoms (or both) are probably associated with changes in either receptor function (“subsensitivity,” “downregulation”) or other functional characteristics of the GH control system involving relevant receptors.

Separate analyses of baseline data suggested that anxious patients, in addition to showing blunted GH clonidine responses, might also have had higher GH levels following intravenous catheter insertion and study initiation. Evidence for this was not robust; patients in the pure anxiety group did not show significantly elevated GH levels relative to their matched control subjects at any specific preclonidine time point. They did have the highest initial preclonidine GH levels, however, and showed declines in GH levels across the baseline period that were considerably steeper than seen in other groups. Patients in the predominant anxiety disorder group were the only ones who showed significantly greater declines across the baseline period than matched control subjects. Evidence from prior research demonstrates that GH is acutely responsive to stress (Abplanalp et al 1977; Brown and Heninger 1975; Kosten et al 1984; Noel et al 1976; Rose and Hurst 1975), and GH elevations have been observed in anxious individuals without drug administration. Anxiety patients might have had greater GH reactivity to study conditions (e.g., fear or novelty) than nonanxious patients. Consistent with the hypothesis that this GH elevation is circumstance-related, resting GH levels in panic disorder are not abnormal (Abelson et al 2005). Future research addressing this issue is needed before drawing firm conclusions. If such hyper-reactivity is present in anxiety patients, it might represent a phenomenon (noradrenergic or nonnoradrenergic) separate from whatever mechanism produces GH blunting, because there was no significant relationship between baseline GH levels and degree of blunting following clonidine.

The data showed a substantial gender effect on baseline GH levels, with women showing higher levels than men, both before and after clonidine. This finding supports the importance of always using control subjects matched for gender (and other relevant factors) in GH studies. Careful use of specifically matched control subjects and reliance on analyses that compared patients with their specific control group ensured that this gender effect could not influence any of the reported diagnosis-related effects.

One caveat in interpreting these results is the use of DSM-IV definitions of pure depression and pure anxiety. Milder, nonexclusionary symptoms of the other pure disorder might have been present in either or both pure diagnostic groups. Our results nonetheless indicate that the DSM-IV definitions used identified groups different in a physiologically meaningful way. Second is use of the categorization “predominant.” Although “principal Axis I diagnosis” is specified as a categorization by the SCID and



defined as the main focus of clinical attention or the reason for the clinical encounter, it is not commonly used in research studies. Thus, predominant, defined for this study as the disorder having greater negative impact as judged by both subject and investigators, has not yet been shown to be a reliable and valid rating; however, as with the first caveat, it did identify groups that differed in a meaningful way. Third, unlike some (but not all) prior studies, no placebo control subjects were used. Fourth, this study involved only one measure of brain noradrenergic activity. No conclusion can be made regarding the status of brain noradrenergic function other than that assessed by GH responses to the alpha2 adrenoreceptor agonist clonidine, mediated by GH-releasing hormone and somatostatin, and potentially involving other receptors and neurotransmitters (where the source of any identified functional abnormality might actually reside) in addition to this noradrenergic system (Frohman et al 1992; Reichlin 1989).

These results for panic disorder and social phobia are consistent with findings from prior studies demonstrating that the pathophysiology of several anxiety disorders within the DSM-IV diagnostic schema involve noradrenergic (and other) brain circuits controlling GH release, including alpha2 adrenoreceptors. Particularly, they support prior evidence for noradrenergic abnormalities in social phobia (Gelernter et al 2004; Stein et al 1992; Tancer et al 1993). Although the benefit of serotonergically active drugs in social phobia implies serotonin involvement (Fedoroff et al 2001; Van Ameringen et al 2003), they do not necessarily act at the primary site of physiologic dysfunction, and their effectiveness is not evidence against involvement of other systems. Further research is needed to determine which anxiety disorders demonstrate consistent evidence for noradrenergic dysfunction.

We hypothesized and observed that, with proper study design, major depression would not be associated with a blunted GH response; however, because many prior depression studies did report such blunting, this finding requires careful replication before full acceptance. Multiple factors in prior depression studies probably contributed to the blunting seen. GH elevation in anxiety disorders due to novelty or stress (or both) also requires replication.

Future research will need to determine mechanism(s) underlying GH blunting. This study did not find evidence for abnormalities in GH axis feedback status as reflected by somatomedin-C levels, GH blunting due to elevated preclonidine GH levels, or clonidine-related imidazoline receptor dysfunction. Diagnostically and situationally relevant symptoms (but not overall syndrome severity) were associated with blunting, even though separated on average by approximately a week, suggesting that anxiety symptoms in individuals with panic disorder or social phobia represent a correlate of tonic changes in noradrenergic function. Based on blunting in predominantly anxious comorbid individuals, but not in predominantly depressed, the anxious–depressive comorbid state might not be physiologically homogeneous. Potential involvement of brain trophic factors related to GH control, such as insulinlike growth factors I and II (Harel and Tannenbaum 1992; Schneider et al 2003), should be evaluated. Potential relationships of this noradrenergic system to other systems such as the hypothalamic–pituitary–adrenocortical system, which is known to be abnormal in depressive disorders (Amsterdam et al 1989a; Boyer 2000; Gold and Chrousos 2002; Kiraly et al 1997; Young et al 1994), in both healthy individuals and those individuals with these and other (including comorbid) disorders, also require investigation. Finally, the question of

whether the physiologic abnormality underlying GH blunting reflects an effect of anxiety, an associated dysfunction, or a cause must be addressed. Future studies can use GH clonidine responding, for example, to evaluate CNS noradrenergic tone, or as a method of physiologic differentiation of phenomenologically related syndromes such as in genetic studies.

*This work was supported by Grant No. MH57751 (all authors), MH01931 (EAY), and MO1 RR00042 (University of Michigan General Clinical Research Center). We thank Kathleen Singer R.N. and the staff of the General Clinical Research Center at the University of Michigan Medical Center for their assistance in completing this research.*

- Abelson JL, Curtis GC, Uhde TW (2005): Twenty-four hour growth hormone secretion in patients with panic disorder. *Psychoneuroendocrinology* 30:72–79.
- Abelson JL, Glitz D, Cameron OG, Lee MA, Bronzo M, Curtis GC (1991): Blunted growth hormone response to clonidine in patients with generalized anxiety disorder. *Arch Gen Psychiatry* 48:157–162.
- Abelson JL, Glitz D, Cameron OG, Lee MA, Bronzo M, Curtis GC (1992): Endocrine, cardiovascular and behavioral responses to clonidine in patients with panic disorder. *Biol Psychiatry* 32:18–25.
- Abplanalp JM, Livingston L, Rose RM, Sandwisch D (1977): Cortisol and growth hormone responses to psychological stress during the menstrual cycle. *Psychosom Med* 39:158–177.
- Altomonte L, Zoli A, Mirone L, Berchicci M, Travaglini R, Pellicano P, Greco AV (1988): Impaired growth hormone response to clonidine in obesity. *Exper Clin Endocrinol* 92:231–234.
- Amsterdam JD, Maislin G (1990): Comparison of growth hormone response after clonidine and insulin hypoglycemia in affective illness. *Biol Psychiatry* 28:308–314.
- Amsterdam JD, Maislin G, Gold P, Winokur A (1989a): The assessment of abnormalities in hormonal responsiveness at multiple levels of the hypothalamic–pituitary–adrenocortical axis in depressive illness. *Psychoneuroendocrinology* 14:43–62.
- Amsterdam JD, Maislin G, Skolnick B, Berwisch N, Winokur A (1989b): Multiple hormone responses to clonidine administration in depressed patients and healthy volunteers. *Biol Psychiatry* 26:265–278.
- Anseau M, Von Frenckell R, Cerfontaine JL, Papart P, Franck G, Timsit-Berthier M, et al (1988): Blunted response of growth hormone to clonidine and apomorphine in endogenous depression. *Br J Psychiatry* 153:65–71.
- Aston-Jones G, Rajkowski J, Cohen J (1999): Role of locus coeruleus in attention and behavioral flexibility. *Biol Psychiatry* 46:1309–1320.
- Ballidin J, Berggren U, Eriksson E, Lindstedt G, Sundkler A (1993): Guanfacine as an alpha-2-agonist inducer of growth hormone secretion—a comparison with clonidine. *Psychoneuroendocrinology* 18:45–55.
- Balon R, Yeragani VK, Pohl R, Muench J, Berchou R (1990): Somatic and psychological symptoms during isoproterenol-induced panic attacks. *Psychiatry Res* 32:103–112.
- Bamberger CM, Monig H, Mill G, Godde E, Schulte HM (1995): Growth hormone secretion in response to a new centrally acting antihypertensive agent moxonidine in normal human subjects: Comparison to clonidine. *Exper Clin Endocrinol Diab* 103:205–208.
- Barbee JG (1998): Mixed symptoms and syndromes of anxiety and depression: Diagnostic, prognostic and etiologic issues. *Ann Clin Psychiatry* 10:15–29.
- Bousquet P, Dontenwill M, Greney H, Feldman J (1998): I1-imidazoline receptors: An update. *J Hypertension* 16(suppl):S1–S5.
- Boyer P (2000): Do anxiety and depression have a common pathophysiological mechanism? *Acta Psychiatr Scand* 406(suppl):24–29.
- Brambilla F, Perna G, Garberi A, Nobile P, Bellodi L (1995): Alpha 2-adrenergic receptor sensitivity in panic disorder: I GH responses to GHRH and clonidine stimulation in panic disorder. *Psychoneuroendocrinology* 20:1–9.
- Bremner JD, Krystal JH, Southwick SM, Charney DS (1996): Noradrenergic mechanisms in stress and anxiety: I Preclinical studies. *Synapse* 23:28–38.

- Brown WA, Heninger G (1975): Cortisol, growth hormone, free fatty acids and experimentally evoked affective arousal. *Am J Psychiatry* 132:1172–1176.
- Cameron OG (1994): The symptoms of adrenergic activation. In: Cameron OG, editor. *Adrenergic Dysfunction and Psychobiology*. Washington, DC: American Psychiatric Press 237–255.
- Cameron OG, Lee MA, Curtis G, McCann DS (1987): Endocrine and physiological changes during “spontaneous” panic attacks. *Psychoneuroendocrinology* 12:321–331.
- Cameron OG, Minoshima S (2002): Regional brain activation due to pharmacologically induced adrenergic interoceptive stimulation in humans. *Psychosom Med* 64:851–861.
- Cameron OG, Nesse RM (1988): Systemic hormonal and physiological abnormalities in anxiety disorders. *Psychoneuroendocrinology* 13:287–307.
- Cameron OG, Zubietta JK, Grunhaus L, Minoshima S (2000): Effects of yohimbine on cerebral blood flow, symptoms and physiological functions in humans. *Psychosom Med* 62:549–559.
- Charney DS, Heninger GR, Breier A (1984): Noradrenergic function in panic anxiety. Effects of yohimbine in healthy subjects and patients with agoraphobia and panic disorder. *Arch Gen Psychiatry* 41:751–763.
- Charney DS, Heninger GR, Sternberg DE (1982a): Failure of chronic antidepressant treatment to alter growth hormone response to clonidine. *Psychiatry Res* 7:135–138.
- Charney DS, Heninger GR, Sternberg DE, Hafstad KM, Giddings S, Landis DH (1982b): Adrenergic receptor sensitivity in depression. Effects of clonidine in depressed patients and healthy subjects. *Arch Gen Psychiatry* 39:290–294.
- Charney DS, Woods SW, Krystal JH, Nagy LM, Heninger GR (1992): Noradrenergic neuronal dysregulation in panic disorder: The effects of intravenous yohimbine and clonidine in panic disorder patients. *Acta Psychiatr Scand* 86:273–282.
- Checkley SA, Glass IB, Thompson C, Corn T, Robinson P (1984): The GH response to clonidine in endogenous as compared with reactive depression. *Psychol Med* 14:773–777.
- Checkley SA, Slade AP, Shur E (1981): Growth hormone and other responses to clonidine in patients with endogenous depression. *Br J Psychiatry* 138:51–55.
- Coplan JD, Papp LA, Martinez J, Pine D, Rosenblum LA, Cooper T, et al (1995): Persistence of blunted human growth hormone response to clonidine in fluoxetine-treated patients with panic disorder. *Am J Psychiatry* 152:619–622.
- Correa H, Duval F, Claude MM, Bailey P, Trembeau F, Diep TS, et al (2001): Noradrenergic dysfunction and antidepressant treatment response. *Eur Neuropsychopharmacol* 11:163–168.
- Curtis GC, Nesse R, Buxton M, Lippman D (1979): Plasma growth hormone: Effect of anxiety during flooding in vivo. *Am J Psychiatry* 136:410–414.
- Fedoroff IC, Taylor S (2001): Psychological and pharmacological treatments of social phobia: A meta-analysis. *J Clin Psychopharmacol* 21:311–324.
- Fornai F, Blandizzi C, del Tacca M (1990): Central alpha-2 adrenoceptors regulate central and peripheral functions. *Pharmacol Res* 22:541–554.
- Frohman LA, Downs TR, Chomczynski P (1992): Regulation of growth hormone secretion. *Front Neuroendocrinol* 13:344–405.
- Fu CH, Reed LJ, Meyer JH, Kennedy S, Houle S, Eisfeld BS, Brown GM (2001): Noradrenergic dysfunction in the prefrontal cortex in depression: An [<sup>15</sup>O]H<sub>2</sub>O PET study of the neuromodulatory effects of clonidine. *Biol Psychiatry* 49:317–325.
- Gann H, Riemann D, Stoll S, Berger M, Muller WE (1995): Growth hormone response to growth hormone-releasing hormone and clonidine in depression. *Biol Psychiatry* 38:325–329.
- Gelernter J, Page GP, Stein MB, Woods SW (2004): Genome-wide linkage scan for loci predisposing to social phobia: Evidence for a chromosome 16 risk linkage. *Am J Psychiatry* 161:59–66.
- Gil-Ad I, Gurewitz R, Marcovici O, Rosenfeld J, Laron Z (1984): Effect of aging on human plasma growth hormone response to clonidine. *Mech Ageing Dev* 27:97–100.
- Gold PW, Chrousos GP (2002): Organization of the stress system and its dysregulation in melancholic and atypical depression: High versus low CRH/NE states. *Molec Psychiatry* 7:254–275.
- Gurguis GN, Vitton BJ, Uhde TW (1997): Behavioral, sympathetic and adrenocortical responses to yohimbine in panic disorder patients and normal controls. *Psychiatry Res* 71:27–39.
- Harel Z, Tannenbaum GS (1992): Synergistic interactions between insulin-like growth factors-I and -II in central regulation of pulsatile growth hormone secretion. *Endocrinology* 131:758–764.
- Hasey GM, Stancer HC, Warsh JJ, Persad E (1985): Neurotransmitter metabolites and endocrine responses in depression. *Prog Neuropsychopharmacol Biol Psychiatry* 9:613–617.
- Hollander E, DeCaria C, Nitsescu A, Cooper T, Stover B, Gully R, et al (1991): Noradrenergic function in obsessive-compulsive disorder: Behavioral and neuroendocrine responses to clonidine and comparison to health controls. *Psychiatry Res* 37:161–177.
- Horton RW, Katona CL, Theodorou AE, Hale AS, Davies SL, Tunnicliffe C, et al (1986): Platelet radioligand and neuroendocrine challenge tests in depression. *Ciba Found Symp* 123:84–105.
- Johnson MR, Lydiard RB (1995): The neurobiology of anxiety disorders. *Psychiatr Clin North Am* 18:681–725.
- Katona CL, Healy D, Paykel ES, Theodorou AE, Lawrence KM, Whitehouse A, et al (1993): Growth hormone and physiological responses to clonidine in depression. *Psychol Med* 23:57–63.
- Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eschleman S, et al (1994): Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. *Arch Gen Psychiatry* 51:8–19.
- Kessler RC, Stang P, Wittchen HU, Stein M, Walters EE (1999): Lifetime comorbidities between social phobia and mood disorders in the US national comorbidity survey. *Psychol Med* 29:555–567.
- Kessler RC, Stang PE, Wittchen HU, Ustun TB, Roy-Byrne PP, Walters EE (1998): Lifetime panic-depression comorbidity in the national comorbidity survey. *Arch Gen Psychiatry* 55:801–808.
- Kimber J, Sivenandran M, Watson L, Mathias CJ (2001): Age- and gender-related growth hormone responses to intravenous clonidine in healthy adults. *Growth Horm IGF Res* 11:128–135.
- Kiraly SJ, Ancill RJ, Dimitrova G (1997): The relationship of endogenous cortisol to psychiatric disorder: A review. *Can J Psychiatry* 42:415–420.
- Kirschbaum C, Pirke KM, Hellhammer DH (1993): The “Trier Social Stress Test”—a tool for investigating psychobiological stress responses in a laboratory setting. *Neuropsychobiology* 28:76–81.
- Koob GF (1999): Corticotropin-releasing factor, norepinephrine and stress. *Biol Psychiatry* 46:1167–1180.
- Kosten TR, Jacobs S, Mason J, Wahby V, Atkins S (1984): Psychological correlates of growth hormone response to stress. *Psychosom Med* 46:49–58.
- Lader M (1988): Beta-adrenoceptor antagonists in neuropsychiatry: An update. *J Clin Psychiatry* 49:213–223.
- Lee MA, Cameron OG, Gurguis GN, Glitz D, Smith CB, Hariharan M, et al (1990): Alpha 2-adrenoreceptor status in obsessive-compulsive disorder. *Biol Psychiatry* 27:1083–1093.
- Lydiard RB (1991): Coexisting depression and anxiety: Special diagnostic and treatment issues. *J Clin Psychiatry* 52(suppl):48–54.
- Matussek N, Ackenheil M, Hippus H, Muller F, Schroder HT, Schultes H (1980): Effect of clonidine on growth hormone release in psychiatric patients and controls. *Psychiatry Res* 2:25–36.
- Matussek N, Laakmann G (1981): Growth hormone response in patients with depression. *Acta Psychiatr Scand* 290(suppl):122–126.
- Mendlewicz J, Linkowski P, Kerkhofs M, Desmedt D, Golstein J, Copinschi G, Van Cauter E (1985): Diurnal hypersecretion of growth hormone in depression. *J Clin Endocrinol Metab* 60:505–512.
- Mitchell P, Smythe G, Parker G, Wilhelm K, Brodaty H, Hickie I (1991): Growth hormone and other hormonal responses to clonidine in melancholic and nonmelancholic depressed subjects and controls. *Psychiatry Res* 37:179–193.
- Mitchell PB, Beam JA, Corn TH, Checkley SA (1988): Growth hormone response to clonidine after recovery in patients with endogenous depression. *Br J Psychiatry* 152:34–38.
- Morris P, Hopwood M, Maguire K, Norman T, Schweitzer I (2004): Blunted growth hormone response to clonidine in post-traumatic stress disorder. *Psychoneuroendocrinology* 29:269–278.
- Nesse RM, Cameron OG, Curtis GC, McCann DS, Huber-Smith MJ (1984): Adrenergic function in patients with panic anxiety. *Arch Gen Psychiatry* 41:771–776.
- Noel GL, Dimond RC, Earll JM, Frantz AG (1976): Prolactin, thyrotropin and growth hormone release during stress associated with parachute jumping. *Aviat Space Environ Med* 47:543–547.
- Piletz JE, Halaris A, Nelson J, Qu Y, Bari M (1996): Platelet I1-imidazoline binding sites are elevated in depression but not generalized anxiety. *J Psychiatr Res* 30:147–168.



- Regunathan S, Reis DJ (1996): Imidazoline receptors and their endogenous ligands. *Annu Rev Pharmacol Toxicol* 36:511–544.
- Reichlin S (1989): Neuroendocrinology of the pituitary gland. *Toxicol Path* 17:250–255.
- Ressler KJ, Nemeroff CB (2000): Role of serotonergic and noradrenergic systems in the pathophysiology of depression and anxiety disorders. *Depr Anx* 12(suppl 1): 2–19.
- Robbins TW (1984): Cortical noradrenaline, attention and arousal. *Psychol Med* 14:13–21.
- Rose RM, Hurst MW (1975): Plasma cortisol and growth hormone responses to intravenous catheterization. *J Human Stress* 1:22–36.
- Roy-Byrne PP, Stang P, Wittchen HU, Ustun B, Walters EE, Kessler RC (2000): Lifetime panic-depression comorbidity in the national comorbidity survey. Associations with symptoms, impairment, course and help-seeking. *Br J Psychiatry* 176:229–235.
- Schafer SG, Kaan EC, Christen MO, Low-Kroger A, Mest HJ, Molderings GJ (1995): Why imidazoline receptor modulator in the treatment of hypertension? *Ann N Y Acad Sci* 763:659–672.
- Schittecatte M, Anseau M, Charles G, Machowski R, Papart P, Pichot W, Wilmotte J (1992): Growth hormone response to clonidine in male patients with panic disorder untreated by antidepressants. *Psychol Med* 22:1059–1062.
- Schittecatte M, Charles G, Machowski R, Wilmotte J (1989): Tricyclic wash-out and growth hormone response to clonidine. *Br J Psychiatry* 154:858–863.
- Schneider HJ, Pagatto U, Stalla GK (2003): Central effects of the somatotropic system. *Europ J Endocrinol* 149:377–392.
- Shear MK (1986): Pathophysiology of panic: A review of pharmacologic provocative tests and naturalistic monitoring data. *J Clin Psychiatry* 47(suppl):18–26.
- Siever LJ, Insel TR, Jimerson DC, Lake CR, Uhde TW, Aloï J, Murphy DL (1983): Growth hormone response to clonidine in obsessive-compulsive disorder. *Br J Psychiatry* 142:184–187.
- Siever LJ, Insel T, Uhde T (1981): Noradrenergic challenges in the affective disorders. *J Clin Psychopharmacol* 1:193–206.
- Siever LJ, Trestman RL, Coccaro EF, Bernstein D, Gabriel SM, Owen K, et al (1992): The growth hormone response to clonidine in acute and remitted depressed male patients. *Neuropsychopharmacology* 6:165–177.
- Siever LJ, Uhde TW (1984): New studies and perspectives on the noradrenergic receptor system in depression: Effects of the alpha 2-adrenergic agonist clonidine. *Biol Psychiatry* 19:131–156.
- Stanford SC (1995): Central noradrenergic neurons and stress. *Pharmacol Therap* 68:297–342.
- Stein MB, Tancer ME, Uhde TW (1992): Heart rate and plasma norepinephrine responsivity to orthostatic challenge in anxiety disorders. Comparison of patients with panic disorder and social phobia and normal control subjects. *Arch Gen Psychiatry* 49:311–317.
- Sullivan GM, Coplan JD, Kent JM, Gorman (1999): The noradrenergic system in pathological anxiety: A focus on panic with relevance to generalized anxiety and phobias. *Biol Psychiatry* 46:1205–1218.
- Tanaka M, Yoshida M, Emoto H, Ishii H (2000): Noradrenaline systems in the hypothalamus, amygdala and locus coeruleus are involved in the provocation of anxiety: Basic studies [review]. *Eur J Pharmacol* 405:397–406.
- Tancer ME, Mailman RB, Stein MB, Mason GA, Carson SW, Golden RN (1994–95): Neuroendocrine responsivity to monoaminergic system probes in generalized social phobia. *Anxiety* 1:16–23.
- Tancer ME, Stein MB, Uhde TW (1990): Growth hormone (GH) response to clonidine and growth-hormone releasing factor (GRF) in normal controls. *Psychoneuroendocrinology* 15:253–259.
- Tancer ME, Stein MB, Uhde TW (1993): Growth hormone response to intravenous clonidine in social phobia: Comparison to patients with panic disorder and healthy volunteers. *Biol Psychiatry* 34:591–595.
- Tyrer P (1988): Current status of beta-blocking drugs in the treatment of anxiety disorders. *Drugs* 36:773–783.
- Van Ameringen M, Allgulander C, Bandelow B, Greist JH, Hollander E, Montgomery SA, et al (2003): WCA recommendations for the long-term treatment of social phobia. *CNS Spectr* 8(8 suppl): 40–52.
- Woods SW, Charney DS, McPherson CA, Gradman AH, Heninger GR (1987): Situational panic attacks. Behavioral, physiologic and biochemical characterization. *Arch Gen Psychiatry* 44:365–375.
- Young EA, Abelson JL, Cameron OG (2004): Effect of comorbid anxiety disorders on the hypothalamic-pituitary-adrenal axis response to a social stressor in major depression. *Biol Psychiatry* 56:113–120.
- Young EA, Haskett RF, Grunhaus L, Pande A, Weinberg VM, Watson SJ, Akil H (1994): Increased evening activation of the hypothalamic-pituitary-adrenal axis in depressed patients. *Arch Gen Psychiatry* 51:701–707.