Endocrine, *vol. 21, no. 3, 267–272, August 2003* 0969–711X/03/21:267–272/$25.00

Longitudinal Changes in Pituitary-Adrenal Hormones in South African Women With Burnout

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The authors' goal was to document baseline pituitary-adrenal hormonal and related metabolic variables in 16 female patients with burnout. Then, following stress management intervention, to compare the changes with an equal number of untreated control subjects. At monthly intervals for 4 mo, 24-h urine samples were obtained for determination of free cortisol excretion. In addition, fasting blood samples were analyzed for levels of cortisol, dehydroepiandrosterone sulfate (DHEA-S), ACTH, aldosterone, and catecholamines. Other biochemical measurements included growth hormone, prolactin, insulin, glucose, and lipid components. The Maslach Burnout Inventory, General Health Questionnaire-28, and Zung depression rating scale were completed on each consecutive visit. The most striking finding was the reduction of urine free-cortisol excretion in the patients compared with controls. Initial urinary free cortisol was significantly lower in the patients (mean ± SEM = 47.2 ± 11.0 vs 79.0 ± 6.8 nmol/L, p = 0.02) and remained significantly reduced at 4 mo (mean ± SEM = 44.0 ± 6.1 vs 91.1 ± 8.8 nmol/L, p = 0.0001). There were no significant changes in the other hormonal and biochemical data. We conclude that there is functional hypocortisolism in burnout, which is not immediately restored on stress management intervention despite clinical and psychological improvement.

Key Words: Burnout; HPA axis; cortisol; ACTH; rating scales, depression.

Introduction

Burnout has been defined as a syndrome in which depletion of emotional, cognitive, and physical energy results in symptoms *(1)*:

1. Emotional depletion leads to emotional exhaustion, tearfulness, apathy, perceived meaninglessness, and detachment from work.
2. Cognitive depletion is evidenced by reduced attention span and a reduction in professional efficacy.
3. Depletion of physical functioning includes overwhelming fatigue (with concomitant insomnia), headaches, and nonspecific pain.

It can be measured using the Maslach Burnout Inventory (MBI) in which high levels of emotional exhaustion and depersonalization, coupled with low levels of personal accomplishment, are indicative of burnout *(2)*.

The etiology of the syndrome was originally linked with the unremitting emotional stress experienced by social service providers and caregiving professionals *(3)*. However, it is now recognized that all workers are exposed to job and life stressors that may precipitate the phenomenon *(4)*. Additional predictors of burnout include lack of decision-making involvement at work, deficient coping skills, and poor social support *(5)*.

Since Selye's *(6)* pioneering work on stress in the 1930s, the association between stress and increased cortisol secretion has been used as a model to explain the development of disease as a result of dysregulation in the homeostatic responses of the body's stress system *(7)*. While activation of the hypothalamic–pituitary–adrenal (HPA) axis and the resultant increase in the secretion of cortisol from the adrenal cortex is considered a normal response to stress, the allostatic load incurred during prolonged or excessive HPA axis activation may lead to illness *(8)*. An example of this is the melancholia subtype of major depressive disorder , where the stress response appears hyperactive and patients commonly experience dysphoric arousal with symptoms such as anxiety, insomnia, and decreased appetite *(9)*.

In direct contrast to this model, however, a number of studies have now provided convincing evidence that the adrenal cortex is hypoactive in some stress-related states *(10)*. This phenomenon, termed "functional hypocortisolism" *(11)*, has mainly been applied to patients who experienced a traumatic event and subsequently developed post-traumatic stress disorder *(12)*. However, hypocortisolism has also been reported in patients with chronic fatigue syndrome

Received March 20, 2003; Revised May 22, 2003; Accepted June 11, 2003.
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Table 1
Fasting 8.00 AM Serum Concentrations of Pituitary and Adrenal Hormones
Before and During 4 mo of Therapy for Stress Burnout in Patients, and Untreated Control Subjects (Mean ± SEM)

	Patients					Control Subjects	
	Baseline	1 mo	2 mo	3 mo	4 mo	Baseline	4 mo
Number of Subjects	16	16	16	16	16	16	16
Growth hormone (mIU/L)	3.7 ± 2.1	6.1 ± 1.8	4.5 ± 1.4	5.0 ± 1.2	8.7 ± 2.2	7.7 ± 2.3	8.7 ± 2.9
Prolactin (µg/L)	8.1 ± 1.9	7.7 ± 1.6	7.2 ± 1.4	8.0 ± 1.3	8.9 ± 2.5	8.6 ± 1.1	8.8 ± 1.3
ACTH (pmol/L)	40.0 ± 10.0	36.6 ± 8.4	44.9 ± 14.5	22.2 ± 2.7	42.6 ± 9.3	71.0 ± 14.7	40.8 ± 7.1[a]
Urine free cortisol (nmol/24hr)	47.2 ± 11[b]	45.8 ± 5.4	49.9 ± 6.7	48.4 ± 7.0	44.0 ± 6.1[c]	79.0 ± 6.8	91.1 ± 8.8
Cortisol (nmol/L)	621 ± 92	686 ± 102	790 ± 135	658 ± 125	524 ± 71[d]	894 ± 129	1031 ± 122
DHEA-S (µmol/L)	2.6 ± 0.4	2.7 ± 0.5	2.6 ± 0.5	2.6 ± 0.5	2.8 ± 0.6	2.0 ± 0.3	2.0 ± 0.3
Aldosterone (pmol/L)	277 ± 45	311 ± 60	373 ± 112	265 ± 46	406 ± 80	345 ± 46	358 ± 69

[a] Significance of values in the control group at baseline compared with four months: $p = 0.01$.
[b] Significance of values in the patient group compared with control subjects at baseline: $p = 0.02$.
[c] Significance of values in the patient group compared with control subjects at four months: $p = 0.002$.
[d] Significance of values in the patient group compared with control subjects at four months: $p = 0.001$.

Table 2
Fasting Serum Biochemical Concentrations
Before and During 4 mo of Therapy for Stress Burnout in Patients, and Untreated Control Subjects (Mean ± SEM)

	Patients					Control Subjects	
	Baseline	1 mo	2 mo	3 mo	4 mo	Baseline	4 mo
Number of Subjects	16	16	16	16	16	16	16
Glucose (mmol/L)	4.8 ± 0.1	5.0 ± 0.1	4.9 ± 0.1	4.7 ± 0.1	4.6 ± 0.2	4.8 ± 0.2	5.0 ± 0.2
Insulin (mIU/L)	8.3 ± 1.3	10.1 ± 1.9	9.5 ± 1.5	10.4 ± 1.2	9.0 ± 1.2	7.3 ± 0.8	8.0 ± 1.2
Free fatty acids (mmol/L)	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.6 ± 0.1	0.5 ± 0.1
Total cholesterol (mmol/L)	4.6 ± 0.3	4.7 ± 0.2	4.9 ± 0.3	4.8 ± 0.2	4.7 ± 0.3	4.9 ± 0.2	5.1 ± 0.2
HDL-cholesterol (mmol/L)	1.4 ± 0.1	1.5 ± 0.1	1.5 ± 0.1	1.5 ± 0.1	1.5 ± 0.1	1.6 ± 0.1	1.6 ± 0.1
LDL-cholesterol (mmol/L)	2.8 ± 0.2	2.7 ± 0.2	3.0 ± 0.3	2.8 ± 0.2	2.7 ± 0.2	2.8 ± 0.2	3.0 ± 0.2
Triglycerides (mmol/L)	1.0 ± 0.1	1.0 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	1.1 ± 0.1

(13), fibromyalgia *(14),* rheumatoid arthritis *(15),* asthma *(16)*, and atypical depression *(17).* The pathophysiology of many of these disorders has been related to stress, with fatigue being a central component of the symptomatology.

Because fatigue is a key symptom of burnout, and this symptom is shared by other syndromes in which hypocortisolism is a feature, this study was undertaken to determine if a similar biochemical status exists in burnout patients and to assess the longitudinal changes during a treatment period of 4 mo.

Results

Pituitary and Adrenal Hormones (Table 1)

Compared with control subjects, mean urine free-cortisol levels in the patients were significantly lower both at baseline ($p = 0.02$) and at 4 mo ($p = 0.0001$), consistently below the lower level of the normal adult range. However, the mean serum cortisol level in patients was significantly lower than controls only at 4 mo ($p = 0.001$). Apart from significant elevation of serum adrenocorticotrophic hormone (ACTH) at baseline in control subjects as compared with 4 mo ($p = 0.01$), and raised serum growth hormone (GH) at baseline in controls compared with patients (p = NS), all the other mean fasting serum concentrations of pituitary and adrenal hormones measured before and during 4 mo of therapy were similar.

Biochemical Data (Table 2) and BMI

There were also no statistically significant differences in mean fasting serum concentrations before and during 4 mo of therapy, in patients versus control subjects for glucose,

Table 3
Fasting Plasma Concentrations of Catecholamines
Before and During 4 mo of Therapy for Stress Burnout in Patients, and Untreated Control Subjects (Median and Range)

	Patients					Control Subjects	
	Baseline	1 mo	2 mo	3 mo	4 mo	Baseline	4 mo
Number of Subjects	16	16	16	16	16	16	16
Epinephrine (pmol/L)	222 (49–4036)	563 (42–6361)	334 (76–4431)	206 (10–3144)	151 (14–2211)	206 (15–1672)	114 (0–454)
Norepinephrine (pmol/L)	1271 (395–5436)[a]	1570 (244–4960)	1442 (87–7203)	1816 (619–3325)	2313 (699–7538)	2338 (452–3974)	2704 (1351-4337)

[a]Significance of values in the patient group compared with control subjects at baseline: $p = 0.03$.

insulin, free fatty acids (FFA), total cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol, and triglycerides . In addition, there was no significant difference in mean body mass index (BMI) between patients and controls at baseline (mean ± SEM = 23.9 ± 0.9 vs 24.8 ± 0.9 kg/m^2, p = NS) and at 4 mo (mean ± SEM = 23.3 ± 0.8 vs 24.6 ± 0.8 kg/m^2, p = NS).

Catecholamines (Table 3)

There were no differences in median levels of plasma epinephrine between patients and controls. The median plasma norepinephrine level at baseline, however, was significantly higher in the control group than in the patients ($p = 0.03$).

Clinical Ratings

A composite graph showing a similar trend for the results of the clinical ratings is shown (Fig. 1). Because emotional exhaustion is regarded as the most stable burnout dimension of the MBI *(18),* only this subscale of the MBI was graphically depicted.

Regarding the MBI, mean scores of emotional exhaustion declined significantly over the 4 mo ($p < 0.0001$) as compared with baseline measurements. There were significant differences between patients and controls at baseline in emotional exhaustion ($p < 0.0001$), depersonalization ($p = 0.001$), and personal accomplishment ($p = 0.0001$). Patients varied significantly from controls at four mo in their scores of emotional exhaustion ($p = 0.001$) and depersonalization ($p = 0.03$).

For the General Health Questionnaire (GHQ28), patients' scores declined over the 4 mo significantly from baseline measurements ($p < 0.0001$). There was a significant difference between patients and controls at baseline ($p < 0.0001$) and at 4 mo ($p < 0.01$).

The Zung depression rating scale (ZDRS) also showed a declining trend, with patients scoring significantly higher at baseline than in the subsequent 4 mo ($p < 0.0001$). In comparison with controls, patients' scores were significantly different at baseline ($p < 0.0001$) and at 4 mo ($p = 0.0002$).

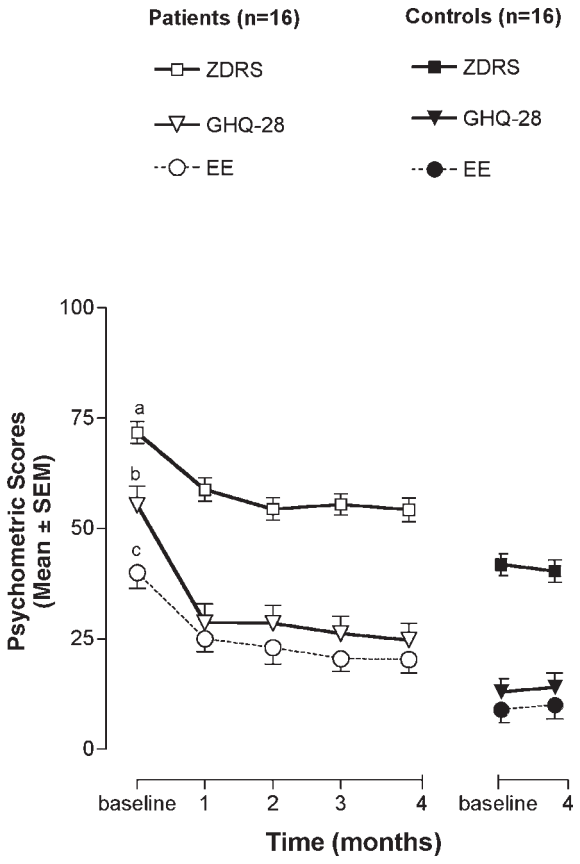

Fig. 1. Mean Zung depression rating scale (ZDRS), General Health Questionnaire-28 (GHQ-28), and Maslach Burnout Inventory Emotional Exhaustion scores in patients and control subjects at baseline and 4 mo. Vertical bars show SEM. [a]Significant difference in ZDRS scores for patients between baseline and 1, 2, 3, and 4 mo ($p < 0.0001$) and for patients vs controls at baseline ($p < 0.0001$) and at 4 mo ($p = 0.0002$). [b]Significant difference in GHQ-28 scores for patients at baseline and 1, 2, 3, and 4 mo ($p < 0.0001$) and for patients vs controls at baseline ($p < 0.0001$) and at 4 mo ($p < 0.01$). [c]Significant difference in emotional exhaustion scores for patients at baseline and 1, 2, 3, and 4 mo ($p < 0.0001$) and for patients vs controls at baseline ($p < 0.0001$) and at 4 mo ($p = 0.001$).

Discussion

Pituitary Adrenal Function

In this investigation, the most consistent endocrine finding was a reduction of urine free-cortisol excretion in the patient group, suggesting a situation of functional hypoadrenalism in burnout. No significant recovery of cortisol excretion occurred during the study, implying an increased predisposition to future burnout episodes.

The normal 0800 h serum cortisol levels in patients in the face of low urinary cortisol excretion is difficult to explain. Because all the patients had normal creatinine clearance, it is improbable that impaired renal function influenced cortisol excretion. We concur with Crofford et al. *(14)* who postulate that in fibromyalgia the low 24-h levels may reflect reduced cortisol pulsatility during the 24-h period, with preservation of the early morning peak.

Serum levels of ACTH above the normal range in the patients cast doubt as to the central origin of the functional hypoadrenalism. However, as patients were not subjected to dexamethasone suppression of cortisol, ACTH challenge testing with corticotropin-releasing-hormone (CRH) stimulation, or insulin-induced hypoglycemia, the functional integrity of the HPA pathway in burnout remains uncertain and warrants further study.

In addition, although control subjects rested for 30 min prior to blood sampling, mean ACTH (and norepinephrine) levels also exceeded normal ranges.This may reflect a stress response to the needle-stick, or could highlight high "background" levels of stress in this group. In the South African context, chronic, unavoidable stress factors include the high incidence of violent crime and trauma *(19)* and the impact of AIDS, both socially and economically on the developing population *(20).* Despite these biochemical anomalies, the controls showed no burnout symptoms.

Our findings resemble the reduced adrenocortical hormonal secretion that has been documented for other stress-related illnesses, e.g., post-traumatic stress disorder (PTSD) *(12),* chronic fatigue syndrome *(13),* and fibromyalgia *(14).* Hypocortisolism may be a relevant factor in the pathogenesis of all these disorders, since the lack of cortisol availability may cause symptoms common to these conditions: vulnerability to autoimmune disorders, inflammation, chronic pain, asthma, and allergies *(21).*

Potential Effect of Drug Therapy

The putative action of chronic psychotropic medication on the HPA axis is inhibitory, probably by suppression of hypothalamic CRH and/or arginine vasopressin release *(22).* Despite these central inhibitory effects, in studies on alprazolam, citalopram, and imipramine (a tricyclic antidepressant similar to dothiepin), treatment did not affect basal plasma ACTH and cortisol levels, nor did it influence urinary free cortisol excretion *(22–24).*

Link Between Burnout and Depression

The possible link between burnout and depression deserves comment. All patients enrolled in the study were assessed to be depressed at baseline (according to the ZDRS). According to Arana, up to 45% of depressives exhibit HPA axis hyperarousal *(25).* Gold and Chrousos *(26)* recently reviewed HPA axis functioning in two diagnostic subtypes of depression and clarify that the biochemical "signature" of melancholic depression is typified by hyperactivity of the HPA axis, with increased CRH, ACTH, and cortisol secretion, and decreased sensitivity of the negative feedback system. In contrast, neuroendocrinologic features of atypical depression highlight underactivity of the HPA axis (with decreased CRH, ACTH, and cortisol secretion and a supersensitized negative feedback system) *(22).* Symptomatically, patients with atypical depression present with the antithesis of melancholia: they are lethargic, hypersomnic, and hyperphagic. In burnout patients we found high ACTH levels but low cortisol secretion, which may reflect an "alternate or mixed" type of depression—which is also distinct both symptomatically and biochemically from PTSD.

Study Limitations

Certain limitations of our study should be noted: The relatively small number of patients and controls involved, the lack of 24-h plasma cortisol profiling, and the restricted period of follow-up observations. Notwithstanding these limitations, after undergoing an integrated stress management program, patient recovery was significant over the 4-mo period when charted on the MBI, the GHQ28, and the ZDRS. Interestingly, during this period, the decrease in emotional exhaustion, psychiatric symptoms and depression was not accompanied by a corresponding rise in urine free-cortisol levels. This suggests that clinical improvement following stress management measures precedes any accompanying change in biochemical measurements.

In Conclusion

Because responses to chronic stress and its management are multifactorial and dependent on varied aspects, e.g. genetic vulnerability, coping skills, intrinsic personality, and previous exposure to stress, interindividual variability in biochemical responses is to be expected *(8).* In highlighting hypocortisolism as a feature of burnout, this study indicates possible therapeutic strategies for treatment-resistant patients. For example, low-dose cortisol supplementation could be considered as an interim measure, as is the case in patients with chronic fatigue syndrome *(27).*

In view of the intense interest currently being focused on the functioning of the HPA axis following acute and chronic stress after recent tragic international catastrophes *(28),* our findings provide insight into the hormonal changes associated with burnout.

Patients and Methods

Patients

Sixteen female patients (mean age ± SEM = 38.1 ± 2.9 yr; range 25–59 yr) were enrolled in a multipoint study; two patients were postmenopausal. On initial clinical and psychological assessment they were diagnosed by a psychiatrist (J.D.M.) as suffering from stress burnout. This diagnosis was based on a standardized clinical examination in addition to a series of psychometric rating scales and symptom checklists *(29).* These included the MBI, the GHQ-28, and the ZDRS. Patients with any psychiatric diagnosis other than major depression or subsyndromal depression were excluded from the study. All patients were biochemically euthyroid. Sixteen age-matched women (mean age ± SEM = 37.3 ± 2.9 yr; range 19–58 yr) were recruited as control subjects; three control subjects were postmenopausal. In order for comparisons to reflect meaningful differences, the control population was drawn from the working hospital environment. In this way, the stress experienced by the controls paralleled the stresses of daily living in both the working and greater environment, but they had not developed any burnout symptoms. Patients and control subjects gave written, informed consent to participate in the study, which was approved by the Ethics Committee For Research On Human Subjects (Medical) of the University of the Witwatersrand.

Study Protocol

Study participants began a 24-h urine collection at home at 0800 h the day prior to their blood collection, and fasted from 2200 h that night. At 0800 h on the morning of the study, subjects reported to the Centre for Stress-Related Illnesses, Milpark Hospital, where the clinical studies were conducted. Subjects were seated in comfortable chairs and a 21-gauge catheter was inserted into an antecubital vein of one arm. This experimental procedure was performed at the start of the study, after which patients began treatment, and was repeated at monthly intervals for four further consecutive visits. For the control subjects, the same protocol was followed on two occasions, at baseline and at 4 mo. Measurements of height and weight were recorded at baseline and 4 mo for both patients and controls, and BMI was calculated.

Clinical Ratings

At each visit according to the above protocol, patients and controls completed the MBI, GHQ-28, and ZDRS. The MBI comprises three subscales, which measure the three main components of burnout: emotional exhaustion, depersonalization or cynicism, and reduced personal accomplishment. Values of ⊕27 for emotional exhaustion, ⊕13 for depersonalization, and ≤31 for personal accomplishment were indicative of burnout. The GHQ-28 is a measure of general psychopathology with four subscales. These differentiate "somatic" symptoms, anxiety and insomnia, social dysfunction, and depression, but the cumulative GHQ score enables the identification of psychiatric "cases." In this study, scores of 5 and above were used as the indicator. The ZDRS is a symptoms-based checklist for assessing depression. Scores of 50–59 indicate mild depression, 60–69 moderate depression, 70–79 severe depression, and >80 extreme depression.

Interventions

Patients participated in a stress management program from 0800 h to 1400 h for 5–10 consecutive days, which included exercise, diet, and behavior modification.

Medication consisted of a benzodiazepine (alprazolam) and antidepressants (citalopram or dothiepin). The benzodiazepine was initiated at a dose of 1mg qid for 2 d, then tapered over 10 days to 1 mg nocte when necessary. Antidepressant therapy was initiated at the start of the study, and patients continued with this treatment throughout the study. Patients were started on 20 mg citalopram daily; however, two patients could not tolerate this drug, and they were given dothiepin 25 mg mane and 75 mg nocte.

Hormone Assays and Biochemical Measurements

After a 30-min resting period, blood samples were collected in iced tubes and centrifuged; plasma/serum aliquots were separated and stored at –20°C, except for catecholamines, which were analyzed immediately. Epinephrine and norepinephrine concentrations were measured using high-pressure liquid chromatography (Bio-Rad Laboratories, Hercules, CA) according to the method of Koch and Polzin *(30)* (respective normal ranges: 0–366 pmol/L; 560–2636 pmol/L). Plasma glucose levels were determined by a standard glucose oxidase method (normal range: 3.0–6.0 mmol/L). Insulin, GH, and prolactin concentrations were measured by immunoassay using direct chemiluminometric technology and reagents supplied by Diagnostic Products Corporation, Los Angeles, CA (respective normal ranges: 6.0–27.0 mIU/L; 0.16–13.0 mIU/L; 2.8–29.2 μg/L [premenopause] and 1.8–20.3 μg/L [postmenopause]). Radioimmunoassay kits were used to measure ACTH, cortisol, dehydroepiandrosterone sulfate (DHEA-S) (Diagnostic Systems Laboratories, Inc., Webster, Texas), and aldosterone (Diagnostic Products Corporation, Los Angeles, CA) (respective normal ranges: 2.2–19.8 pmol/L; 138–690 nmol/L [7:00–9:00 AM]; 1.0–7.3 μmol/L [female]; 28–444 pmol/L [recumbent]; FFA triglycerides, total cholesterol, and HDL-cholesterol levels were determined by enzymatic, colorimetric methods using reagents supplied by Roche Diagnostics, Basel, Switzerland (respective normal ranges: 0.3–0.8 mmol/L; 0.0–2.0 mmol/L; <6.2 mmol/L; >1.6 mmol/L). LDL-cholesterol was calculated according to the formula of Friedewald et al. *(31)* (normal range: <4.1 mmol/L). Urine free-cortisol concen-

trations were measured by a competitive immunoassay (Bayer Corporation, Tarrytown, NY) (normal range: 55–250 nmol/24 h). Intraassay coefficients of variation for these assays were all <5%.

Statistical Analysis

Results are expressed as mean ± SEM except for catecholamines, where the medians with ranges are stated due to the non-parametric distribution of the data. Statistical significance of non-parametric data was assessed by the Friedman repeated measures test, Mann–Whitney "U" test, and the Wilcoxon signed rank test; parametric data were assessed by the Student's *t*-test (two-tailed) for paired and unpaired samples. Repeated measures analysis of variance was used to examine differences in patients' psychometric rating scales from baseline to 4 mo. The Bonferroni multiple comparisons test was used to determine significances at each timepoint. A value of $p < 0.05$ was considered significant.

Acknowledgments

This research was funded in part by financial grants from the Iris and Ellen Hodges Trust for Stress and Emotional Research, the Witwatersrand University Medical Faculty Research Endowment Fund, and a University Research Committee grant.

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