

# Salivary Cortisol as a Predictor of Postoperative Fatigue

G. JAMES RUBIN, PhD, MATTHEW HOTOPF, PhD, ANDREW PAPADOPOULOS, PhD, AND ANTHONY CLEARE, PhD

**Objective:** Some patients with chronic fatigue syndrome (CFS) exhibit low basal cortisol levels, but it is not known whether low cortisol is a cause of CFS, predates the onset of CFS symptoms, or is an epiphenomenon caused by the behavioral changes typical of CFS. Because elective surgery is one of the few predictable risk factors for chronic fatigue, in this study, we followed a cohort of surgery patients from before to 6 months after their operation to test these theories. **Method:** One hundred sixty-one patients completed fatigue questionnaires and provided salivary cortisol samples before undergoing an elective inpatient surgical procedure, and then 2 days, 3 weeks, and 6 months afterward. **Results:** Controlling for relevant demographic and surgical variables and for preoperative fatigue, low preoperative cortisol did not predict postoperative fatigue severity on any occasion ( $p > .05$ ). Similarly, there was no correlation between low postoperative cortisol and postoperative fatigue severity at 3 weeks or 6 months ( $p > .05$ ). Although 16 patients met our case definition for "chronic fatigue" at the 6-month follow up, low preoperative and low postoperative cortisol did not significantly predict fatigue caseness ( $p > .05$ ). **Conclusions:** Any association between chronic fatigue and low cortisol would seem to develop after the onset of fatigue symptoms. Low cortisol is therefore unlikely to be the primary cause of chronic fatigue states. **Key words:** cortisol, fatigue, chronic fatigue syndrome, surgery, HPA axis, adrenal function.

**AuC** = area under the curve; **ASA** = American Society of Anesthesiologists physical status score; **CBT** = cognitive behavioral therapy; **CFS** = chronic fatigue syndrome; **MD** = mean difference; **T1** = before surgery; **T2** = 2 days after surgery; **T3** = 3 weeks after surgery; **T4** = 6 months after surgery.

## INTRODUCTION

Chronic fatigue syndrome (CFS) is an illness characterized by medically unexplained fatigue of more than 6 months' duration, together with at least four other symptoms such as sleep disturbance, concentration difficulties, headaches, and joint pain (1). Many theories have been put forward regarding the etiology of the illness (2), several of which center around putative neuroendocrine abnormalities (3). These neuroendocrine theories were prompted by the finding that some CFS sufferers exhibit abnormally low basal levels of cortisol (4,5). Given that other conditions typified by low levels of cortisol, including Addison's disease and postbilateral adrenalectomy, are also associated with persistent fatigue (6), it has been suggested that low cortisol may be a causal factor in the pathogenesis of CFS (3). Some support for this theory comes from two studies of glucocorticoid replacement treatment for CFS. The first compared a placebo against a full replacement dose of hydrocortisone administered in doses intended to replicate the normal diurnal rhythm of cortisol secretion (7). The treatment produced mild improvements in overall well-being, although subjective fatigue levels remained relatively unaffected. In the second study, smaller doses of hydrocortisone produced large reductions in fatigue in 28% of treated patients compared with 9% of those given a placebo (8).

---

From the Section of General Hospital Psychiatry, Division of Psychological Medicine, Institute of Psychiatry and Guy's, King's and St. Thomas' School of Medicine, King's College London, London, UK (G.J.R., M.H., A.C.); the Section of Neurobiology of Mood Disorders, Division of Psychological Medicine, Institute of Psychiatry, King's College London, London, UK (G.J.R., A.C.); and the Affective Disorders Unit, Bethlem Royal Hospital, South London and Maudsley NHS Trust, London, UK (A.P., A.C.).

Address correspondence and reprint requests to G. James Rubin, PhD, Section of General Hospital Psychiatry (PO62), Weston Education Centre, Cutcombe Road, London SE5 9RJ, UK. E-mail: g.rubin@iop.kcl.ac.uk

Received for publication July 13, 2004; revision received November 25, 2004.

This research was supported by an MRC studentship awarded to James Rubin.

DOI: 10.1097/01.psy.0000161207.73744.4e

Although potential side effects probably preclude such treatments as routine therapy for CFS, these results suggest that low cortisol may be a factor in the cause or maintenance of the illness.

It is not yet clear when low cortisol develops in the pathogenesis of CFS. One suggestion is that the neuroendocrine abnormality may predate the symptoms and mark out initially asymptomatic individuals as being particularly at risk of developing chronic fatigue after a physiological or psychosocial stressor. For example, low cortisol may be a mediating link between factors such as early life stress or genetics and CFS (9). However, evidence relating to this theory is sparse owing to difficulties in obtaining premorbid cortisol samples from patients who already have CFS.

An alternative suggestion is that low cortisol is the result, rather than the cause, of chronic fatigue. For example, alterations in sleep patterns can substantially affect the normal diurnal variation of cortisol secretion (10), and it has been shown that otherwise healthy individuals whose sleep habits mirror those of nightshift workers have patterns of cortisol secretion that are similar to those seen in CFS (11). It is therefore possible that the abnormal cortisol levels sometimes found in CFS are an epiphenomenon caused by disrupted sleep (12). In support of this, it has recently been shown that a course of cognitive behavioral therapy (CBT) designed to normalize the daily routines of patients with CFS can also normalize their cortisol levels (13).

One method for testing which of these theories is the most accurate is to use prospective cohort studies to follow up groups of patients who are particularly at risk of developing chronic fatigue. For example, Candy et al. (14) recently studied a sample of patients with glandular fever for 1 year after their diagnosis, assessing salivary cortisol levels and fatigue "caseness" at 3 and 6 months postdiagnosis. Although glandular fever is a recognized risk factor for chronic fatigue (15), these researchers found no evidence to suggest any association between postinfection cortisol levels and fatigue status.

Another phenomenon that might lend itself to this type of prospective cohort study is postoperative fatigue. After surgery, patients often report increased sensations of fatigue (16), which may be qualitatively similar to those experienced in CFS (17). For most patients, energy levels return to normal

within 2 to 3 months of their operation, but a small proportion continue to feel tired for much longer than this, with a minority reporting high levels of fatigue for 6 months or more (16). Some patients may even go on to develop CFS after surgery or anesthesia (18,19). Although levels of cortisol are usually elevated in the days after surgery as part of the so-called "surgical stress response" (20–23), little is known about any longer-term changes. Little is also known about the relationship between cortisol levels and postoperative fatigue, although one study has previously reported finding no significant correlation between the two variables 20 days after major abdominal surgery (24).

In this study, we followed up 161 patients for 6 months after an operation, and assessed their fatigue and salivary cortisol levels before surgery and then 2 days, 3 weeks, and 6 months afterward. We have previously reported on the psychologic status of this sample and whether psychologic variables predicted postoperative fatigue (25). In this paper, we describe the pre- and postoperative cortisol levels of the patients and test two hypotheses: that low preoperative cortisol would predict high postoperative fatigue and that low postoperative cortisol would correlate with high postoperative fatigue.

## METHODS

### Sample

Patients aged 18 to 75 years and scheduled to undergo elective inpatient surgery at King's College Hospital, London, were asked to take part in the study. Patients were excluded if they had already had an operation within the past 6 months, had metastatic cancer, were scheduled to undergo chemotherapy or radiotherapy, had a fatigue-related diagnosis (e.g., CFS), had a psychotic disorder, or if there was any reason that would have made completing the study questionnaires impractical (e.g., inability to read English). Patients with nonpsychotic psychiatric disorders such as depression were not excluded.

### Design

In this prospective cohort study, participants were asked to complete questionnaires and provide saliva samples on four occasions: before surgery (T1; a median of 18 days before surgery [range, 1–114 days]), 2 days after surgery (T2), 3 weeks after surgery (T3), and 6 months after surgery (T4). The two dependent variables were self-reported fatigue severity at T2, T3, and T4, and chronic fatigue caseness at T4. The main independent variables were having "low" total daily output levels of salivary cortisol at T1, T2, T3, and T4. Secondary independent variables were actual total daily output and maximum, minimum, mean, and diurnal change cortisol values.

### Fatigue Assessment

Self-reported fatigue severity was assessed on each occasion using the validated Chalder Fatigue Scale, which measures the subjective sensations of mental and physical fatigue and which includes questions such as "are you lacking in energy," "do you feel sleepy or drowsy," and "do you need to rest more" (26). This questionnaire was used to produce two outcome measures. First, a fatigue severity score was calculated for each participant on each occasion using the questionnaire's Likert scoring method. Second, the bimodal scoring method was used to identify a group of patients at T4 who reported clinically significant fatigue, defined as reporting greater than usual levels of fatigue for four or more out of 11 questionnaire items. In a previous study of a large community sample, the use of this cutoff resulted in 38% of respondents being categorized as having clinically significant fatigue (27). In the present study, participants who reported clinically significant fatigue at T4

and who also reported having been fatigued for 6 months or more were categorized as chronic fatigue cases.

### Cortisol Collection and Assay

Participants were asked to provide four saliva samples at each of the four occasions. These samples were collected at 8 AM, 12 PM, 4 PM, and 8 PM using plain salivettes (Sarstedt, Leicester, UK). Saliva samples at T1, T3, and T4 were provided at the participants' homes and returned to us the following day using first-class mail. Samples at T2 were usually provided in the hospital under the supervision of the first author. Participants were instructed not to eat for 1 hour or drink for 10 minutes before providing a sample, and were also asked to remain seated for 20 minutes beforehand. A short diary was provided on each occasion, which participants used to record any deviations from this protocol as well as any "hassles or worries" that they had experienced in the hour before giving each sample.

On arrival at the laboratory, saliva samples were stored at  $-20^{\circ}\text{C}$  and then assayed over a 3-month period after the end of the study's data collection phase. The time-resolved immunofluorescent cortisol assay that was used has been reported in detail elsewhere (28,29). Initially, all salivettes were thawed overnight and centrifuged for 10 minutes at 3500 rpm. The clear fluid was then pipetted into small tubes and stored at  $-40^{\circ}\text{C}$  until analysis. On the day of analysis, after further centrifugation at 3500 rpm for 3 minutes, a Genesis 100 Robotic Sample Processor (TECAN, Goring on Thames, UK) was used to add 50  $\mu\text{L}$  of room temperature saliva, standard or control, to the wells of a prewashed plate coated with goat antirabbit immunoglobulin G. Two duplicate wells were filled for each sample. One hundred microliters of cortisol antibody in assay buffer (1 in 4500 dilution in assay buffer) was added by hand to each well and the plate incubated for 30 minutes on a Wallac plate shaker at 600 oscillations per minute. One hundred microliters of Europium-labeled cortisol (1 in 65 dilution in assay buffer) was then added to each well and the plate shaken for another 30 minutes. Plates were then washed four times with wash buffer (1 in 25 dL water) and dried by tapping over paper towels. Two hundred microliters of enhancement solution was added to each well and the plates incubated for a further 5 minutes. Finally, the fluorescence of each well was measured using an ARCUS 1234 fluorometer. Cortisol concentrations were calculated as the mean of the two duplicates for each sample and were quantified using a calibration graph based on the fluorescence of eight standards of known concentration (0–40 nmol/L) using Multicalc software. Samples for which the percentage variance between the duplicates was more than 10% were reassayed. Unusually high or low cortisol values were crosschecked against the relevant diary for that participant; those which were likely to have been affected by a deviation from the collection protocol were discarded.

Apart from the cortisol antibody (batch 21051565; Biogenesis, Poole, Dorset, UK), all reagents were supplied by Perkin Elmer Life Sciences (Cambridge, UK).

### Demographic and Surgical Data

Certain demographic and surgical data were recorded as variables that might need to be controlled for in the analyses. The following demographic variables were assessed at T1: age, sex, ethnicity (white versus other), socioeconomic status (manual versus nonmanual work), and educational level (educated past age 16 versus not educated past age 16). The surgical data were extracted from patients' notes at T4 and consisted of type of operation (minor surgery, major abdominal or vascular surgery, gynecologic surgery, or cardiac surgery), ASA status (a subjective global health rating usually completed by the patient's anesthetist), duration of anesthesia, whether a blood transfusion was given, mean daily intake of opioid analgesia (in morphine equivalent dosage (30)), and whether the patient experienced a surgical complication.

### Procedure

Potentially eligible patients were contacted by letter and invited to participate in a study looking at why some people recover faster from surgery than others. Patients who agreed to participate were asked to provide informed written consent and were then given the first study questionnaire and first set of salivettes to complete at home and return using a prepaid first-class

# CORTISOL AND POSTOPERATIVE FATIGUE

envelope. Participants were then visited in the hospital 2 days after their operation and asked to complete the T2 questionnaire and the second set of salivettes. The questionnaire itself was completed between 12 PM and 4 PM. Three weeks and 6 months after their operation, patients were sent the T3 and T4 questionnaires by mail together with the third and fourth sets of salivettes. These were completed at home and returned by mail. Participants who did not return these materials received two written reminders and one follow-up telephone call.

## Ethics

This research was conducted in accordance with the Declaration of Helsinki. Ethical approval for the study was given by the King's College Hospital Research Ethics Committee (Committee reference 00-033).

## Statistical Analysis

To boost the power of the analyses, multiple regressions were first used to impute the missing cortisol value for participants who returned only three usable saliva samples for a given occasion. These regressions used the three available cortisol values for that day as predictors. Most of the regressions had fair to good fit with the data ( $28.6\% \leq R^2_{adj} \leq 58.7\%$ ), except for those for T1 (8 AM), T1 (8 PM), T3 (8 AM), T4 (8 AM), and T4 (8 PM); missing values for these five data points were not imputed.

Total daily output of salivary cortisol was calculated for T1, T2, T3, and T4 as the area under the curve (AuC) using the trapezoidal method (14). For the purposes of the primary hypothesis tests, participants in the bottom quartile of the AuC distributions for each occasion were categorized as having "low cortisol." Values for maximum, minimum, mean, and diurnal change (slope of graph, calculated using linear regression) were also calculated for each set of four cortisol concentrations.

Independent sample *t* tests and Pearson's correlations were used to examine the univariate relationships between each of the six cortisol variables (having low cortisol, actual AuC value, maximum, minimum, mean, diurnal change) at T1 and fatigue severity at T1, T2, T3, and T4, as well as the correlations between the postoperative cortisol values and concurrent fatigue severity. *t* tests were also used to provide a univariate comparison between fatigue cases and noncases in terms of AuC value, maximum, minimum, mean, and diurnal change cortisol values at T4.

Multiple regressions were used to assess the importance of each cortisol variable at T1 in predicting fatigue severity at T2, T3, and T4, and of postoperative cortisol as a correlate of postoperative fatigue severity. For each analysis, an initial regression was run with postoperative fatigue as the dependent variable and one of the six cortisol variables as an independent variable. Preoperative fatigue and all surgical and demographic variables were also included as independent variables that might need to be controlled for. Any surgical or demographic variables that were not significantly associated

with postoperative fatigue ( $p > .1$ ) were then removed and the regression model rerun. For the purposes of these analyses, type of surgery was transformed into three dummy variables, with minor surgery taken as the reference category.

Finally, logistic regressions were used to assess the role of cortisol at T1 and T4 in predicting chronic fatigue caseness at T4. Again, these regressions controlled for the effects of preoperative fatigue and any surgical or demographic variables that showed a significant ( $p > .1$ ) multivariate association with fatigue caseness.

## RESULTS

Of the 371 patients considered for inclusion in this study, 245 were eligible to take part. Only two were excluded because of preexisting chronic fatigue. One hundred sixty-one patients (65.7%) were willing and able to complete the study questionnaires and provide us with at least one saliva sample. Of these, 29 underwent a minor procedure (e.g., laparoscopic cholecystectomy), 16 a major abdominal or vascular procedure (e.g., hemicolectomy), 41 a gynecologic procedure (e.g., total abdominal hysterectomy), and 75 a cardiac procedure (e.g., coronary artery bypass graft). The mean age for the sample was 56.0 years (standard deviation [SD] = 12.9), with 86 (53.4%) of the participants being men. Most of the participants were white (80.1%), had nonmanual occupations (56.1%), and had not been formally educated past age 16 (55.3%). Details for the surgical variables are presented in Table 1.

Fatigue scores were available for 99.4% of participants at T1, 87.6% at T2, 86.3% at T3, and 79.5% at T4. Forty-nine participants (38.3%) reported clinically significant fatigue at T4 (see Fig. 1), of whom 16 reported having been fatigued for 6 months or more and were categorized as chronic fatigue cases. The mean fatigue scores (SD) for the sample as a whole at T1, T2, T3, and T4 were 14.9 (4.7), 19.3 (5.6), 16.8 (5.3), and 13.7 (5.3), respectively.

A total of 2048 usable saliva samples were collected. Eight of these appeared to have been affected by a deviation from the collection protocol and were discarded. A further 28 values were imputed using multiple regressions. In all, it was possible to calculate AuC, maximum, minimum, mean, and

TABLE 1. Descriptive Data for Fatigue, Cortisol and Surgical Variables<sup>a</sup>

Variable	T1 (n = 160)	T2 (n = 141)	T3 (n = 139)	T4 (n = 128)
Fatigue (0 to 33; higher scores indicate greater fatigue)	14.9 (4.7)	19.3 (5.6)	16.8 (5.3)	13.7 (5.3)
Total daily output of salivary cortisol (AuC; nmol/L/h)	79.3 (30.5)	118.7 (62.7)	79.3 (30.1)	73.9 (23.4)
Maximum cortisol (nmol/L)	11.9 (4.7)	15.3 (7.4)	11.8 (4.6)	11.7 (4.1)
Minimum cortisol (nmol/L)	3.0 (1.5)	6.3 (4.2)	3.1 (2.1)	2.8 (1.4)
Mean cortisol (nmol/L)	6.8 (2.4)	10.2 (5.2)	6.8 (2.5)	6.5 (1.9)
Diurnal change or slope	-1.2 (0.8)	-1.1 (1.2)	-1.0 (1.0)	-1.2 (0.7)
Percent with ASA status 3 or 4 (i.e., with poorer health)	37.6%	—	—	—
Duration of anesthesia (mins)	175.0 (96.3)	—	—	—
Percent receiving a blood transfusion	34.5%	—	—	—
Mean daily opioid intake (mg of morphine)	9.6 (7.9)	—	—	—
Percent with one or more surgical complications	31.7%	—	—	—

T1 = preoperatively; T2 = 2 days postoperatively; T3 = 3 weeks postoperatively; T4 = 6 months postoperatively; AuC = area under the curve.

<sup>a</sup>All values are mean (standard deviation) unless stated otherwise. Sample sizes relate to the number of participants for whom fatigue scores were available at that time point.

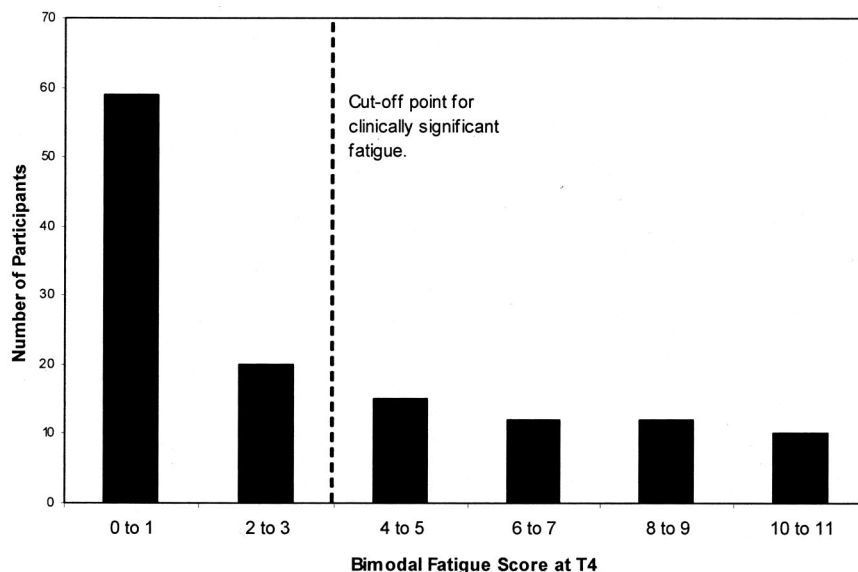


Figure 1. Bimodal fatigue scores 6 months after surgery. A score of 4 or more indicates clinically significant fatigue. Participants with clinically significant fatigue and who also reported having been fatigued for 6 months or more were classified as chronic fatigue cases.

diurnal change values for 149 participants at T1 (92.5%), 121 participants at T2 (75.2%), 127 participants at T3 (78.9%), and 113 participants at T4 (70.2%). These values are shown in Table 1. For the 16 chronic fatigue case participants, cortisol data could be calculated for 13 (81.3%) at T1, T2, and T3, and for 12 (75%) at T4.

#### Univariate Associations Between Cortisol and Fatigue

*t* tests revealed no significant differences between participants with and without low cortisol at T1 in terms of fatigue severity at T1, T2, T3, or T4 ( $p > .05$ ). Similarly, no univariate associations were found between low cortisol at T2, T3, or T4 and contemporaneous fatigue severity ( $p > .05$ ). No significant correlations were identified between maximum, minimum, mean, AuC, or diurnal change values at T1, and fatigue severity scores at T1, T2, T3, or T4 ( $p > .05$ ). In terms of the correlations between these cortisol values at T2 and fatigue severity at T2, significant associations were found for the minimum ( $r = 0.25, p = .005$ ), maximum ( $r = 0.21, p = .02$ ), AuC ( $r = 0.24, p = .01$ ), and mean ( $r = 0.25, p = .01$ ) values, although not for diurnal change ( $p = .46$ ). No significant correlations were identified between these five cortisol values at T3 and fatigue at T3 ( $p > .05$ ) or between most cortisol values at T4 and fatigue at T4 ( $p > .05$ ). The only exception was a small but significant correlation between minimum cortisol and fatigue severity at T4 ( $r = 0.24, p = .01$ ).

No significant differences were found between fatigue cases and noncases in terms of their T4 values for AuC (mean difference [MD] = 6.2, 95% confidence interval [CI] = -8.4, 20.8;  $p = .40$ ), maximum (MD = 0.1, 95% CI = -2.4, 2.6;  $p = .96$ ), mean (MD = 0.6, 95% CI = -0.6, 1.8;  $p = .33$ ), or diurnal change (MD = -0.04, 95% CI = -0.5, 0.4;  $p = .86$ ) cortisol values. However, fatigue cases did have significantly higher minimum cortisol values than noncases (MD = 1.2, 95% CI = 0.4, 2.0;  $p < .01$ ).

#### Preoperative Cortisol as a Multivariate Predictor of Postoperative Fatigue Severity

The results of the multiple regressions using low preoperative cortisol as the main independent variable are shown in Table 2. Of the surgical and demographic variables included in the regressions that used fatigue at T2 or T3 as the dependent variable, only operative category showed any association with postoperative fatigue ( $p < .1$ ); all other surgical and demographic variables were therefore removed from these regression models. For the regression with fatigue at T4 as the dependent variable, economic status, ethnicity, and ASA status all showed an association with postoperative fatigue ( $p < .1$ ) and were retained in the model. Controlling for these variables and for preoperative fatigue, being in the lowest AuC quartile before surgery was not significantly associated with postoperative fatigue at T2 ( $p = .3$ ), T3 ( $p = .5$ ), or T4 ( $p = .8$ ).

Fifteen other regressions were also calculated using preoperative AuC, maximum, mean, minimum, and diurnal change values as the independent variables and fatigue severity at T2, T3, and T4 as dependent variables (data not shown). Of these, only one revealed any significant effect, with mean cortisol at T1 showing a significant relationship to fatigue at T4 when ASA status, socioeconomic status, ethnicity, operation type, and preoperative fatigue were held constant ( $\beta = 0.2, p = .05$ ).

#### Postoperative Cortisol as a Multivariate Correlate of Postoperative Fatigue Severity

The results of the multiple regressions using postoperative low cortisol as the main independent variable are shown in Table 3. For the regression with fatigue at T2 as the dependent variable, operative category, age, sex, and whether the participant received a blood transfusion were retained in the regression model as variables we needed to control for. For the regression with fatigue at T3 as the dependent variable, operative category and ethnicity were retained. For the regression

TABLE 2. Low Preoperative Cortisol as a Predictor for Postoperative Fatigue Severity

	Fatigue at T2 as Dependent Variable	Fatigue at T3 as Dependent Variable	Fatigue at T4 as Dependent Variable
Overall regression fit	$F(5,122) = 1.4, p = .2$ $R^2_{adj} = 1.7\%, n = 128$	$F(5,121) = 2.9, p = .02$ $R^2_{adj} = 7.0\%, n = 127$	$F(5,89) = 8.8, p < .001$ $R^2_{adj} = 29.2\%, n = 95$
Preoperative fatigue	$\beta = 0.0, p = .7$	$\beta = 0.2, p = .03$	$\beta = 0.6, p < .001$
Major abdominal or vascular surgery <sup>a</sup>	$\beta = 0.3, p = .02$	$\beta = 0.2, p = .04$	Not kept in model
Gynecologic surgery <sup>a</sup>	$\beta = 0.1, p = .5$	$\beta = 0.2, p = .06$	Not kept in model
Cardiac surgery <sup>a</sup>	$\beta = 0.1, p = .3$	$\beta = 0.3, p = .05$	Not kept in model
Nonmanual socioeconomic status	Not kept in model	Not kept in model	$\beta = 0.1, p = .4$
Being white	Not kept in model	Not kept in model	$\beta = 0.2, p = .1$
Higher ASA status	Not kept in model	Not kept in model	$\beta = -0.02, p = .8$
Being in the bottom quartile of AuC distribution at T1	$\beta = -0.1, p = .3$	$\beta = -0.1, p = .5$	$\beta = -0.8, p = .4$

T1 = preoperatively; T2 = 2 days postoperatively; T3 = 3 weeks postoperatively; T4 = 6 months postoperatively; AuC = area under the curve.  
<sup>a</sup>With minor surgery as the reference category.

TABLE 3. Low Postoperative Cortisol as a Correlate of Postoperative Fatigue Severity

	Fatigue at T2 as Dependent Variable	Fatigue at T3 as Dependent Variable	Fatigue at T4 as Dependent Variable
Overall regression fit	$F(8,90) = 2.5, p = .02$ $R^2_{adj} = 10.8\%, n = 99$	$F(6,118) = 1.9, p = .09$ $R^2_{adj} = 4.2\%, n = 125$	$F(4,107) = 14.0, p < .001$ $R^2_{adj} = 31.8\%, n = 112$
Preoperative fatigue	$\beta = 0.2, p = .09$	$\beta = 0.3, p = .01$	$\beta = 0.5, p < .001$
Major abdominal or vascular surgery <sup>a</sup>	$\beta = 0.3, p = .03$	$\beta = 0.1, p = .2$	Not kept in model
Gynecologic surgery <sup>a</sup>	$\beta = 0.1, p = .4$	$\beta = 0.1, p = .3$	Not kept in model
Cardiac surgery <sup>a</sup>	$\beta = 0.3, p = .1$	$\beta = 0.1, p = .5$	Not kept in model
Being white	Not kept in model	$\beta = 0.1, p = .2$	$\beta = 0.2, p = .06$
Being male	$\beta = 0.2, p = .2$	Not kept in model	$\beta = 0.1, p = .4$
Age	$\beta = -0.2, p = .1$	Not kept in model	Not kept in model
Receiving a transfusion	$\beta = -0.4, p = .002$	Not kept in model	Not kept in model
Being in the bottom quartile of postoperative AuC distribution	$\beta = -0.1, p > .9$	$\beta = -0.1, p = .6$	$\beta = -0.1, p = .5$

T1 = preoperatively; T2 = 2 days postoperatively; T3 = 3 weeks postoperatively; T4 = 6 months postoperatively; AuC = area under the curve.  
<sup>a</sup>With minor surgery as the reference category.

with fatigue at T4 as the dependent variable, only sex and ethnicity were retained. Controlling for these variables and for preoperative fatigue, being in the lowest AuC quartile was not associated with fatigue severity at T2 ( $p > .9$ ), T3 ( $p = .6$ ), or T4 ( $p = .5$ ).

Fifteen other regressions were performed using the relevant postoperative AuC, mean, maximum, minimum, and diurnal change values as independent variables (data not shown). For fatigue at T2 as the dependent variable, significant associations were found with AuC ( $\beta = 0.3, p = .007$ ), minimum ( $\beta = 0.3, p = .003$ ), maximum ( $\beta = 0.2, p = .05$ ), and mean ( $\beta = 0.3, p = .007$ ), although not with diurnal change ( $p > .9$ ). For those regressions using fatigue at T3 and T4 as the dependent variable, only minimum cortisol at T4 showed any significant relationship with fatigue severity ( $\beta = 0.2, p = .03$ ).

### Pre- and Postoperative Cortisol as Multivariate Predictors of Chronic Postoperative Fatigue

The preliminary logistic regressions using low cortisol at T1 and T4 as predictors of chronic postoperative fatigue caseness showed that we did not need to control for any of the surgical or demographic variables ( $p > .1$ ). With these variables removed, the regression model with low cortisol at T1 as the main independent variable showed a significant fit to the data (model chi square = 11.6,  $df = 2, p < .005$ ) with 88.4% of participants being correctly classified as case or noncase. Controlling for the effects of preoperative fatigue, having low cortisol at T1 did not significantly predict chronic fatigue caseness at T4 (odds ratio = 0.9; 95% CI = 0.2, 5.0). Similarly, although the regression model with low cortisol at T4 as the main independent variable also showed a good fit to the data (chi square = 9.1,  $df = 2, p < .01$ , 87.5% of participants correctly classified), with preoperative fatigue held constant, low cortisol at T4 did not predict chronic fatigue caseness at T4 (odds ratio = 0.9; 95% CI = 0.2, 3.7).

Similar logistic regressions conducted using T1 and T4 AuC, mean, maximum, minimum, and diurnal change values as predictors were also conducted (data not shown). Of these, only one showed any significant result, with minimum cortisol at T4 showing a significant relationship with chronic fatigue caseness (odds ratio = 1.8; 95% CI = 1.1, 2.8).

### DISCUSSION

As with previous studies (16), our research identified a significant increase in fatigue in the period immediately after surgery, rising to a mean of 19.3 2 days after surgery before decreasing to a mean of 13.7 6 months later. By way of comparison, a previous study of over 15,000 members of the general public using the same questionnaire (27,32) also identified a mean baseline fatigue level of 13.7 (95% CI = 13.7, 13.8), although that sample had a relatively low mean age (32.4 years). Six months after surgery, 16 of our respondents (14.2%) reported clinically significant fatigue that had been present for at least 6 months; again, this seems to be comparable to the 18.3% of people in the general community who have previously been found to report chronic fatigue (27).

We found no evidence to implicate reduced cortisol in the etiology of this fatigue. There was also no evidence to suggest that low cortisol represents a preexisting trait reflecting a propensity to suffer from fatigue after physical or psychosocial stressors. Although some significant multivariate associations were found between cortisol variables and postoperative fatigue, these all suggested that high, rather than low, cortisol was correlated to the symptom, particularly in the days immediately after surgery. As such, the results of our study do not seem to support the suggestion that low cortisol is important in the etiology of chronic fatigue-related conditions such as CFS (3).

However, it is important to note that our study did not use strictly defined CFS as the outcome. Whether it is appropriate to extrapolate from the outcome we did use, namely chronic fatigue, to CFS is debatable. On the one hand, having high levels of subjective fatigue, which has been present for at least 6 months, is the key defining feature of CFS. Although the presence of at least four other symptoms is also necessary for the diagnosis to be made, no other single symptom is specifically required to be present (1). On the other hand, the differences between chronic fatigue and CFS in terms of the typical demographic makeup of the patients and the fact that other symptoms are involved do suggest that caution is warranted, because there is no certainty that the two conditions share the same pathogenic factors. We would therefore recommend that larger studies of postoperative convalescence using CFS as the outcome now be conducted to validate our findings.

The use of a surgical sample may also have had other implications for the validity of our results. For reasons that are not yet clear (33), the majority of patients experience some degree of fatigue after the types of surgery examined in this study (16). Thus, the high incidence of acute fatigue at T2 and T3, which may have been caused by any number of surgical, pharmacologic, psychologic, or nutritional factors, may have prevented us from observing a small association between fatigue and low cortisol in a minority of participants at these time points. Conversely, it is also possible that the small number of patients who had chronic fatigue at T4 may have prevented us from observing any association between the two variables at that occasion as a result of a type II error.

Nevertheless, our results do seem to be consistent with those from previous studies. In particular, it is notable that Candy et al's glandular fever study was also unable to find any evidence of low cortisol in patients who went on to develop chronic fatigue, or any evidence of an association between low cortisol in the immediate period after the glandular fever diagnosis and subsequent fatigue status (14). One possible explanation for this is may be that chronic fatigue, unlike CFS, is unrelated to low cortisol. On the other hand, similar findings do also appear in the CFS literature. Most studies that have identified low cortisol in CFS samples have tended to examine patients who have been ill for a relatively long period of time (3). In contrast, those that have examined patients with CFS with shorter illness durations have not found such clearcut

## CORTISOL AND POSTOPERATIVE FATIGUE

neuroendocrine abnormalities (34,35). Meanwhile, Cleare et al. have recently shown that using cognitive behavioral therapy to normalize the behavioral routines and sleep cycles of patients with CFS has the added effect of normalizing their cortisol levels (13). Taken together, these findings suggest that reduced cortisol may develop relatively late in the natural history of chronic fatigue illnesses and is therefore not their primary cause, although this is not to suggest that neuroendocrine abnormalities, once developed, have no detrimental effects on health (7,8).

Finally, our finding that higher cortisol at T2 was significantly correlated with higher fatigue also fits well with the results of previous studies. An increase in cortisol immediately after surgery and which varies according to the magnitude of the operation has been well-documented as part of the surgical stress response (20–23). Although one study has previously failed to identify any association between cortisol and fatigue after major abdominal surgery, this study only assessed the two variables 20 days after the operation (24). Other studies that have examined more acute postoperative fatigue have reported significant correlations with other markers of the surgical stress response such as raised cytokine and norepinephrine levels (21,36). Whether these findings indicate that surgical stress per se is an important cause of early postoperative fatigue remains unclear, however. Although this is possible, the role of variables that covary with operative severity such as anxiety, pain, and expectations of fatigue still requires clarification (33).

*We thank the patients and staff of King's College Hospital for their help with this study as well as Lucia Poon for her help in organizing and running the cortisol assays.*

### REFERENCES

1. Fukuda K, Straus S, Hickie I, Sharpe M, Dobbins J, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Ann Intern Med* 1994;121:953–9.
2. Wessely S, Hotopf M, Sharpe M. *Chronic fatigue and its syndromes*. Oxford: Oxford University Press, 1998.
3. Cleare AJ. The neuroendocrinology of chronic fatigue syndrome. *Endocr Rev* 2003;24:236–52.
4. Poteliakhoff A. Adrenocortical activity and some clinical findings in chronic fatigue. *J Psychosom Res* 1981;25:91–5.
5. Demitrack M, Dale J, Straus S, Laue L, Listwak SJ, Kruesi MJP, Chrousos G, Gold P. Evidence of impaired activation of the hypothalamic–pituitary–adrenal axis in patients with chronic fatigue syndrome. *J Clin Endocrinol Metab* 1991;73:1224–34.
6. Riordain D, Farley D, Young W, Grant C, van Heerden J. Long term outcome of bilateral adrenalectomy in patients with Cushing's syndrome. *Surgery* 1994;116:1088–93.
7. McKenzie R, O'Fallon A, Dale J, Demitrack M, Sharma G, Deloria M, Garica-Borreguero D, Blackwelder W, Straus SE. Low-dose hydrocortisone treatment of chronic fatigue syndrome: results of a placebo controlled study of its efficacy and safety. *JAMA* 1998;280:1061–6.
8. Cleare AJ, Heap E, Malhi GS, Wessely S, O'Keane V, Miell J. Low-dose hydrocortisone in chronic fatigue syndrome: a randomised crossover trial. *Lancet* 1999;353:455–8.
9. Heim C, Ehler U, Hellhammer DH. The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders. *Psychoneuroendocrinology* 2000;25:1–35.
10. Shinkai S, Watanabe S, Kurokawa Y, Torii J. Salivary cortisol for monitoring circadian rhythm variation in adrenal activity during shift-work. *Int Arch Occup Environ Health* 1993;64:499–502.
11. Leese G, Chattington P, Fraser W, Vora J, Edwards R, Williams G. Short-term night-shift working mimics the pituitary–adrenocortical dysfunction of chronic fatigue syndrome. *J Clin Endocrinol Metab* 1996;81:1867–70.
12. Fischler B. Review of clinical and psychobiological dimensions of the chronic fatigue syndrome: differentiation from depression and contribution of sleep dysfunctions. *Sleep Med Rev* 1999;3:131–46.
13. Cleare AJ. The neuroendocrinology of chronic fatigue syndrome [Abstract]. *Neuroendocrine Abstracts* 2003;5:S35.
14. Candy B, Chalder T, Cleare AJ, Peakman M, Skowera A, Wessely S, Weinman J, Zuckerman M, Hotopf M. Predictors of fatigue following the onset of infectious mononucleosis. *Psychol Med* 2002;33:847–55.
15. White P, Thomas J, Amess J, Crawford DH, Grover SA, Kangro H, Clare A. Incidence, risk and prognosis of acute and chronic fatigue syndromes and psychiatric disorders after glandular fever. *Br J Psychiatry* 1998;173:475–81.
16. Rubin GJ, Hardy R, Hotopf M. A systematic review and meta-analysis of the incidence and severity of post-operative fatigue. *J Psychosom Res* 2004;57:317–26. (Erratum appears in *J Psychosom Res* 2004;58:113).
17. Howard Fee JP. Getting back to normal. *Anaesthesia* 1993;48:745–7.
18. Salit IE. Precipitating factors for the chronic fatigue syndrome. *J Psychiatr Res* 1997;31:59–65.
19. Clements A, Sharpe M, Simtin S, Borrill J, Hawton K. Chronic fatigue syndrome: a qualitative investigation of patients' beliefs about the illness. *J Psychosom Res* 1997;42:615–24.
20. Jakeways MS, Mitchell V, Hashim IA, Chadwick SJ, Shenkin A, Green CJ. Metabolic and inflammatory responses after open or laparoscopic cholecystectomy. *Br J Surg* 1994;81:127–31.
21. Rorarius MGF, Kujansuu E, Baer GA, Suominen P, Teisala K, Miettinen A. Laparoscopically assisted vaginal and abdominal hysterectomy: comparison of postoperative pain, fatigue and systemic response. A case–control study. *Eur J Anaesthesiol* 2001;18:530–9.
22. Hakanson E, Rutberg H, Jorfeldt L, Wiklund L. Endocrine and metabolic responses after standardized moderate surgical trauma: influence of age and sex. *Clin Physiol* 1994;4:461–73.
23. Hall GM, Peerbhoy D, Shenkin A, Parker CJR, Salmon P. Hip and knee arthroplasty: a comparison and the endocrine, metabolic and inflammatory responses. *Clin Sci* 2000;98:71–9.
24. Christensen T, Stage JG, Galbo H, Christensen NJ, Kehlet H. Fatigue and cardiac and endocrine metabolic response to exercise after abdominal surgery. *Surgery* 1989;105:46–50.
25. Rubin GJ, Cleare AJ, Hotopf M. Psychological factors in post-operative fatigue. *Psychosom Med* 2004;66:959–64.
26. Chalder T, Berelowitz G, Pawlikowska T, Watts L, Wessely S, Wright D, Wallace EP. Development of a fatigue scale. *J Psychosom Res* 1993;17:147–53.
27. Pawlikowska T, Chalder T, Hirsch S, Wallace P, Wright DJM, Wessely SC. Population based study of fatigue and psychological distress. *BMJ* 1994;308:763–6.
28. Bearn J, Buntwal N, Papadopoulos A, Checkley S. Salivary cortisol during opiate dependence and withdrawal. *Addict Biol* 2001;6:157–62.
29. Pariante C, Papadopoulos A, Poon L, Checkley S, English J, Kerwin RW, Lightman S. A novel prednisolone suppression test for the hypothalamic pituitary adrenal axis. *Biol Psychiatry* 2002;51:922–30.
30. McRae AL, Sonne SC. Opioid equivalency: a review. *J Pharmacy Pract* 1998;11:394–404.
31. Deleted in proof.
32. Chalder T, Wessely S. Statistics are improbable [Authors' reply]. *BMJ* 2000;320:515.
33. Salmon P, Hall GM. A theory of postoperative fatigue: an interaction of biological, psychological, and social processes. *Pharmacol Biochem Behav* 1997;56:623–8.
34. Young A, Sharpe M, Clements A, Dowling B, Hawton K, Cowen P. Basal activity of the hypothalamic–pituitary–adrenal axis in patients with the chronic fatigue syndrome (neurasthenia). *Biol Psychiatry* 1998;43:236–7.
35. Wood B, Wessely S, Papadopoulos A, Poon L, Checkley S. Salivary cortisol profiles in chronic fatigue syndrome. *Neuropsychobiology* 1998;37:1–4.
36. Hall GM, Salmon P. Physiological and psychological influences on post-operative fatigue. *Anesth Analg* 2002;95:1446–50.