

24-Hour Pulsatile and Circadian Patterns of Cortisol Secretion in Alcoholic Men

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Pulsatile and circadian patterns of cortisol secretion during acute (3 to 16 days) and chronic (29 to 39 days) abstinence were examined in alcoholic men with no clinical or laboratory evidence of hepatic dysfunction or nutritional deficiencies. Mean and integrated 24-hour serum concentrations of cortisol determined by sampling the blood every 20 minutes over a 24-hour period were increased in six out of 10 alcoholic subjects during acute abstinence when compared with normal controls. Sustained abstinence in seven subjects with follow-up studies caused significant decreases in the mean maximal cortisol peak amplitude (13 ± 1.0 SEM acutely vs. 10.3 ± 0.52 $\mu\text{g}/\text{dl}$ follow-up; $P = 0.01$), mean 24-hour serum cortisol concentrations (10.9 $\mu\text{g}/\text{dl} \pm 1.2$ vs. 8.5 $\mu\text{g}/\text{dl} \pm 0.26$; $P = 0.047$), interpulse valley mean (9.3 $\mu\text{g}/\text{dl} \pm 0.88$ vs. 6.5 $\mu\text{g}/\text{dl} \pm 0.34$; $P = 0.007$), and valley nadir (7.9 $\mu\text{g}/\text{dl} \pm 0.69$ vs. 5.4 $\mu\text{g}/\text{dl} \pm 0.30$; $P = 0.0036$) concentrations. Cortisol pulse frequency was normal. Although circadian cortisol rhythmicity was maintained in alcoholics, the timing of the circadian acrophase was delayed significantly ($P = 0.006$) during acute abstinence (1022 [clocktime] ± 34

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min) as compared with normal controls (0743 [clocktime] ± 34 min), and the amplitude of circadian cortisol rhythms exceeded normal in five of 10 alcoholics. Analysis of data in one alcoholic subject by a new multiparameter deconvolution method demonstrated increases in secretory burst amplitude (0.64 $\mu\text{g}/\text{dl} \pm 0.08$ SD), mass of cortisol released per burst (9.8 $\mu\text{g}/\text{dl} \pm 1.2$ SD), and daily endogenous cortisol production rate (22 mg ± 2.4 SD) during acute abstinence. These values were statistically different when compared with seven normal controls and the subjects' values during sustained abstinence ($P < 0.02$). In conclusion, the results of the present study suggest increased daily production of cortisol as a possible mechanism underlying the elevated serum cortisol concentrations in chronic alcoholics during acute abstinence. This abnormality is shown to be reversible with sustained abstinence from alcohol.

Key words: cortisol, adrenal, hypothalamic-pituitary-adrenal, alcohol, ethanol, alcoholism, biologic rhythms.

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Acute and chronic intake of alcohol has been reported to alter hypothalamic-pituitary-adrenal function in both animals (Keith et al, 1983; Guaza and Borrell, 1983; Rivier et al, 1984) and humans (Bellett et al, 1970; Stokes, 1973; Linkola et al, 1979). Such alterations are usually manifested as increased plasma cortisol concentrations and elevated levels of urinary free cortisol as well as nonsuppressibility of plasma cortisol after dexamethasone administration (Swartz and Dunner, 1982; Del Porto et al, 1985; Burov et al, 1986). The presence and severity of these changes are determined by several factors, including 1) duration of alcohol intake (acute vs. chronic); 2) timing of the study (during or following alcohol intake); and 3) presence or absence of related disorders such as pancreatitis, malnutrition, and/or cirrhosis of the liver.

Under physiologic conditions, cortisol is secreted episodically and maintains a circadian rhythmicity. Such patterns can be identified by frequent blood sampling extending over a 24-hour period (Krieger et al, 1971; Weitzman et al, 1971). Repetitive venous sampling has been used to define the pathophysiology of abnormalities in a variety of disorders affecting the hypothalamic-pituitary-adrenal axis (Van Cauter and Refetoff, 1985; Linkowski et al, 1985; Tourniaire et al, 1986). Such studies have been limited in alcoholics (Prinz et al, 1980; Bertello et al, 1982; Rosman et al, 1982) and have not addressed

cortisol secretory patterns in otherwise healthy chronic alcoholics during abstinence from alcohol.

The present study was designed to assess the nature of abnormalities in the 24-hour pulsatile and circadian patterns of cortisol secretion in otherwise healthy chronic alcoholic men shortly after discontinuation of alcohol. These investigations were repeated in the same individuals to determine the effect of longer periods of abstinence on the recovery of the hypothalamic-pituitary-adrenal axis.

Materials and Methods

Subjects

As described in Table 1, a total of 10 alcoholic men with ages ranging from 29 to 59 years (mean 41 ± 11) participated in this study. All subjects met DSM III criteria for alcohol dependence (American Psychiatric Association, 1980) and had been consuming alcohol for a period of 4 months or longer. A detailed history and physical examination and appropriate laboratory testing (serum albumin, transferrin, prothrombin time, hepatic and renal function tests, electrolytes, T₃RU, T₄, TSH, and prolactin [PRL]) were performed to rule out any associated medical conditions or consumption of drugs that could have adverse effects on the hypothalamic-pituitary-adrenal axis. As a selection criterion for this study, all subjects were screened and agreed to participate in a 4-week inpatient alcoholic rehabilitation program. Informed consent, approved by the Institutional Investigation Committee, was obtained from all subjects. Seven normal nonalcoholic male volun-

TABLE 1. Characteristics of Alcoholic Subjects During Baseline and Follow-up Studies

Subjects	Age (Years)	Alcohol History		Withdrawal Symptoms on Study Day	Days of Abstinence		Mean 24-Hour Cortisol ($\mu\text{g/dl}$)	
		Type	Duration		Baseline Study	Follow-up Study	Baseline	Follow-up
D.K.	38	Beer	> 1 yr	No	6	39	9.86	8.53
M.R.	51	Beer	4 months	No	3	29	8.64	7.88
C.W.	29	Beer	> 1 yr	No	5	35	8.24	7.95
R.W.	54	Whiskey	> 1 yr	No	7	38	9.95	7.97
H.R.	32	Beer	> 1 yr	Yes	6	32	17.22	9.76
J.R.	39	Whiskey	> 1 yr	No	9	39	9.33	8.42
T.T.	42	Beer	7 months	Yes	3	38	13.24	9.16
H.J.*	59	Beer	> 1 yr	No	9	—	7.30	—
Y.W.*	34	Whiskey	1 yr	No	16	—	12.96	—
B.R.*	30	Beer	> 1 yr	No	3	—	10.89	—

*Follow-up studies could not be done in these patients.

teers who met the above laboratory screening requirements in the age range of 21 to 66 years (mean 33 ± 18) served as controls.

Study Design

The protocol was designed to study each alcoholic subject twice: once during acute abstinence and again after sustained abstinence from alcohol. The exact timing of the studies in each individual as related to his last drink of alcohol is shown in Table 1. Each individual participated continuously in the inpatient alcohol rehabilitation program during the interval between the two study periods. Daily supervision and random weekly blood alcohol determinations were used to monitor the patient's abstinence from alcohol. Each study period lasted 24 hours. Samples of blood were drawn through an I.V. catheter every 20 minutes as described previously (Veldhuis et al, 1984). Serum concentration of cortisol was determined on each individual sample obtained during the 24-hour period.

Assays

Serum concentrations of cortisol were measured by RIA using a kit from Clinical Assays (Dade, Baxter-Travenol Diagnostics, Inc., Cambridge, MA). Each sample was assayed in duplicate and all samples from one subject were assayed in the same run to avoid interassay variations. The sensitivity of the RIA was $0.5 \mu\text{g}/\text{dl}$, with intra-assay coefficients of variations of 2.7% to 4.5% and interassay variability of 3.4% to 5.6%.

Pulse Analysis

Cluster analysis was employed to quantitate objectively the pulsatile properties of cortisol (Veldhuis and Johnson, 1986). Samples obtained at 20-minute intervals over a 24-hour period were used to assess mean 24-hour cortisol levels, number of pulses, interpulse intervals, peak duration, peak height (maximal height of peak), fractional pulse amplitude (% increase above nadir), peak increment (increase above nadir), along with interpulse valley mean and nadir concentrations. The variance model used in Cluster analysis was the median experimental within-sample standard deviation determined from all 73 samples in each subject. The test nadir and peak sizes were 2 and 1 samples, respectively, with t statistics of 2.62 to allow for a maximal false-positive rate of 5% on random measurements (signal-free noise).

Circadian Rhythmicity

The 24-hour cortisol concentration time series was analyzed as a Fourier expansion. The Fourier transform of the concentration data yields a function that traverses all the data points exactly as a linear composite of distinct cosine and sine functions with $(N-1)/2$ periodicities. Since each coefficient of this linear combination of sine and cosine functions is orthogonal, the standard deviation of the individual coefficients can be determined by linear least-squares estimation models (Bloomfield, 1976).

Evaluation of Endogenous Secretory Episodes and Clearance

A multiple parameter deconvolution model (Veldhuis et al, 1987) was used to determine the locations, amplitudes, and durations of all statistically significant underlying cortisol secretory bursts, while simultaneously estimating the endogenous half-life of cortisol disappearance.

Data Analysis

The 24-hour mean cortisol concentration as well as pulsatile cortisol characteristics in alcoholic men during acute and sustained abstinence were compared with each other and to the results obtained in normal healthy controls. The two-tailed Student's paired and unpaired t -tests were employed to evaluate differences in the mean 24-hour, as well as interpulse valley and nadir concentrations of cortisol. Because of departures from normality, other cortisol pulse characteristics, including pulse frequency, interpulse interval, peak width, maximum peak height, percent increase in peak height, and peak increment, were analyzed by the Wilcoxon (nonparametric) test. Paired tests were used to compare the data in alcoholic subjects during acute and sustained abstinence, while unpaired tests were employed to assess differences between alcoholics and controls.

Results

Of 10 alcoholic individuals who participated in the first phase of the study, seven successfully finished the 4-week alcoholic rehabilitation program and could be studied a second time. Serum levels of T_3 , T_4 , TSH, PRL, transferrin, albumin, hemoglobin and prothrombin time were normal in all subjects. Mild elevations of liver enzymes (< 3 -fold) were present in 30% of the patients but resolved in a period of 1 to 3 weeks after admission.

Mean 24-Hour Cortisol Levels

The mean 24-hour serum cortisol concentration of $10.76 \mu\text{g}/\text{dl} \pm 0.94$ (SEM) in 10 alcoholic men during acute abstinence (3 to 16 days) was not significantly different from that of normal controls ($9.24 \mu\text{g}/\text{dl} \pm 0.25$ SEM; $P > 0.05$). However, as shown in Fig. 1A, the individual 24-hour integrated serum cortisol concentration was increased above the normal range (95% confidence limit) in six of the alcoholic subjects. Follow-up studies in seven men after 29 to 39 days of abstinence showed a significant decrease in the mean serum cortisol concentration from a mean of 10.9 ± 1.2 (SEM) to a mean of $8.5 \pm 0.26 \mu\text{g}/\text{dl}$ ($P = 0.047$). While there was a decrease in the mean serum cortisol concentration in each one of the seven alcoholics (Fig. 1A), it was most prominent in subjects with

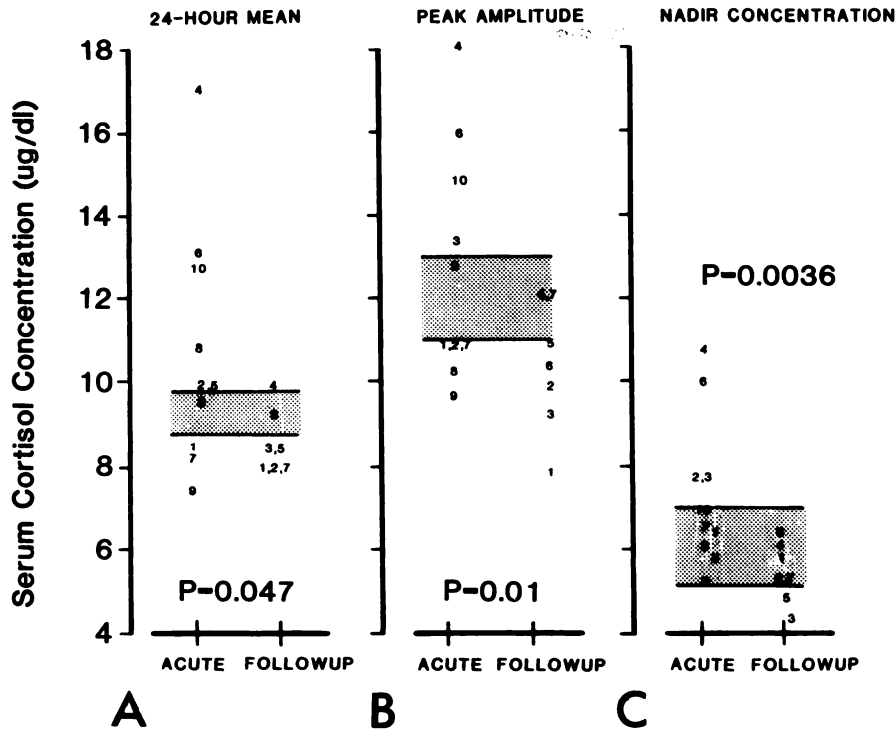


Fig. 1. Mean 24-hour serum concentrations, peak amplitudes, and nadir concentrations of cortisol during acute and sustained abstinence in alcoholic subjects. The numbers denote individual volunteers. The stippled area encompasses the 95% confidence limits of the normal range.

abnormally high levels of cortisol during the acute phase.

Episodic Cortisol Secretion

The 24-hour cortisol pulsatile characteristics of normal and alcoholic men are shown in Table 2. Even though the peak amplitude (Fig. 1B) and nadir con-

centration (Fig. 1C) of cortisol was increased in some of the alcoholic men during acute abstinence, there were no significant differences in cortisol peak frequencies and other pulse properties between alcoholic men as a group and normal controls. Nonetheless, sustained abstinence (29 to 39 days) caused a significant decrease in maximal cortisol peak ampli-

TABLE 2. Pulsatile Cortisol Properties in Chronic Alcoholics (Baseline and Follow-up) and Normal Controls Studied over 24 hours*

Subjects (Status)	24-hour Mean (μg/dl)	Number of Pulses/ 24 hr	Interpulse Interval (min)	Peak Characteristics			Valley		
				Duration (min)	Height (μg/dl)	Peak Increase (%)	Increment (μg/dl)	Mean (μg/dl)	Nadir μg/dl)
Alcoholics									
Baseline									
10 (No.)†	10.8 ± 0.94	7.6 ± 0.43	169 ± 8	119 ± 7	12.9 ± 0.87	198 ± 13.6	5.1 ± 0.48	8.5 ± 0.74	7.3 ± 0.57
7 (No.)‡	10.9 ± 1.2	8.0 ± 0.53	165 ± 11	115 ± 9	13.0 ± 1.0	185 ± 11.3	4.9 ± 0.52	9.3 ± 0.88	7.9 ± 0.69
Follow-up									
7 (No.)	8.5 ± 0.26	7.7 ± 0.18	154 ± 9	111 ± 8.0	10.3 ± 0.52	220 ± 18	4.5 ± 0.50	6.5 ± 0.34	5.4 ± 0.30
Normal controls									
7 (No.)	9.2 ± 0.25	8.1 ± 0.51	160 ± 11	114 ± 8	12 ± 0.56	202 ± 13	5.2 ± 0.30	7.4 ± 0.35	6.0 ± 0.32

*All values are presented as mean ± SEM.

†Mean values in 10 alcoholic men who were studied during acute abstinence.

‡Mean values in seven of 10 alcoholic men who were studied both during acute and sustained abstinence.

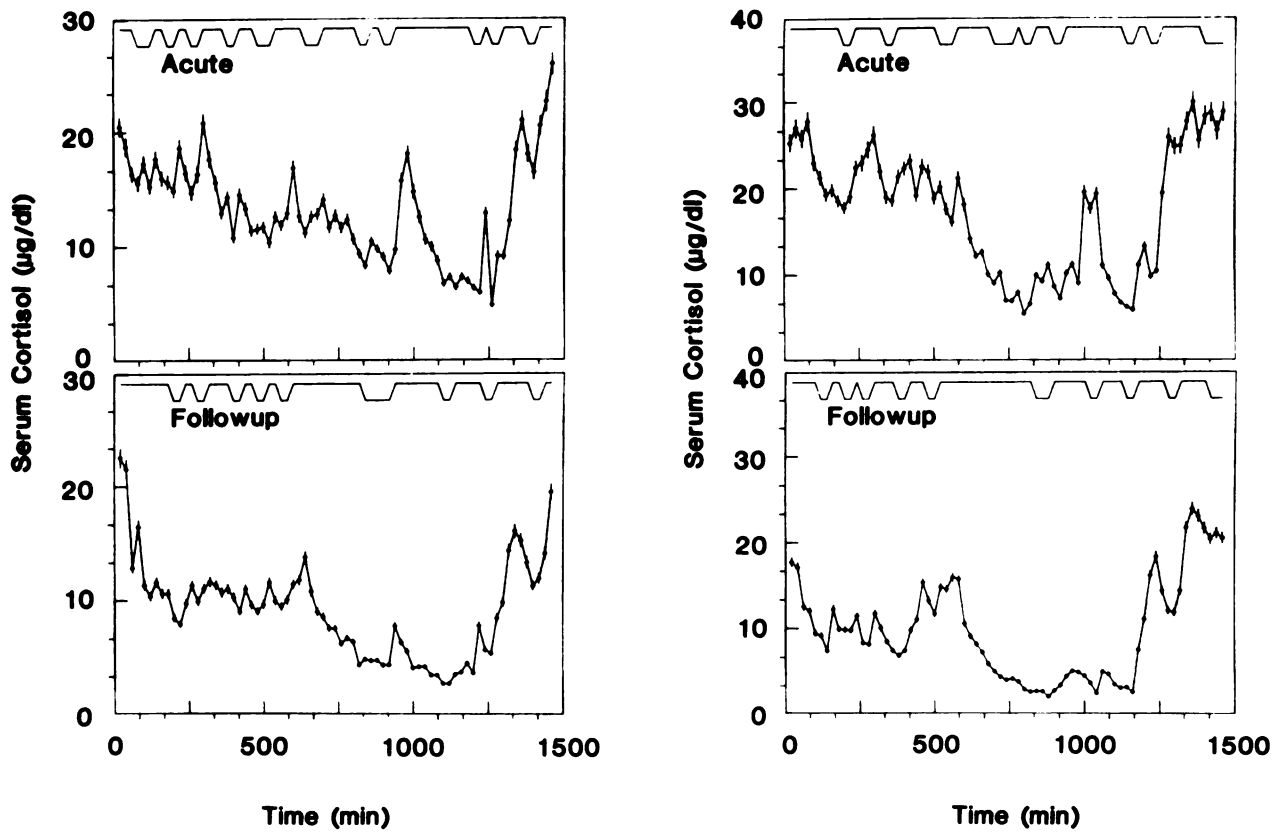


Fig. 2. Illustrative profiles of spontaneous cortisol pulsatility in two alcoholic men (subjects T.T. and H.R., Table 1) with elevated mean 24-hour serum cortisol concentrations during acute abstinence. Lower panels are cortisol profiles in the same subjects after sustained abstinence. Each data point represents a sample whose mean value was determined from duplicate measurements; vertical bars designate the intrasample standard deviation of the replicates. Schematized deflections on the top of each panel denote cluster identified peaks.

tude (Fig. 1B: $P = 0.01$), mean interpulse valley nadir (Fig. 1C: $P = 0.0036$), and mean valley concentration of cortisol ($P = 0.007$).

Profiles for individual (Fig. 2) and group mean (Fig. 3) serum cortisol concentrations revealed significant normal circadian patterns (quantitation of circadian patterns is discussed below). However, differences between the 24-hour cortisol concentration curves in alcoholics and normal subjects seemed to occur mostly during the wake period with a tendency to disappear at the time of circadian acrophase. This observation was examined further by dividing each 24-hour cortisol time series into two 12-hour periods, designated as "wake" and "sleep." The sleep period, extending from 0 to 1200 hours, was intended to cover the timing of circadian acrophase in both normal and alcoholic men. The wake period extended from 1200 to 2400 hours. Mean serum cortisol concentrations of $9.73 \mu\text{g/dl} \pm 1.13$ during the wake period in seven alcoholic men (acute abstinence) were

significantly different from the follow-up (sustained abstinence) mean of $7.15 \mu\text{g/dl} \pm 0.48 \text{ SEM}$ ($P = 0.03$) and the mean of $7.1 \mu\text{g/dl} \pm 0.46$ in normal controls ($P = 0.05$). On the other hand during the sleep period, there were no statistically significant differences between serum mean cortisol concentrations in alcoholic men at baseline ($11.86 \mu\text{g} \pm 1.36$), follow-up ($9.8 \mu\text{g} \pm 0.45$; $P = 0.87$), and in normal controls ($11.25 \mu\text{g} \pm 0.27$). Analysis of data in the individual alcoholics with elevated mean serum cortisol concentrations showed increases in cortisol levels during both periods but increases during the wake period were more prominent.

Circadian Rhythmicity

To quantitate circadian variations in serum cortisol concentrations, the data in alcoholic and normal men were subjected to Fourier analysis. Significant cortisol circadian rhythmicity was maintained in alcoholics but, as illustrated in Fig. 4, the timing of the

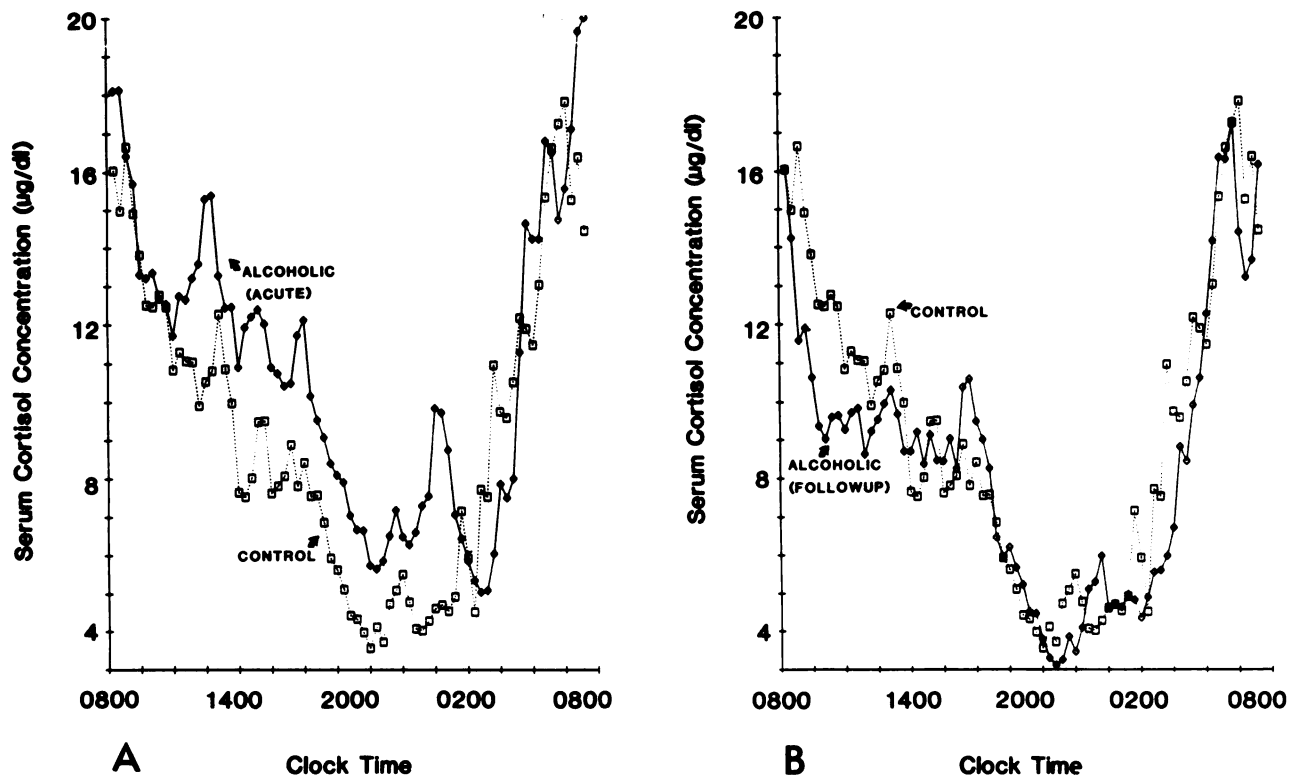


Fig. 3. Mean 24-hour profile of serum cortisol concentrations in seven alcoholic men during acute (A) and sustained (B) abstinence compared with seven normal men. Each data point represents the mean serum cortisol value for the groups of alcoholic and normal men. Serum cortisol concentrations were determined in each individual blood sample collected at 20-minute intervals over a 24-hour period. For comparison, the control curve is shown in both panels.

circadian acrophase (maximal cortisol concentration) was delayed during acute abstinence in all but one of the subjects. The mean baseline circadian acrophase in the alcoholics occurred at 1022 (clocktime) \pm 34 minutes. This value was significantly delayed when compared with 0743 (clocktime) \pm 34 minutes found in the normal group ($P = 0.006$). In addition, the amplitudes of circadian cortisol rhythms significantly exceeded the normal range in five of 10 alcoholics (Fig. 5). While longer periods of abstinence (29 to 39 days) from alcohol resulted in normalization of circadian cortisol amplitude (Fig. 5), the timing of acrophase continued to be delayed in four of the seven subjects studied for the second time (Fig. 4).

Estimation of Endogenous Secretion and Clearance Rate

To determine endogenous secretion and clearance rate of cortisol, the 24-hour time series in one of the alcoholic men with the highest mean 24-hour cortisol level was subjected to analysis by a multiple param-

etric deconvolution model (Veldhuis et al, 1987). Figure 6 illustrates the 24-hour profiles of serum cortisol concentrations in this subject during acute and sustained abstinence. Serial cortisol concentrations collected at 20-minute intervals are shown in the upper panels. The lower panel in each figure plots the resolved (computed) cortisol secretory bursts underlying the serum pulsatile profile. The specific properties of cortisol secretory events in this subject as inferred by multiple parameter deconvolution are summarized in Table 3. When compared with normal controls, secretory burst amplitude, mass of cortisol released per burst and daily endogenous cortisol production rate during acute abstinence were significantly increased (all P -values < 0.02). In contrast, the resolved half-life of endogenous cortisol disappearance, the half-duration of cortisol secretory bursts and the mean intersecretory burst intervals were not different. These findings indicate increased secretion rather than decreased clearance of cortisol during

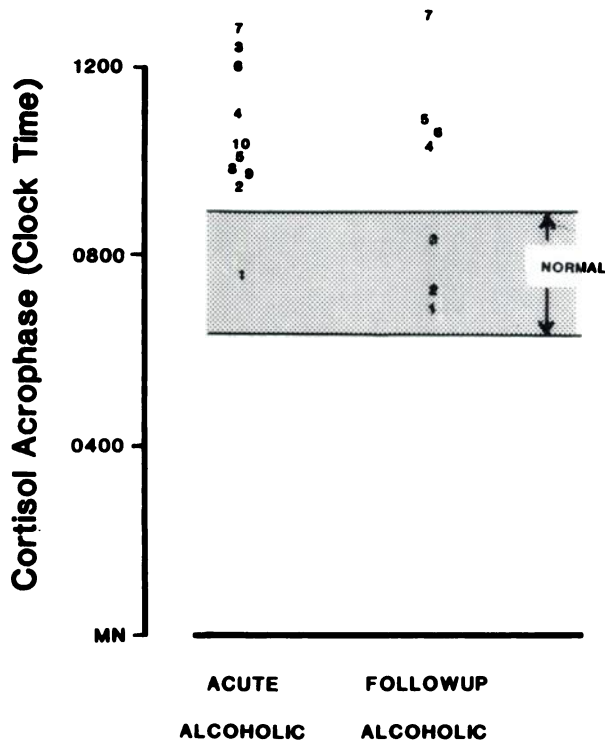


Fig. 4. Clocktime of circadian acrophases for serum cortisol concentrations in alcoholic men during acute (1022 ± 34 min SEM) and chronic (0940 ± 51 min SEM) abstinence. The numbers correspond to individual volunteers. The stippled area contains the normal range (95% confidence limits).

acute abstinence, an abnormality that was reversible in this subject with longer periods of abstinence (Table 3).

Discussion

Studies of pulsatile and circadian patterns of cortisol secretion in alcoholic subjects are limited in number and do not provide consistent results. In a study of acute and chronic effects of alcohol withdrawal in normal men during sleep, Prinz et al (1980) did not observe significant alterations in plasma cortisol levels or the diurnal timing of the cortisol rise. Bertello and his colleagues (1982) have also reported a normally synchronized circadian rhythm in their study of alcoholic men with hypogonadal features and a moderate degree of liver disease who continued to consume alcohol on a regular basis. Twenty-four-hour pulsatile and circadian patterns of cortisol release in patients with chronic alcoholic liver disease have been studied by Rosman et al (1982). These authors reported normal mean 24-hour total and

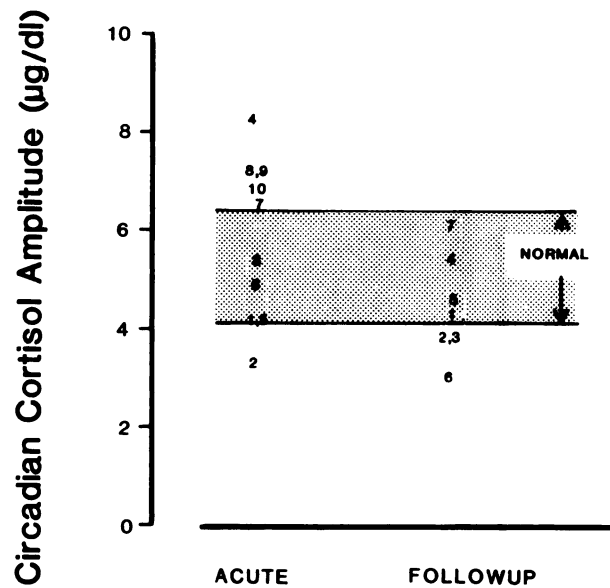


Fig. 5. Amplitude of circadian cortisol rhythmicity in alcoholics during acute ($5.7 \mu\text{g/dl} \pm 0.53$ SEM) and sustained abstinence ($4.3 \mu\text{g/dl} \pm 0.42$ SEM). The numbers correspond to individual volunteers. The stippled area is the normal range (95% confidence limits).

free plasma cortisol accompanied by a normal circadian rhythmicity but decreased circadian amplitude, decreased pulse frequency, decreased 24-hour "secretory time," and presumptively prolonged disappearance rate of cortisol. In contrast to these reports, we found an elevated integrated mean 24-hour serum cortisol concentration, normal cortisol pulse frequency, increased circadian amplitude, and delayed timing of the circadian acrophase in alcoholic men during acute abstinence. In addition, estimation of endogenous cortisol secretion and clearance in one of our subjects revealed a normal disappearance with an increased production rate of cortisol. These contradictory results are not surprising, because alcoholics can form a heterogeneous group due to enormous variations in their ages, nutritional states, and presence or absence of liver disease. Our study in a selected subgroup of chronic alcoholics who did not have any clinical or laboratory evidence of hepatic failure or nutritional deficiency allowed investigation of a more homogeneous group.

The pathogenesis of abnormal cortisol secretory dynamics in chronic alcoholics is not clear. Such changes could be due to direct effects of ethanol, sympathetic hyperactivity associated with withdrawal, and/or associated depressive disorders. While

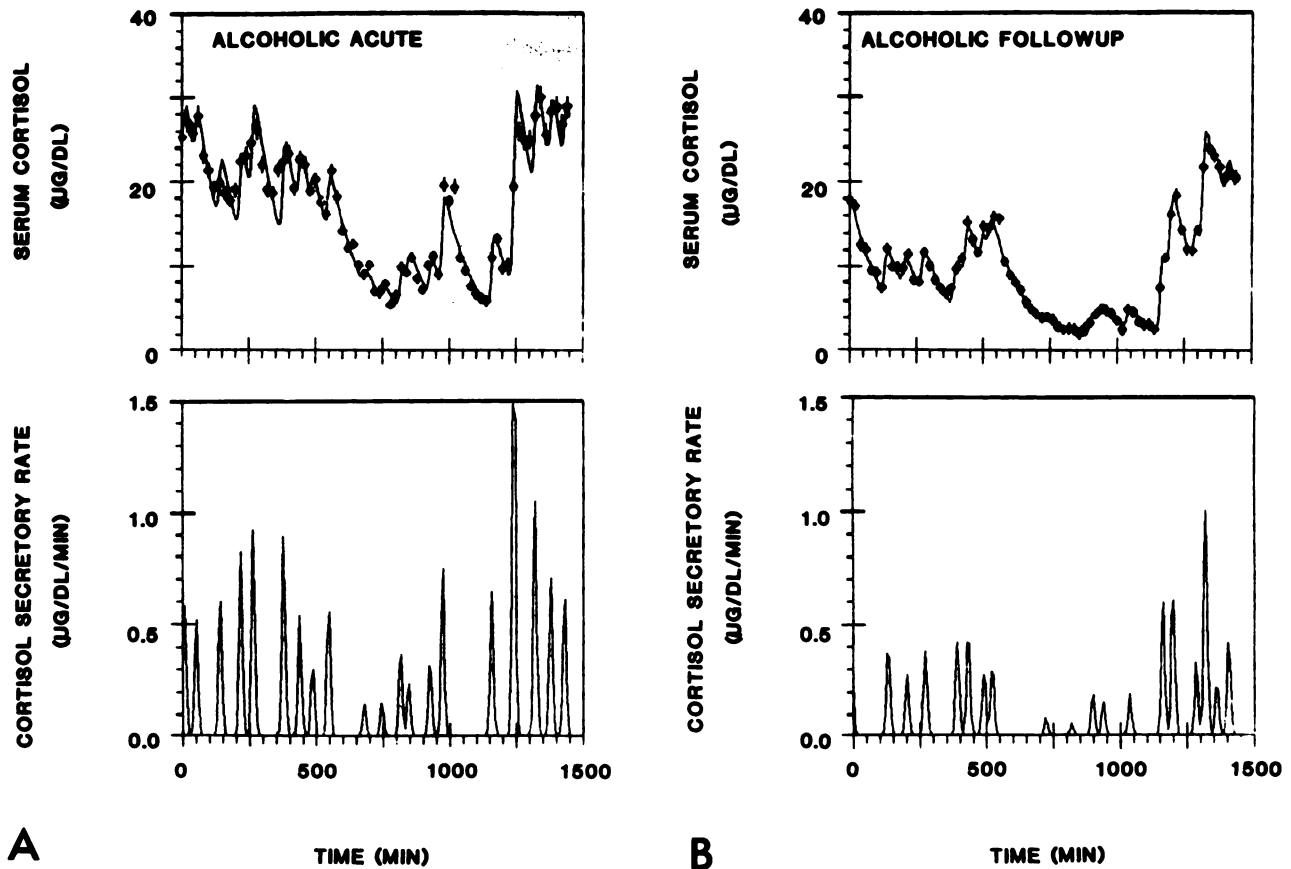


Fig. 6. Twenty-four-hour profile of serum cortisol concentrations in one alcoholic man during acute (A) and sustained (B) abstinence. The upper panels depict serial cortisol concentrations measured in blood collected at 20-minute intervals for 24 hours. Vertical marks through each sample mean denote the intrasample variance calculated by a power function fit of all sample replicates against dose. The continuous line through the observed serum cortisol concentrations represents a reconvolution fit calculated from the multiple parameter deconvolution model of combined secretion and clearance (Veldhuis et al, 1987). In the lower panels, the calculated secretion function is plotted against time. The secretion function comprises a finite number of distinct secretory bursts of defined amplitude, half-duration, and location in time.

ethanol is reported to have a direct effect on the hypothalamic-pituitary-adrenal axis (Magraf et al, 1967), it does not seem to be a likely mechanism in our study since all subjects were studied 3 days or more after their last drink of alcohol and elevated mean 24-hour cortisol concentrations were observed as late as 16 days into abstinence.

Changes in cortisol secretory dynamics could be secondary to the stress of withdrawal, inasmuch as abnormalities of cortisol secretion are reported to occur with both physical and emotional stress (Czeisler et al, 1976; Curtis et al, 1978; McIntosh et al, 1981). The postsurgical stress-induced changes in cortisol secretion described by McIntosh et al (1981) are very similar to the findings in our alcoholic men. These authors reported a postoperative increase in mean 24-hour serum cortisol concentrations in the

presence of a normal pulse frequency, sustained circadian rhythmicity but delayed timing of the circadian acrophase.

Withdrawal from ethanol is believed to be associated with overactivity of the sympathetic nervous system (Linnoila et al, 1987), which could alter the function of the hypothalamic-pituitary-adrenal axis. Administration of an alpha-1 adrenoreceptor agonist has been reported to stimulate ACTH secretion in a dose-dependent manner (Al-Damluji et al, 1986). In addition, studies of 24-hour cortisol time series have shown that adrenergic stimulation increases the plasma cortisol concentration only during the "wake" hours, without having any stimulatory effect on the early morning circadian surge of cortisol secretion (Al-Damluji et al, 1987). Such a finding has led to the belief that potentially distinct control mechanisms

TABLE 3. Deconvolution Estimates of Cortisol Secretion and Clearance During Acute and Sustained Abstinence from Alcohol in One Alcoholic Man*

Secretory or Clearance Parameter	Acute Abstinence	Sustained Abstinence	Controls
Half-life of endogenous cortisol disappearance (min)	87 ± 11 (NS)	88 ± 5	73 ± 5.8
Half-duration of cortisol secretory burst (min)	14 ± 2 (NS)	15 ± 1	16 ± 0.61
Inter-secretory burst interval (min)	75 ± 8.3 (NS)	79 ± 10	77 ± 4.3
Secretory burst amplitude (μg/dl/min)	0.64 ± 0.080†	0.39 ± 0.055	0.45 ± 0.049
Mass of cortisol released per burst (μg/dl)	9.8 ± 1.2†	6.3 ± 0.89	7.5 ± 0.67
Daily endogenous cortisol production rate (mg/day)‡	22 ± 2.4†	12 ± 1.6	16 ± 3.8

*Data are means ± SEM (N = 6 men) for the controls and means ± SD for the alcoholic subject. NS = significantly different from follow-up or control.

†P less than 0.02 vs. follow-up and/or control.

‡Assuming an average distribution volume of 11.3 liters.

may be involved in the regulation of cortisol secretion at different times during the 24-hour period, with adrenergic stimulation predominantly operative during the wake hours. In this regard, we note that the 24-hour pattern of cortisol secretion in our alcoholics as a group was maintained at a higher baseline level only during the wake hours. This observation was further verified when the 24-hour time series were divided into wake and sleep periods. The mean serum cortisol concentration in seven alcoholic men as a group during baseline studies (acute abstinence) was significantly increased only during the wake period. Therefore, it can be suggested that the sympathetic overactivity associated with alcohol withdrawal represents a plausible mechanism underlying the derangement in the hypothalamic-pituitary-adrenal axis during acute abstinence. However, this interpretation should be viewed with caution since increases in both wake and sleep periods were present when alcoholics with elevated levels of cortisol were considered individually. Nonetheless, even in these individuals the cortisol increment was higher during the wake period.

Alterations in cortisol secretory patterns could be secondary to depression, which is commonly (28% to 59%) associated with alcoholism (Dackis et al, 1986). Elevated serum concentrations of cortisol and diminished suppression by dexamethasone have been reported in both depression and alcoholism. Moreover, an attenuated ACTH and a normal cortisol response to ovine corticotropin releasing hormone is similarly reported in alcoholic subjects (Linnoila et al, 1987) and depressed individuals (Gold et al, 1986). Additionally, akin to our findings in chronic alcoholic men, subjects affected by major depressive illnesses

are reported to have an increased mean 24-hour cortisol level, a normal cortisol pulse frequency, an increased pulse amplitude, and a normal circadian rhythmicity (Linkowski et al, 1985). Nonetheless, recovery of the hypothalamic-pituitary-adrenal axis with sustained abstinence, as demonstrated by us and others (Willenbring et al, 1984; Del Porto et al, 1985) without any specific antidepressive therapy, would militate against depression as a predominant explanation for cortisol abnormalities in alcoholism. The degree of similarity between depression and chronic alcoholism in the dynamics of cortisol secretion suggests the existence of a common underlying mechanism, the nature of which deserves further study.

In conclusion, we have demonstrated elevated mean and integrated 24-hour serum cortisol concentrations and delay of the circadian cortisol acrophase in a group of chronic alcoholic men during acute abstinence. We have also shown that although serum cortisol concentrations become normal with longer periods of abstinence (29 to 39 days), some delay in cortisol circadian acrophase persists. Deconvolution results permit us to postulate increased cortisol secretion as a probable mechanism underlying the abnormally high levels of cortisol during acute abstinence in these subjects. Although adrenergic stimulation of the hypothalamic-pituitary-adrenal axis during withdrawal may have a role, the exact mechanism(s) subserving these changes are not yet clear. Future studies are needed to verify the presently demonstrated abnormalities in cortisol release, as well as to clarify the underlying pathogenesis and to assess complete recovery of circadian rhythmicity with longer periods of abstinence.

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References

- Al-Damluji S, Grossman A, Besser GM. Central alpha-1 adrenoceptors stimulate ACTH secretion in man. *J Physiol* 1986; 374:45P(Abstr).
- Al-Damluji S, Cunnah D, Perry L, Grossman A, Besser GM. The effect of alpha adrenergic manipulation on the 24 hour pattern of cortisol secretion in man. *Clin Endocrinol* 1987; 26:61-66.
- American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 3rd ed (DMS III). Am Psychiatric Ass, 1980.
- Bellet S, Roman L, DeCastro O, Herrera M. Effect of acute ethanol intake on plasma 11-hydroxycorticosteroid levels. *Metabolism* 1970; 19:664-667.
- Bertello P, Agrimonti F, Gurioli L, Frairia R, Fornaro D, Angeli A. Circadian patterns of plasma cortisol and testosterone in chronic male alcoholics. *Alcoholism (NY)* 1982; 6:475-481.
- Bloomfield P. Fourier analysis of time series: an introduction. New York: John Wiley and Sons, 1976.
- Burov YV, Treskov VG, Vedernikova NN, Shevelyova OS. Types of alcohol withdrawal syndrome and dexamethasone suppression test. *Drug Alcohol Depend* 1986; 17:81-88.
- Curtis GC, Nesse R, Buxton M, Lippman D. Anxiety and plasma cortisol at the crest of the circadian cycle: reappraisal of a classical hypothesis. *Psychosom Med* 1978; 40:368-378.
- Czeisler CA, Moore-Ede MC, Regestein QR, Kisch ES, Fang VS, Erlich EN. Episodic 24-hour cortisol secretory patterns in patients awaiting elective cardiac surgery. *J Clin Endocrinol Metab* 1976; 42:273-283.
- Dackis CA, Stuckey RF, Gold MS, Pottash ALC. Dexamethasone suppression test testing of depressed alcoholics. *Alcoholism (NY)* 1986; 10:59-60.
- Del Porto JA, Monteiro MG, Laranjeira RR, Jorge MR, Masur J. Reversal of abnormal dexamethasone suppression test in alcoholics abstinent for four weeks. *Biol Psychiatry* 1985; 20:1156-1160.
- Gold PW, Loriaux DL, Roy A, Kling MA, Calabrese JR, Kellner CH, Nieman LK, Post RM, Pickar D, Gallucci W, Avgerinos P, Paul S, Oldfield EH, Cutler GB, Chrousos GP. Responses to corticotropin-releasing hormone in the hypercortisolism of depression and Cushing's Disease: pathophysiology and diagnostic implications. *N Engl J Med* 1986; 314:1329-1335.
- Guaza C, Borrell S. Adrenomedullary responses to acute and chronic ethanol administration to rats. *Biochem Pharmacol* 1983; 32:3091-3095.
- Keith LD, Crabbe JC, Robertson LM, Young ER. Ethanol dependence and the pituitary adrenal axis in mice. II. Temporal analysis of dependence and withdrawal. *Life Sci* 1983; 33:1889-1897.
- Krieger DT, Allen W, Rizzo F, Krieger HP. Characterization of the normal temporal pattern of plasma corticosteroid levels. *J Clin Endocrinol Metab* 1971; 32:266-284.
- Linkola J, Fyhrquist F, Ylikahri R. Renin, aldosterone and cortisol during ethanol intoxication and hangover. *Acta Physiol Scand* 1979; 106:75-82.
- Linkowski P, Mendlewicz J, Leclercq R, Brasseur M, Hubain P, Golstein J, Copinschi G, Van Cauter E. The 24-hour profile of adrenocorticotropin and cortisol in major depressive illness. *J Clin Endocrinol Metab* 1985; 61:429-438.
- Linnoila M, Mefford I, Nutt D, Adinoff B. Alcohol withdrawal and noradrenergic function. *Ann Intern Med* 1987; 107:875-889.
- McIntosh TK, Lothrop DA, Lee A, Jackson BT, Nabseth D, Egdahl RH. Circadian rhythm of cortisol is altered in post-surgical patients. *J Clin Endocrinol Metab* 1981; 53:117-122.
- Margraf HW, Moyer CA, Ashford LE, Lavalle LW. Adrenocortical function in alcoholics. *J Surg Res* 1967; 7:55-62.
- Prinz PN, Roehrs TA, Vitaliano PP, Linnoila M, Weitzman ED. Effect of alcohol on sleep and nighttime plasma growth hormone and cortisol concentrations. *J Clin Endocrinol Metab* 1980; 51:759-764.
- Rivier C, Bruhn T, Vale W. Effect of ethanol on the hypothalamic pituitary-adrenal axis in the rat: role of corticotropin-releasing factor (CRF). *J Pharmacol Exp Ther* 1984; 229:127-131.
- Rosman PM, Farag A, Benn R, Tito J, Mishik A, Wallace EZ. Modulation of pituitary-adrenocortical function: decreased secretory episodes and blunted circadian rhythmicity in patients with alcoholic liver disease. *J Clin Endocrinol Metab* 1982; 55:709-717.
- Stokes PE. Adrenocortical activation in alcoholics during chronic drinking. *Ann NY Acad Sci* 1973; 215:77-83.
- Swartz CM, Dunner FJ. Dexamethasone suppression testing of alcoholics. *Arch Gen Psychiatry* 1982; 39:1309-1312.
- Tournaire J, Chalendar D, Rebattu B, Fevre-Montange M, Bajard L, Mazonod B, Dechaud H, Abou Samra AB, Van Cauter E. The 24-h cortisol secretory pattern in Cushing's syndrome. *Acta Endocrinol* 1986; 112:230-237.
- Van Cauter E, Refetoff S. Evidence for two subtypes of Cushing's disease based on the analysis of episodic cortisol secretion. *N Engl J Med* 1985; 312:1343-1349.
- Veldhuis JD, Evans WS, Rogol AD, Drake C, Thorner MO, Merriam GR, Johnson ML. Intensified rates of venous sampling unmask the presence of spontaneous high frequency pulsations of luteinizing hormone in man. *J Clin Endocrinol Metab* 1984; 59:96-102.
- Veldhuis JD, Johnson ML. Cluster analysis: a simple, versatile and robust algorithm for endocrine pulse detection. *Am J Physiol* 1986; 250:E486-E493.
- Veldhuis JD, Carlson ML, Johnson ML. The pituitary gland secretes in bursts: appraising the nature of glandular secretory impulses by simultaneous multiple-parameter deconvolution of plasma hormone concentrations. *Proc Natl Acad Sci* 1987; 84:7686-7690.
- Weitzman ED, Fukushima D, Nogeire C, Roffwarg H, Gallagher TF, Hellman L. Twenty-four hour pattern of the episodic secretion of cortisol in normal subjects. *J Clin Endocrinol Metab* 1971; 33:14-22.
- Willenbring ML, Morley JE, Niewoehner CB, Heilman RO, Carlson CH, Shafer RB. Adrenocortical hyperactivity in newly admitted alcoholics: prevalence, course and associated variables. *Psychoneuroendocrinology* 1984; 9:415-422.