the persistence of a renal disturbance far greater than that usually seen in cardiac failure.

The simplest explanation of our findings is that they are a nonspecific stress response, but we have found normal results in patients equally ill from other causes. Espiner (1966), in a study of patients with "medical stress," found raised urinary cortisol excretion accompanied by an increase in the plasma levels, particularly early in the stress period. One of his patients who also was in cardiac failure had plasma cortisol levels similar to those of our patients. We have observed our patients after the first day of admission and seen abnormalities in plasma cortisol levels throughout an episode of cardiac failure. One patient (Case 1) did not show normal suppression with dexamethasone. These results suggest that there might be an alternative mechanism, possibly outside the pituitary-adrenal axis. This might be related to the known abolition of the circadian rhythm of urinary water and electrolyte excretion in congestive cardiac failure (Brod and Fejfar, 1950; Baldwin, Sirota, and Villarreal, 1950; Goldman and Luchsinger, 1956) the mechanism of which is not yet fully elucidated.

Some patients with cardiac failure have secondary aldosteronism. Haemodynamic changes induce a rise in renin-angiotension production, which is largely, if not entirely, responsible for increased aldosterone secretion (Conn, Cohen, and Rovner, 1964). The method used in this study estimates both cortisol and corticosterone. Bledsoe, Island, and Liddle (1966) reported that sodium depletion caused an increased production of aldosterone precursors in subjects maintained on dexamethasone. Secretion of corticosterone, which occurs in the aldosterone metabolic pathway, was increased, while cortisol secretion was unaffected. Thus the possibility that we are observing an increase in corticosterone levels rather than cortisol must be considered.

In the only previous study of cortisol levels in heart failure that we were able to find the authors reported high plasma levels at an unstated time in the evening, with normal morning levels (Pekkarinen, Iisalo, Kasanen, Laihinen, and Thomasson, 1960). They did not report such a complete return to normal as we have seen, nor did they report failure to suppress cortisol secretion with dexamethasone.

Further investigations are being carried out in an attempt to elucidate our findings and if possible to correlate them with the disturbance in the electrolyte and water excretion. We report them at this preliminary stage because we feel that the diagnosis of Cushing's syndrome, based on plasma cortisol levels, in patient's with concomitant congestive cardiac failure should be made with caution.

Summary

Abolition of the circadian rhythm in plasma cortisol levels, with elevation of the midnight values, is reported in five patients with congestive cardiac failure. The disturbance in rhythm persisted throughout an episode of failure and appears to be unrelated to other nonspecific stress mechanisms. The possible mechanisms causing these disturbances are discussed. These findings are of importance in the differential diagnosis of Cushing's syndrome, based on plasma cortisol levels where there is concomitant congestive cardiac failure.

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Circadian Rhythm of Plasma 11-Hydroxycorticosteroids in Depressive Illness, Congestive Heart Failure, and Cushing's Syndrome

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A well-marked circadian rhythm—that is, a rhythm with a periodicity of 24 hours—in the adrenal output of cortisol was first suspected from the pattern of urinary 17-hydroxycorticosteroid excretion (Pincus *et al.*, 1948). This was confirmed by Migeon *et al.* (1956), who measured plasma levels of 17-hydroxycorticosteroids. Doe *et al.* (1960) reported the absence of this rhythm in Cushing's syndrome. A study of plasma cortisol, as 17-hydroxycorticosteroid or as free 11-hydroxycorticosteroid content, at two or more times in the day has now become a standard investigation in cases of suspected Cushing's syndrome (Cope, 1965, 1966). A knowledge of the circadian rhythm of 11-hydroxycorticosteroid in other diseases is therefore of increasing importance.

Perkoff *et al.* (1959) studied 80 patients in an American hospital. They found that the plasma 17-hydroxycorticosteroid rhythm was similar to that of healthy people not in hospital, except in patients with disturbed consciousness or with fever. The only difference was in the level at 04.00 hours. This was usually higher in subjects in hospital and closer to the level at 08.00 hours than to that at 24.00 hours. A possible explanation is the early hour of awakening in American hospitals. These authors did not include patients with psychiatric illness, cardiac failure, or Cushing's syndrome. Pekkarinen *et al.* (1960) pub-

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lished values for conjugated and free 17-hydroxycorticosteroids in the plasma of 120 patients with cardiac insufficiency. They compared values in blood samples taken at 08.00 and 20.00 hours and found that the normal rhythm was lost or even reversed in many severe cases. They have shown similar disturbances after surgical operations, in renal disease, and to a less marked extent in diabetes (Iisalo and Pekkarinen, 1965). Though we have not found reports of similar studies in depressive illness, Lobban *et al.* (1963) demonstrated an increase in the nocturnal urine volume and its electrolyte content when such patients were compared with "neurotic" controls.

In this paper we describe the results of plasma 11-hydroxycorticosteroid studied over 24-hour periods in depressive illness, congestive heart failure, and Cushing's syndrome.

Material and Methods

The circadian rhythm of plasma was studied in four groups:

Controls—Group 1A: This comprised seven persons in good health, including hospital doctors, medical students, and their wives. *Group 1B:* These seven patients were in hospital awaiting operation for conditions not thought to be associated with a disturbed rhythm.

Group 2. Six Patients with Depressive Illness (Cases 1–6).—Their ages ranged from 41 to 65. They were ambulant in a psychiatric ward of a general hospital. None of them had received drugs during the preceding two days and none had shown any improvement with admission to hospital. The principal symptom was of a persistent lowering of mood, mostly in the morning. All had a history of early morning waking—that is, 2 to 4 a.m.—of at least four weeks' duration. Other symptoms included feelings of self-deprecation and depressive delusions. All later improved and were discharged from hospital within six weeks.

Group 3. Ten Patients with Congestive Cardiac Failure (Cases 7–16).—Brief details of these patients are given in Table I. All except two were in bed. Seven were receiving digitalis, and none received diuretics on the day of the study. Most of them were orthopnoeic, but none was acutely dyspnoeic. All had signs of right-sided heart failure. Three patients with chronic rheumatic heart disease had had prolonged or recurrent cardiac failure, and one of these had probable cirrhosis of the liver due to cardiac failure.

TABLE I.—*Patients With Congestive Heart Failure*

Case No.	Age	Sex	Diagnosis	Treatment
7	23	F	Aortic incompetence	Digoxin. Previous diuretics
8	55	M	Hypertensive heart disease	Not receiving drugs
9	53	M	Ischaemic heart disease	" "
10	69	M	Cor pulmonale	Digoxin. Previous diuretics
11	77	M	Ischaemic heart disease	" " "
12	46	F	Chronic rheumatic heart disease	" " "
13	53	M	Probably cardiomyopathy	Digoxin. No diuretics
14	68	F	Ischaemic heart disease	Not receiving drugs
15	37	F	Chronic rheumatic heart disease	Digoxin. Previous diuretics
16	54	F	" " " "	" " "

Group 4. Five Patients with Cushing's Syndrome (Cases 17–21).—Brief details of these are given in Table II. One case of adrenal carcinoma, one case of adrenal adenoma, and three cases of adrenal hyperplasia (one with a large pituitary adenoma) were studied.

Except for the healthy controls all were in hospital and most were studied during the first week as inpatients. None of the patients received sedatives, tranquillizers, or antidepressants during the period of study. Except for the depressive group none of the patients had very disturbed sleep rhythms, though some of those in heart failure had occasional episodes of wakefulness due to orthopnoea. Both the controls and the patients were awakened for the venepunctures, usually they returned fairly quickly to sleep. Venous samples were taken at four-hourly intervals for 24 hours except in group 1B controls, in whom samples were taken at 04.00 and 08.00 hours only. The plasma was separated within an hour and stored at 4° or −20° C. Plasma 11-hydroxycorticosteroids were estimated by the method of Mattingly (1962). The coefficient of variation for this method in our laboratory is 8% (95% limits) over the range 5–30 μg./100 ml.

TABLE II.—*Patients With Cushing's Syndrome*

Case No.	Age	Sex	Diagnosis (Proved at Operation)
17	51	F	Adrenal carcinoma
18	33	F	Adrenal adenoma
19	49	F	Pituitary adenoma with adrenal hyperplasia
20	47	M	Adrenal hyperplasia (normal pituitary fossa)
21	19	F	" " " " "

Results

Controls.—Group 1A (see Fig. 1 and Table III): There was a well-marked rhythm. Maximum values were at 08.00 hours Minimum values were found at 24.00 hours. These results are similar to those found by previous workers. Group IB: The values obtained at 04.00 hours and at 08.00 hours did not differ significantly (P>0.1) from those obtained in Group IA.

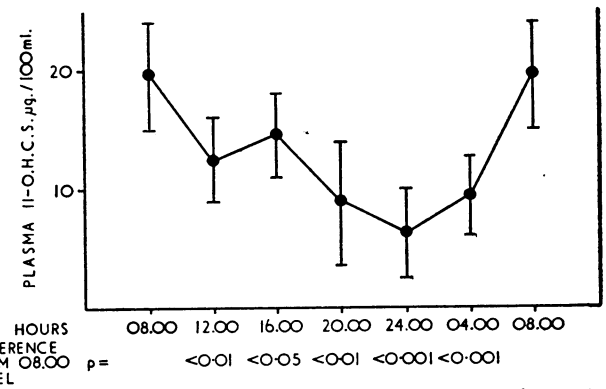

FIG. 1.—Mean concentrations (±1 S.D.) of 11-hydroxycorticosteroid (μg./100 ml.) from control subjects (group I).

TABLE III.—*Plasma 11-Hydroxycorticosteroid Values in μg./100 ml.*

Subject	08.00	12.00	16.00	20.00	24.00	04.00
			Group 1A			
A	25·0	9·3	14·3	1·3	0·6	7·9
B	21·1	12·9	10·0	10·0	6·1	12·4
C	11·5	9·3	18·5	7·9	6·1	4·3
D	18·6	15·6	14·4	8·7	12·0	6·3
E	21·2	8·9	19·6	4·3	3·0	13·2
F	23·0	16·4	—	19·6	9·3	12·2
G	16·6	12·9	9·5	10·2	7·8	7·7
			Group 1B			
H	21·3	—	—	—	—	15·2
I	15·0	—	—	—	—	7·5
J	9·0	—	—	—	—	10·0
K	10·5	—	—	—	—	11·0
L	12·0	—	—	—	—	16·0
M	13·5	—	—	—	—	6·0
N	24·5	—	—	—	—	16·5
			Group 2			
1	16·8	13·7	10·6	13·7	16·8	24·2
2	24·0	13·2	—	6·7	4·7	18·2
3	20·0	10·2	—	8·8	6·0	20·0
4	22·8	18·5	15·6	14·2	5·4	19·4
5	21·0	13·8	15·0	11·4	6·5	17·0
6	23·6	15·9	10·9	7·9	7·9	20·0
			Group 3			
7	30·5	25·5	20·3	20·3	26·5	29·3
8	23·5	12·1	16·2	16·2	11·6	15·6
9	32·0	17·7	22·5	21·4	19·2	23·0
10	37·0	—	38·0	27·0	32·0	40·5
11	15·5	12·5	15·0	10·5	16·5	18·5
12	13·0	10·5	9·0	8·0	5·5	9·5
13	18·0	22·5	14·0	12·0	17·5	26·0
14	23·0	17·5	15·5	33·0	15·5	24·0
15	13·0	10·5	9·0	8·0	5·5	9·5
16	13·0	11·0	8·5	10·5	11·0	22·5
			Group 4			
17	42·2	39	47	46·2	48	59·3
18	24·5	28	19·8	20·5	20·5	23·5
19	49·5	45·5	65+	—	65+	50
20	18·6	20·0	30·0	16·8	20·0	18·0
21	20·5	20·5	25	15·4	17·0	14·2

Group 2 (see Fig. 2 and Table III).—As a group their plasma 11-hydroxycorticosteroids were not significantly different from those of the control subjects except at 04.00 hours. At this time they were significantly higher than in the control group ($P<0.001$), the values having reached the levels normally seen at 08.00 hours.

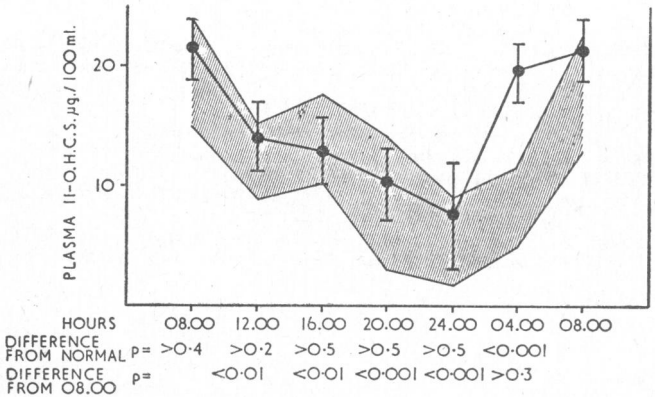

FIG. 2.—Mean concentration (±1 S.D.) of 11-hydroxycorticosteroid (μg./100 ml.) from patients with depressive illness (group 2). The shaded area represents ±1 S.D. from the mean values of control subjects.

Group 3 (see Fig. 3 and Table III).—When considered as a group these patients with congestive heart failure showed no rhythm in their plasma 11-hydroxycorticosteroids. The mean levels were in the normal range until 16.00 hours, after which the mean level and most individual levels were above normal. Two patients (Cases 12 and 15), both with low normal daytime values, had a normal rhythm. The only other patient with chronic rheumatic heart disease (Case 16) had a normal rhythm except for the high value at 04.00 hours.

Group 4 (see Fig. 4 and Table III).—All the patients with Cushing's syndrome showed little variation in plasma 11-hydroxycorticosteroids.

Discussion

Mills (1966) had pointed out that unless serial samples are taken throughout 24 hours the troughs and peaks of a circadian rhythm may be missed. We have attempted to avoid this source of error by taking seven specimens over 24 hours. In previous work on patients with congestive heart failure samples were taken at 08.00 and 20.00 hours only.

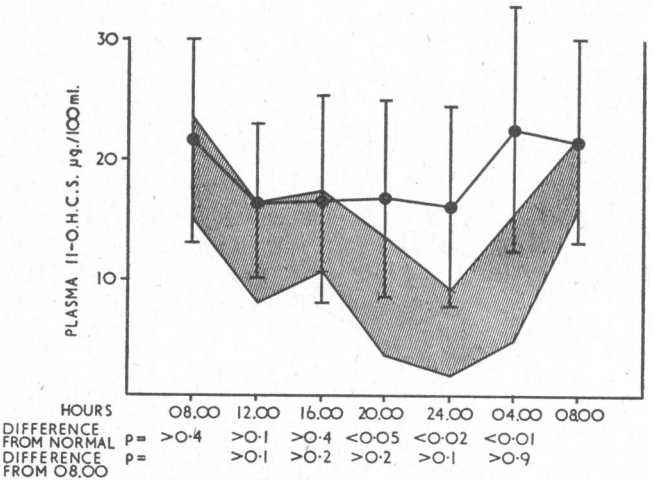

FIG. 3.—Mean concentrations (±1 S.D.) of 11-hydroxycorticosteroid (μg./100 ml.) from patients with congestive heart failure (group 3). The shaded area represents ±1 S.D. from the mean values of control subjects.

The abnormal rhythm which we have shown in patients with depressive illness affects only the period after midnight. It may perhaps be related to the history and observation that all these patients had the typical early waking that occurs in this condition. The normal rhythm of plasma 11-hydroxycorticosteroids has been lost in most of the patients with heart failure. The three patients with heart failure who had a nearly normal rhythm had chronic rheumatic heart disease. They had all been in heart failure before. There did not seem to be any other obvious clinical difference from the remainder of the patients in this group.

Previous workers have shown absent rhythm in Cushing's syndrome due to adenoma, carcinoma, or hyperplasia. This may result in normal morning levels but high levels later in the day. We have confirmed this finding. We have studied

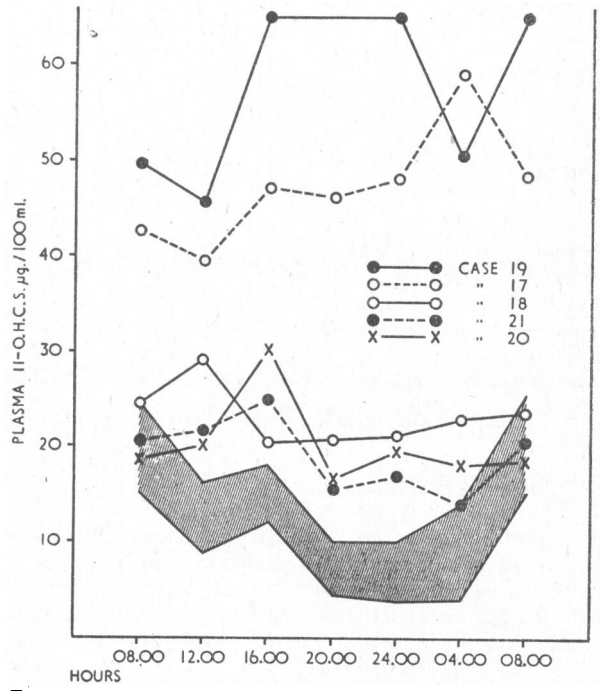

FIG. 4.—Plasma 11-hydroxycorticosteroid (μg./100 ml.) from five cases of Cushing's syndrome. The shaded area represents ±1 S.D. from the mean values of control subjects.

a patient, not included in this paper, who had Cushing's syndrome with a normal rhythm; similar cases have been described in the literature (Ekman *et al.*, 1961). In most patients, however, the absent rhythm is constant enough to allow the use of a single evening estimation of plasma cortisol as a valuable diagnostic test (Doe *et al.*, 1960; Ekman *et al.*, 1961; Mattingly, 1963). The absence of normal variations in plasma 11-hydroxycorticosteroids in heart failure could also cause confusion when heart failure and Cushing's syndrome may coexist.

It is interesting to consider the influence of the changes described on the circadian rhythm of renal function. Patients in congestive heart failure, with depressive illness or with Cushing's syndrome, sometimes have a higher than normal output of urine and electrolytes at night. The primary cause of this may be the disturbance in the circadian rhythm of adrenal function.

Summary

Plasma 11-hydroxycorticosteroids have been measured in plasma samples taken at four-hourly intervals over 24 hours from patients with depressive illness, congestive heart failure, and Cushing's syndrome. In those with depression a normal circadian rhythm was found, except at 04.00 hours. In con-

gestive heart failure and Cushing's syndrome it is unusual to have any obvious rhythm.

ADDENDUM.—Since submitting this paper for publication two reports have appeared of plasma cortisol values in depressive illness. Doig *et al.* (1966) have reported levels at 24.00, 03.00, and 06.00 hours and found a significant difference from controls only at 06.00 hours. Bridges and Jones (1966) have shown in their patients that between 09.30 and 21.30 hours a significant fall in plasma cortisol occurs, as in the depressives we have studied, though the mean values were higher than in our group of patients.

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Preliminary Communications

Relation between Maximal Acid Output of Stomach and Lean Body Mass

Brit. med. J., 1967, **2**, 30–31

The diagnostic value of the augmented histamine test (Kay, 1953) or of any other standard measure of gastric secretory function is seriously impaired by the marked overlap which exists between results obtained in a variety of gastric disorders, including peptic ulcer and gastric cancer, and those found in healthy subjects (Bruce *et al.*, 1959). Attempts to clarify the position by establishing significant associations between maximal acid output and body build by measurements of height, weight, and surface area in both normal adults and ulcer patients have failed (Baron, 1964). However, Ghai *et al.* (1965) were able to demonstrate a significant correlation ($r=0.81$) between body weight and maximal acid output in 16 healthy Indian children. Scrutiny of the data of these authors indicated that the mean weight of the children was 25.3 kg.; this was at least 10 kg. less than the corresponding expected weight of similar children in the United States as calculated from the tables of Nelson (1959). It seemed to us that a possible explanation of this discrepancy in weight might be that, for dietary reasons, the Indian children had less adipose tissue, and therefore their total body weight would tend to approach more closely the lean body mass or fat-free body weight. This paper presents preliminary observations which show that there is a significant correlation between maximal acid output and lean body mass in both normal adults and duodenal ulcer subjects.

METHODS AND MATERIALS

Normal Subjects (3 male, 5 female).—These were healthy volunteers whose ages ranged from 20 to 51, with a mean of 28.4 years. They had no dyspeptic symptoms or a family history of ulcer.

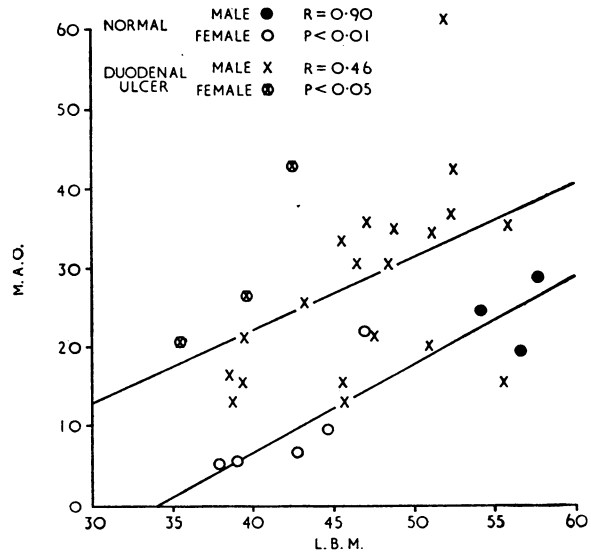
Ulcer Subjects (20 male, 3 female).—Their ages ranged from 16 to 65, with a mean of 41.5 years. Each had a radiologically proved duodenal ulcer.

Maximal acid output was measured by the augmented histamine test meal of Kay (1953).

Lean body mass was calculated from height and weight by the formula of Hume (1966), which is based on the measurement of total body water.

DISCUSSION

Analysis of the normal group (see Chart) shows that there is a significant correlation between the maximal acid output and lean body mass ($P<0.01$; $r=0.90$). Since the maximal acid output is believed to be directly related to the parietal cell mass (Marks, 1956; Card and Marks, 1960), it follows that the parietal cell mass correlates with the lean body mass. The low



L.B.M. = Lean body mass in kilograms. M.A.O. = Maximal acid output in mEq HCl. *Normal group*: Regression line of y (M.A.O.) on x (L.B.M.) is given by $y=1.0932\ x-36.75$. The standard deviation of deviations from the regression line is 19.0. *Duodenal ulcer group*: Regression line of y (M.A.O.) on x (L.B.M.) is given by $y=0.929\ x-15.17$. The standard deviation of deviations from the regression line is 112.9.