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COMPARATIVE STUDIES ON ADRENAL CORTICAL FUNCTION AND CORTISOL METABOLISM IN HEALTHY ADULTS AND IN PATIENTS WITH SHOCK DUE TO INFECTION

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Secretory failure of the adrenal glands has continued to be implicated as a factor in the pathogenesis of peripheral circulatory collapse due to infection since the original reports of Waterhouse (1) and of Friderichsen (2). This association of adrenal function and circulatory failure has been cited in recent reviews (3-5). However, a deficit of adrenal secretory products or their urinary metabolites in peripheral collapse due to infection has not been reported. Investigations in our laboratory have shown that shock produced in dogs by endotoxins of gram-negative bacteria was accompanied by an elevation of the concentration of cortisol in the plasma, and the output of cortisol in adrenal venous blood rose abruptly immediately after the injection of endotoxin (6).

This report is concerned with the assessment of adrenal cortical function in human patients having peripheral circulatory failure due to severe infections. Studies with a 21-hemisuccinate ester of cortisol, which is rapidly hydrolyzed to free cortisol *in vivo*, were undertaken in order to delineate the metabolism of cortisol, the principal adrenal secretory product in man (7).

METHODS

The subjects in this study included 9 healthy adults and 22 patients with severe infections complicated by circulatory collapse. Fifteen of these patients had demonstrable bacteremia at the time the studies were carried out. All of the patients were hypotensive with systolic blood pressures under 90 mm. of Hg. A summary of the clinical data on these patients is recorded in Table I.

Blood samples for the determination of cortisol concentrations in the plasma were analyzed by a modification of the method of Silber and Porter (8) as described by Peterson, Karrer and Guerra (9). This method is specific for steroids with the 17,21-dihydroxy-20-keto configuration including cortisol, cortisone, Compound S and their dihydro- and tetrahydro- derivatives. Of these, only cortisol exists in the plasma in significant concentrations; therefore, the method may be regarded as highly specific for cortisol.

Adrenal stimulation was carried out in eight normal subjects and in six patients with shock due to infection by an intravenous infusion of 25 U.S.P. units of corticotropin (Upjohn, Sterile Corticotropin Injection) dissolved in 500 ml. of 5 per cent dextrose in water, which was given over a period of four hours. Specimens of 15 ml. of heparinized blood were secured initially and at the conclusion of the infusion of corticotropin. The erythrocytes were separated from the plasma within 30 minutes. The samples were frozen and plasma cortisol levels were determined within 72 hours.

In order to determine the rate of disappearance of exogenous cortisol, an intravenous injection of 100 mg. of cortisol sodium succinate dissolved in 2 ml. of distilled water (Upjohn, Hydrocortisone Sodium Succinate) was given to each of 9 normal subjects and to 20 patients with shock. Samples of blood were obtained immediately preceding the injection of cortisol sodium succinate and at 30, 90, 150, 210 and 270 minutes thereafter in the patients with shock. The blood specimens were treated as above. The sodium succinate ester of cortisol was employed because it is highly soluble and because it can be administered in a small volume of aqueous diluent in a few seconds. Hydrolysis of the ester is rapid and complete within 15 minutes after injection. The ester is not extracted from plasma by methylene chloride which is employed as the solvent in the determination of plasma cortisol (10). The rate of removal of cortisol from the plasma of pregnant women was determined after the rapid infusion of cortisol sodium succinate by Christy, Gordon, Longson, Wallace and Jailer (11). The disposal of this cortisol ester did not significantly differ from cortisol removal rates following infusions of cortisol free alcohol. Madsen, Done, Ely and Kelley (12) found no significant differences in the plasma half-time of cortisol whether administered as the free alcohol or the 21-hemisuccinate ester.

In patients with shock these procedures were carried out within a few hours after the recognition of peripheral circulatory failure.

RESULTS

A. Relationship of the clinical status to the outcome

The data recorded in Table I reveal that demonstrable bacteremia was associated with shock in 70 per cent of the cases. Gram-negative bacteria

TABLE I
Clinical data on 22 patients with peripheral circulatory failure due to infection

No. Age Sex	Diagnosis	Bacteriology	Source of bacteria	Blood pressure	Duration of hypo- tension	Temp. in F.	Skin appearance	Outcome
1 28 M	Lobar pneumonia	<i>D. pneumo- coccus</i>	Sputum	80/55	24 hrs.	105.0	Warm, suffused	Recovered
2 70 F	Diabetes, urinary tract infection	<i>E. coli</i>	Blood Urine	60/30	24 hrs.	103.0	Warm, suffused	Recovered
3 64 M	Prostatic hypertrophy, cystoscopy	<i>E. coli</i>	Blood Urine	84/50	16 hrs.	104.4	Warm, suffused	Recovered
4 54 F	Postoperative ovarian cystectomy	<i>E. coli</i>	Urine	50/30	24 hrs.	105.0	Warm, suffused	Recovered
5 60 M	Urethral stricture, cystoscopy	Proteus	Blood Urine	72/50	12 hrs.	103.2	Warm, suffused	Recovered
6 38 M	Pseudomembranous enteritis	Staph.	Feces Blood	64/36	36 hrs.	104.0	Cold, moist	Recovered
7 52 M	Miliary tuberculosis	<i>M. tuberculosis</i>	Sputum	74/44	24 hrs.	104.0	Warm, suffused	Recovered
8 79 M	TUR, metastases from cancer of renal pelvis	<i>E. coli</i>	Blood Urine	80/50	24 hrs.	102.2	Warm, suffused	Recovered
9 58 F	Osteomyelitis, pyelonephritis	Staph.	Blood Wound	86/56	2 wks.	104.0	Cold, moist	Died
10 72 F	Chronic lymphatic leukemia, peritonitis, cirrhosis	Staph.	Blood Peri- toneal fluid	50/0	48 hrs.	101.0	Cold, moist	Died
11 60 F	Peritoneal abscess, metastatic adeno- carcinoma of colon	<i>E. coli</i>	Blood	50/30	48 hrs.	102.0	Cold, moist	Died
12 84 M	Massive pneumonia, renal abscess	Staph.	Blood Sputum	75/50	6 hrs.	102.4	Cold, moist	Died
13 73 M	Cancer of prostate, pneumonia	Staph.	Sputum Urine	40/0	18 hrs.	104.0	Cold, moist	Died
14 48 F	Perforated ulcer with peritonitis	Proteus <i>E. coli</i>	Peri- toneal fluid		8 hrs.	97.0	Cold, cyanotic	Died
15 85 F	Postoperative bowel obstruction, staph. septicemia with metastatic abscesses	Staph.	Blood Urine	70/40	10 hrs.	100.0	Cold, cyanotic	Died
16 62 M	Pyelonephritis, cholangitis, purpura, hepatic abscesses	Pseudomonas <i>E. coli</i>	Blood	60/40	6 days	104.0	Cold, moist	Died
17 53 M	Suppurative peritonitis, postoperative gastrectomy	Pseudomonas	Blood Peri- toneal fluid	55/0	6 days	103.0	Cold, moist	Died
18 62 F	Pulmonary emboli	<i>E. coli</i> <i>Strep. viridans</i>	Urine Blood	80/50	10 days	101.0	Warm, dry	Died
19 67 M	Total gastrectomy for cancer of stomach, post-gastrectomy	Proteus Staph. Pseudomonas	Sub- phrenic abscess Empyema	80/0	10 days	103.0	Cold, cyanotic	Died

TABLE I—Continued

No. Age Sex	Diagnosis	Bacteriology	Source of bacteria	Blood pressure	Duration of hypo- tension	Temp. in F.	Skin appearance	Outcome
20 72 M	Postoperative cholecystectomy, diabetes mellitus	<i>E. coli</i>	Blood	66/30	24 hrs.	102.0	Cold, moist	Died
21 86 M	Urethral stricture	<i>E. coli</i>	Urine Blood	78/50	24 hrs.	101.0	Warm, suffused	Recovered
22 75 M	Postoperative cancer of stomach	<i>Pseudomonas aeruginosa</i>	Urine Sputum	80/54	24 hrs.	103.0	Warm, suffused	Recovered

were most frequently isolated. The severity of the underlying infectious process is emphasized by the fact that staphylococci were isolated from the blood in 50 per cent of those who died. Nine autopsies were performed in the series and no adrenal pathological change could be demonstrated, except in one patient, who had a hematoma of a single adrenal. A characteristic difference in the appearance of those who died from those who recovered was recorded frequently enough to note. The patients who succumbed displayed more often an ashen gray, cold, moist skin with mottling and cyanosis such as is encountered in severe hemorrhagic shock. The survivors had suffused, warm skin and a full pulse in the presence of hypotension. The dichotomy in the clinical picture of shock has been reported by Waisbren (13) and by Hall and Gold (14). The two groups differed significantly in the period of time they remained hypotensive. Whereas the patients who recovered were hypo-

tensive for an average of 23 hours, the patients who succumbed were hypotensive for an average of six to seven days. Pressor substances were used to maintain blood pressure during the hypotensive period and all patients were considered to be hypotensive until they no longer required pressor substances for the maintenance of blood pressure.

B. Concentration of cortisol in the plasma

The results of this study are given in Table II. In the healthy subjects the concentrations of plasma cortisol averaged 13 $\mu\text{g.}$ per 100 ml., with a range of from 7 to 22 $\mu\text{g.}$ per 100 ml. In this control group, all samples were obtained at 8:00 a.m. The mean plasma cortisol concentrations of patients with shock due to infection was 63 $\mu\text{g.}$ per 100 ml., ranging from 30 to 160 $\mu\text{g.}$ per 100 ml. The mean plasma cortisol concentration for the patients in shock was initially higher than

TABLE II
Concentration of cortisol in the plasma

Normal subjects				Patients with shock due to infection							
No.	Age	Sex	$\mu\text{g./100 ml.}$	Survivors				Fatalities			
				No.	Age	Sex	$\mu\text{g./100 ml.}$	No.	Age	Sex	$\mu\text{g./100 ml.}$
1	24	M	11	1	28	M	47	9	58	F	30
2	23	M	12	2	70	F	40	10	72	F	82
3	23	M	9	3	64	M	49	11	60	F	69
4	19	F	22	4	54	F	53	12	84	M	120
5	37	F	10	5	60	M	41	13	73	M	61
6	22	M	16	6	38	M	43	14	48	F	160
7	23	M	7	7	52	M	40	15	85	F	72
8	31	M	17	8	79	M	78	16	62	M	45
9	42	M	11					17	53	M	68
								18	62	F	36
								19	67	M	54
								20	72	M	74

Mean = $13 \pm 4^*$
Range = 7-22

Mean = 50 ± 12
Range = 40-78

Mean = 73 ± 34
Range = 30-160

* Standard deviation.

the mean plasma cortisol concentration in normals after a four hour infusion of corticotropin. In only one patient with shock was the plasma cortisol level within the normal range as obtained in this laboratory. The highest concentrations were found in the moribund patients.

C. Effect of an intravenous infusion of corticotropin on plasma cortisol concentrations

The results for normal subjects and for patients are summarized in Tables III and IV. Four hour intravenous corticotropin tests were performed in eight normal individuals. The mean control value for cortisol was 15 $\mu\text{g.}$ per 100 ml. of plasma, with a range of 5 to 24 $\mu\text{g.}$ per cent. Following the infusion of corticotropin, the concentrations rose to a range of 32 to 63 $\mu\text{g.}$ per cent with a mean of 46 $\mu\text{g.}$ per cent. Rarely have values exceeded 65 $\mu\text{g.}$ per cent in normal subjects after corticotropin. Four hour corticotropin tests were carried out in six patients with shock. The initial plasma cortisol levels averaged 53 $\mu\text{g.}$ per 100 ml. and ranged from 36 to 76 $\mu\text{g.}$ per 100 ml. After a four hour infusion of corticotropin the cortisol levels rose to an average level of 100 $\mu\text{g.}$ per 100 ml. of plasma, with a range of 81 to 119 $\mu\text{g.}$ per 100 ml. Three of the patients given corticotropin, all of whom died (Nos. 18, 19 and 20), had average postcorticotropin infusion levels of 112 $\mu\text{g.}$ per 100 ml. of plasma, whereas the mean value in three patients who recovered was 88 $\mu\text{g.}$ per 100 ml. Sand-

TABLE III

Effect of corticotropin (25 U.S.P. units intravenously over a four hour period) on plasma cortisol concentrations in normal subjects

Subject no.	Age	Sex	Plasma cortisol ($\mu\text{g./100 ml.}$)	
			Before corticotropin	After corticotropin
1	54	M	16	52
2	37	M	5	32
3	45	M	19	40
4	72	M	15	63
5	31	F	10	33
6	52	F	24	44
7	21	F	14	51
8	36	F	21	52
			Mean = 15 \pm 6*	Mean = 46 \pm 10
			Range = 5-24	Range = 32-63

* Standard deviation.

TABLE IV

Effect of corticotropin (25 U.S.P. units intravenously over a four hour period) on plasma cortisol concentrations in patients with shock due to infection

Patient no.	Age	Sex	Outcome	Plasma cortisol ($\mu\text{g./100 ml.}$)	
				Before corticotropin	After corticotropin
18	62	F	Died	36	119
20	72	M	Died	76	104
19	67	M	Died	51	114
3	64	M	Recovered	57	81
21	86	M	Recovered	45	96
22	75	M	Recovered	57	86
				Mean = 53	Mean = 100
				Range = 36-76	Range = 81-119

berg, Eik-Nes, Migeon and Samuels (15) have reported similar values in agonal patients. In their study the injection of cortisol-4-C¹⁴ into dying patients resulted in a reduced urinary excretion of radioactive metabolites when compared with the normal. They concluded that the high levels of plasma cortisol that they obtained were due to impaired metabolism in the presence of normally functioning adrenals. Urinary 17-hydroxycorticosteroid determinations were not made in the patients reported in this study because nearly all of the patients were oliguric and some rapidly developed azotemia. Under usual circumstances the excretion of urinary 17-hydroxycorticosteroids is a valuable index of cortisol production. But in shock, where there exists a reduction in urinary output coupled with retention of conjugated cortisol metabolites in the plasma, the results would be unreliable (16).

D. The rate of disappearance of infused cortisol sodium succinate from the plasma

Levels of plasma cortisol following the rapid infusion of 100 mg. of cortisol sodium succinate are shown in Figure 1. It is to be recalled that the mean initial plasma concentrations of cortisol in the patients who recovered and in those who died were significantly elevated compared to the values found in the normal subjects. However, in the patients who died, the initial levels were higher than those in the patients who survived. Levels of cortisol in the plasma after the infusion of cortisol sodium succinate are plotted on semi-logarithmic paper at various time intervals. The

initial preinfusion or endogenous values are not subtracted from the subsequent postinfusion levels. It should be noted that in the patients who survived most of the postinfusion plasma cortisol concentrations were less than the initial concentration of endogenous cortisol. Scheuer and Bondy (17) demonstrated in healthy subjects that plasma cortisol concentrations were lower than endogenous preinjection concentrations at five to seven hours after the injection of 100 mg. of cortisol-free alcohol. It cannot be assumed that the basal plasma levels of cortisol remain constant after an infusion of cortisol in the "stressed" subject in the light of considerable experimental evidence. Sydnor (18) has shown that the intravenous administration of cortisol to bilaterally adrenalectomized "stressed" rats effectively inhibits corticotropin secretion. Brodish and Long (19) in similar experiments found that complete inhibition of corticotropin release is accomplished within 5 to 20 minutes following the infusion of cortisol. Richards and Pruitt (20), using permanent adrenal vein cannulas in dogs, suppressed maximal adrenal secretory activity after the induction of respiratory acidosis and operative trauma by infusions of cortisol. Thus, it would seem unjustified to subtract initial plasma cortisol values from postinfusion values in patients with shock.

In Table V, the individual plasma biological

TABLE V

Biological half-time of plasma cortisol after the intravenous injection of 100 mg. of cortisol as the 21-hemisuccinate

Healthy adults		Patients with shock due to infection			
Subject no.	T $\frac{1}{2}$ (min.)	Survivors		Fatalities	
		Patient no.	T $\frac{1}{2}$ (min.)	Patient no.	T $\frac{1}{2}$ (min.)
1	110.0	1	106.2	9	169.1
2	102.1	2	79.5	10	332.3
3	78.9	3	85.9	11	566.1
4	65.7	4	87.1	12	661.5
5	112.5	5	105.8	13	300.0
6	131.2	6	80.6	14	592.1
7	70.0	7	95.4	15	360.8
8	142.8	8	120.0	16	578.8
				17	1,020.3
				18	444.3
				19	420.0
				20	173.0
Mean =	101.6	Mean =	95.1	Mean =	468.2
Range =	65.7-142.8	Range =	79.5-120.0	Range =	169.1-1,020.3

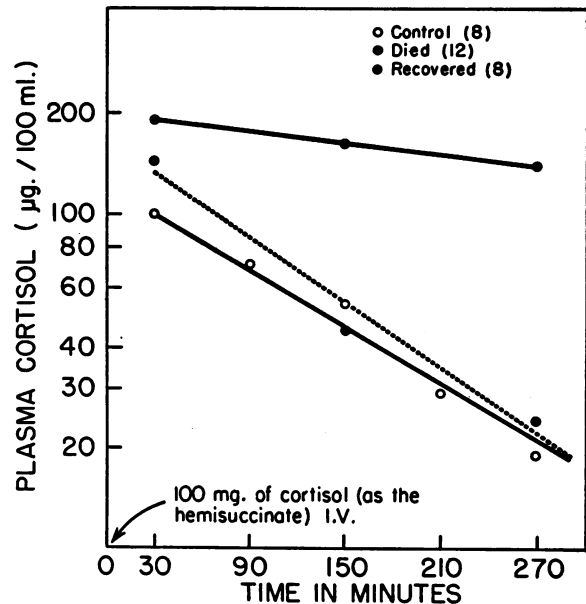


FIG. 1. RATE OF DISAPPEARANCE OF CORTISOL (INJECTED AS THE 21-HEMISUCCINATE) FROM PLASMA OF PATIENTS WITH SHOCK DUE TO INFECTION

half-times for cortisol were compared in healthy subjects, in patients who survived and in patients who died from shock due to severe infection. The mean biological half-time of cortisol in the normal subjects was found to be 101.6 minutes. In patients who recovered, this value was 95.1 minutes and in those who died, 468.2 minutes. The biological half-time of cortisol in the plasma is determined to a large extent by the functional integrity of the liver (16). Liver function tests were performed in six of the moribund patients. These were abnormal in all six patients tested. Liver function was assessed in four of the patients who survived and was found to be normal in all four patients. The half-time values of plasma cortisol in the healthy subjects and in the patients who survived are not significantly different.

DISCUSSION

The most significant feature in this study is that patients with shock due to an infection did not exhibit evidence of adrenal insufficiency. High concentrations of cortisol were present in the plasma in all patients studied. Furthermore, even in agonal patients there was a continued response of the adrenals to stimulation with corticotropin.

The high levels of cortisol in the plasma of the patients who recovered would appear to be solely due to an acceleration of the rate of production of endogenous cortisol because the administered cortisol disappeared from the plasma at a normal rate. On the other hand, the greater concentration of cortisol in the plasma of moribund patients may be accounted for, in part, by factors retarding the removal of cortisol from the blood and by increased cortisol production. The relative contribution of adrenal secretory activity to the high blood levels of cortisol could not be determined in the presence of impeded removal of injected cortisol from the plasma in the moribund patients. However, documented clinical and experimental evidence indicates that adrenal secretion of cortisol may be supranormal under similar conditions, in that the blood cortisol and urinary 17-hydroxycorticosteroid excretion were markedly elevated in patients dying of severe burns (21). Dogs subjected to hemorrhagic shock demonstrated a maximal secretion of cortisol (22). The shock induced in dogs by lethal injections of bacterial endotoxin is associated with high blood levels of cortisol and maximal secretion of cortisol in the adrenal venous effluent (23).

Factors influencing the slope of the plasma cortisol removal curves have been reviewed by Samuels, Brown, Eik-Nes, Tyler and Dominguez (16). If the curves plotted in Figure 1 are extrapolated to zero time it will be seen that the values obtained for the survivors and fatalities are not significantly different. Samuels and co-workers (16) refer to this value as the "apparent distribution volume" of cortisol. Thus, it appears unlikely that changes in the volume distribution of cortisol account for the difference observed. Impairment of hepatocellular function, hepatic blood flow, renal function and thyroid function all operate to reduce the rate of metabolic disposal of cortisol. All patients studied who were moribund were either markedly oliguric or anuric. The patients who survived demonstrated less significant abnormalities of renal function, *i.e.*, mild azotemia and transient oliguria.

Among the patients who died of bacterial shock, significant abnormalities of liver function were demonstrated. In none of the survivors studied was hepatic function significantly disturbed. In human patients major surgical pro-

cedures (24), agonal states (15), certain acute infectious diseases in childhood (25), myxedema (26) and liver disease (27) have been associated with reduced plasma cortisol removal rates. Tourniquet shock (28) retards the turnover of cortisol-4-C¹⁴ in the rat. In the dog lethal doses of endotoxin induce shock and slow the removal of injected cortisol from the plasma (23).

Eik-Nes and Samuels (29) have roughly correlated the severity of "stress" with the degree of impairment of cortisol removal from the plasma of the dog—the more severe or lethal the "stress," the greater the reduction of the rate of removal of cortisol from the plasma. Our own studies confirm this view (30). It should be pointed out that small doses of bacterial polysaccharide (0.1 to 2.0 $\mu\text{g.}$) injected into the dog accelerate the removal of exogenous cortisol from the plasma, whereas larger doses have the opposite effect. These observations supplement the results of McDonald, Weise and Peterson (31) who injected a bacterial pyrogen (Piromen®) into humans and noted a rise in plasma cortisol and an acceleration of the removal of exogenous cortisol from the plasma.

Although several factors probably influence the removal rate of exogenous cortisol from the plasma, it is conceivable that one of the most important independent variables in this study was the size of the bacterial inoculum and the amount of endotoxin made available.

Peterson, Pierce, Wyngaarden, Bunim and Brodie (32) have been unable to correlate the rate of disposal of cortisol or its analogs with its biological activity. Neither does cortisol exert its biological effects as a by-product of its catabolism. Any speculation as to rate of "utilization" of cortisol is not relevant. The term "relative adrenal insufficiency" in vascular collapse due to infection is misleading because the concentration of biologically active cortisol in the plasma is supraphysiologic. Daughaday (33) has demonstrated two protein binding systems for cortisol in the plasma. The first, a globulin, is saturated at plasma levels of between 15 and 30 $\mu\text{g.}$ per 100 ml. The second, albumin, binds cortisol more loosely and can accommodate high plasma concentrations of cortisol. This system is easily reversible and readily allows dissociation of cortisol so that it may traverse the capillary

membranes and become directly available to the tissues. Thus, it is likely that when the globulin system is exceeded the excess of plasma cortisol is freely diffusible. In the present study it would appear that under normal conditions adequate amounts of diffusible cortisol were available to the tissues in all of the patients studied. But under the unphysiologic conditions of shock these hormonal concentrations are insufficient. Observations on patients in shock and investigations in animals with endotoxin shock make it apparent that the necessary amount of exogenous cortisol or its synthetic analogs far exceeds that which can be produced by maximal endogenous secretory activity (5).

The importance of the relationship between the plasma concentration of readily diffusible cortisol and the degree of tissue injury has been demonstrated experimentally. These studies will be reported in detail elsewhere (34), but the essential data can be cited here. After dogs had been injected intravenously with endotoxin prepared from *E. coli*, there was a prompt rise in the plasma concentration of cortisol, and a rise in the level of serum glutamic oxaloacetic transaminase. It is generally assumed that elevations in serum transaminase are associated with cellular injury. It was apparent that maximal endogenous secretion of cortisol did not prevent the rise in transaminase levels. However, when large doses of cortisol were administered to the dogs along with the endotoxin there was only a small rise in the levels of transaminase. These observations suggest that the level of cortisol concentrations found within the physiological range are inadequate for protection against tissue injury. These observations support the concept that if cortisol is to be used as a therapeutic agent in fulminant sepsis with vascular collapse, its action and therefore its dose should be pharmacologic. In this context it does not represent "replacement" therapy.

SUMMARY

1. Adrenal function was studied in 17 healthy adults and in 22 adult patients having shock due to infection. Three quantitative studies were employed. First, the basal plasma cortisol level was determined. Second, the response of the adrenal to stimulation with corticotropin was

measured in terms of change in plasma cortisol concentration. Third, the biological half-time of exogenous cortisol injected as the succinate ester in plasma was evaluated.

2. All of the patients with shock had considerably higher basal concentrations of cortisol in the plasma than did the healthy subjects. In six patients with shock who were studied there was a response to corticotropin similar to that obtained in the healthy adults. The biological half-time of exogenous cortisol was not different from healthy subjects in those patients with shock who survived, but in those patients having fatal shock the biological half-time was considerably more prolonged than that observed in healthy subjects. The significance of these differences is discussed.

3. Accelerated adrenal secretory activity was demonstrated in those patients who survived. In moribund patients unequivocal proof for increased adrenal secretory activity could not be obtained.

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