THE EFFECTS OF SURGERY ON THE BLOOD LEVELS AND METABOLISM OF 17-HYDROXYCORTICOSTEROIDS IN MAN [1,2]

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The role of the adrenal cortex in the maintenance of homeostasis has been reviewed extensively by Sayers (1). It is evident from the experimental data published, as well as from observations on patients with adrenal insufficiency, that the adrenal cortex is necessary for the maintenance of life when untoward conditions are present in the environment. Such conditions have been referred to as "stresses" by Selye (2) and many others. "Stress," however, is such a nonspecific term that its use may lead to confusion. It has become apparent from studies in our laboratory that various noxious agents may have different effects on the circulating levels of 17-hydroxycorticosteroids. Consequently, the concept that all types of "stress" have a similar effect on adrenal secretion and adrenal steroid metabolism does not seem to be justified.

However, in a variety of such "stressful" circumstances (exposure to cold, trauma, histamine, *etc.*) in animals it has been demonstrated that a stereotyped series of events ensues which has been presumed to result from stimulation of the adrenal cortex by adrenocorticotrophic hormone (ACTH) (1, 3). In the adrenal cortex itself the changes have included depletion of ascorbic acid and cholesterol and increase in the weight of the gland. All of these are characteristic effects of ACTH

administration. Such effects are not found after hypophysectomy.

It has also been demonstrated that certain metabolic changes which are similar to the effects which follow the administration of adrenocortical steroids are observable in both man and animals after trauma. A number of studies have shown, however, that although the presence of adrenal hormone is essential for the intensification of the adrenal-controlled metabolic processes following trauma, similar responses are produced in adrenalectomized animals maintained on constant doses of adrenal cortical extract, cortisone or hydrocortisone, where there can be no question of increased adrenal hormone secretion (4–6). Epinephrine, which Cannon (7) demonstrated long ago to be regularly increased after "stress" and trauma, appears not to produce a rise in plasma 17-hydroxycorticosteroid levels in the human but requires the presence of small amounts of adrenal cortical hormone for its adrenal-like metabolic effects to become manifest (8, 9).

These findings suggested that it might be important to evaluate the effect of the trauma of surgical operations on plasma levels of adrenal steroids and on their secretion. It has been demonstrated that the metabolic effects of surgery simulate in certain respects the effects of the administration of adrenal steroids (10, 11).

Sayers and Sayers (12) have presented evidence to support the hypothesis that the apparent stimulation of the adrenal cortex by "stress" might be the result of a compensatory response of the hypophysis to the utilization of circulating steroid by the "stressed" tissue. In this case one would expect that the 17-hydroxycorticosteroid level would first be decreased, stimulating the output of ACTH. Furthermore, the adrenal cortical capacity (ability to secrete additional amounts of

adrenal steroids) might be expected to be impaired because of the increased spontaneous output. In order to examine this hypothesis, we have used a test of adrenal cortical capacity in man. This test is based on the effect of a maximally stimulating intravenous dose of ACTH on the circulating steroid levels. The details of the technique and the results in normal individuals have been presented in detail in an earlier paper (13). The effect of surgical trauma on the rate of disappearance of intravenously administered hydrocortisone was also determined.

METHODS AND MATERIALS

In patients undergoing surgery, blood samples were obtained by venesection when the patient arrived in the operating-room, following the induction of anesthesia, and at regular intervals during and following the surgical procedures. On certain patients control studies were performed at least one week before or four weeks after the operation.

All patients received the usual preoperative medications. These usually consisted of some barbiturate the night before and morphine and atropine on the morning of the operation.

Plasma 17-hydroxycorticosteroid levels were determined by a modification of the method of Eik-Nes, Nelson, and Samuels (14). The term 17-hydroxycorticosteroids, as used in this paper, is understood to refer to adrenal cortical steroids with a 17,21-dihydroxy-20-ketone group, such as cortisone, hydrocortisone, Reichstein's substance S, and the hydrogenated derivatives of these compounds. The method, however, does not measure the conjugated forms of these steroids in plasma. Circulating eosinophils were counted by the method of Randolph (15).
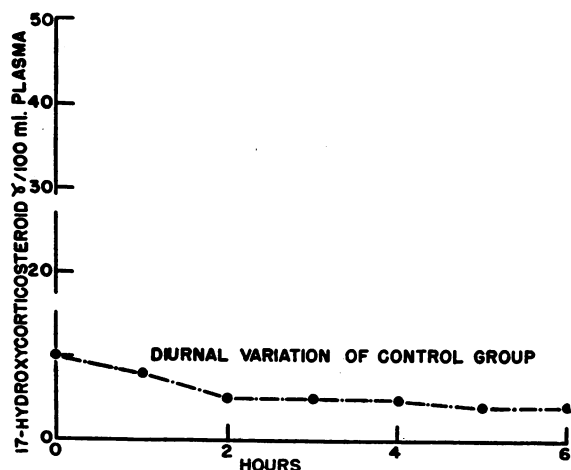

FIG. 1. DIURNAL VARIATION OF PLASMA 17-HYDROXYCORTICOSTEROIDS, BEGINNING AT 8 A.M. (0 HOURS), IN NORMAL SUBJECTS

Adrenal cortical capacity was tested by the intravenous infusion of maximally stimulating amounts of ACTH over a 6-hour period (13). Venous blood samples were drawn for determination of plasma 17-hydroxycorticosteroid levels before and at 2, 4, and 6 hours after the infusion was started.

The ability to remove excess hydrocorticosterone was determined by the infusion of 50 mg. of hydrocortisone (free alcohol) in saline solution containing a small amount of ethanol (16).

RESULTS

Plasma 17-hydroxycorticosteroid levels in normal subjects and the diurnal variations of these levels

During the progress of these experiments plasma 17-hydroxycorticosteroids were determined in 84 non-surgical subjects. The average 8 A.M. level was 13 μg per 100 ml. of plasma with a total range of 3 to 22 μg per 100 ml. of plasma. The average curve of diurnal variation in normal individuals from this series is shown in Figure 1. It will be observed that the level is high in the morning (8 A.M.) with a gradual decline during the day, as previously described (17).

Changes in plasma 17-hydroxycorticosteroids following anesthesia

It will be noted in Table I that none of the 12 patients in whom 17-hydroxycorticosteoid levels were measured at 8 A.M. before the induction of anesthesia showed a plasma 17-hydroxycorticosteroid level above the normal upper limit of 22 μg per 100 ml. of plasma. The average is the same (13 μg per 100 ml.) as that observed in a larger series of normal controls (17). Thus, neither the apprehension of the approaching surgical procedure nor the underlying clinical conditions had a significant effect on the plasma levels of 17-hydroxycorticosteroids. Following the induction of anesthesia the levels of 17-hydroxycorticosteroids rose to an average of 19 μg per 100 ml. of plasma. Although the number of cases is small, it was interesting to note that the induction of general anesthesia (pentothal, cyclopropane, ether) was associated with an increase in the plasma 17-hydroxycorticosteroid levels in seven out of eight cases but that after induction of spinal anesthesia only one patient showed a higher level. Since this last value was higher than that found two

TABLE I

Effect of anesthesia and surgery on plasma concentrations of 17-hydroxycorticosteroids

No.	Age and sex	Anesthesia	17-OH corticosteroids ($\gamma/100$ ml.) after beginning of operation								Operation
			Before anesthesia	After anesthesia	1 hr.	2 hrs.	3 hrs.	4 hrs.	5 hrs.	6 hrs.	
1	59 F	Pentothal and cyclo then ether	15	23	26	47	52		65		Cholecystectomy
2	70 F	Pentothal and ether	18	25	26		40				Smith-Peterson nailing
3	56 F	Pentothal and cyclo	9	11	12	25	24	25			Resection of lung
4	72 F	Pentothal and cyclo	18	25	31	40	38				Cholecystectomy
5	84 M	Cyclo	4	9	2	4	5				Cholecystectomy
6	65 F	Pentothal and cyclo	14	13		40	40	34		42	Abdominal-perineal resection of carcinoma of colon
7	80 M	Pentothal and cyclo	12	33		38					Smith-Peterson nailing
8	56 M	Pentothal cyclo and ether	10	27		43	40	35			Gastrectomy (carcinoma of stomach)
9	70 M	Spinal	9	9		26					Prostatectomy
10	16 F	Spinal	6	6	20	20					Appendectomy
11	50 F	Spinal	20	17	20	30					Hemorrhoidectomy
12	69 M	Spinal	19	35		27					Suprapubic prostatectomy
		Average	13	19	20	31	34	33	65	42	
		General		21							
		Spinal		17							

hours later, during surgery, it may represent a technical error.

Changes in plasma 17-hydroxycorticosteroid levels during surgery

Table I shows the changes in the plasma 17-hydroxycorticosteroids which took place during surgery in each of 12 patients. A gradual rise in the levels occurred which was especially striking when compared to the usual decrease in levels of plasma 17-hydroxycorticosteroids which occurs during this period of the day.

Case No. 5 was an exception to the general pattern observed. This patient was an 84-year-old white male who came to the hospital with severe jaundice due to calculi in the common bile duct. A cholecystectomy and exploration of the common bile duct were performed under cyclopropane anesthesia. The operation lasted three hours. The patient had no complications during or after surgery. On the assumption that the lack of any rise in 17-hydroxycorticosteroids in this patient might have been due to adrenal insufficiency, the patient was given an infusion of 25 I.U. of ACTH over

6 hours four weeks postoperatively. A normal rise in plasma 17-hydroxycorticosteroids occurred. We have no explanation for the lack of rise in his circulating steroids during surgery.

In the other patients there was a rise in the plasma 17-hydroxycorticosteroids during their operative procedures. There was a general tendency for the magnitude of the increase to be directly related to the duration of the procedure and its severity.

Changes in plasma levels of 17-hydroxycorticosteroids following operative procedures

The 17-hydroxycorticosteroid levels immediately following 33 operations and at two hourly intervals thereafter are shown in Table II. Figure 2 demonstrates the average levels after surgery; the changes following procedures lasting less than two hours are compared with those lasting more than two hours. Although operations lasting two hours or less were associated with a rise in 17-hydroxycorticosteroid plasma levels during the procedure, there was little change thereafter. Levels, however, did not return to the preoperative

TABLE II

Effect of surgery on plasma concentrations of 17-hydroxycorticosteroids following operational procedures

No.	Age and sex	Length of op. in hrs.	Anesthesia	17-OH corticosteroids ($\gamma/100\ ml.$) in plasma after operation				Operations and remarks
				0 hrs.	2 hrs.	4 hrs.	6 hrs.	
13	60 M	2	General	21	20	19	18	Removal of kidney stone
14	65 M	4	High spinal	23	46	84	102	Gastrectomy
15	60 M	2	High spinal	14	22	20	20	Prostatectomy
16	40 M	1½	High spinal	5	17	19	25	Renal stone removed
17	52 F	4½	General	60		48	24	Cholecystectomy
18	55 M	4½	High spinal	20	40	68	100	Cholecystectomy
19	50 M	4¾	General	34	35	45	29	Bilateral thoraco-lumbar sympathectomy
20	35 F	4	General	15	21	38	31	Cholecystectomy
21	57 F	4½	General	38	46	53	148	Ca of pancreas. Jejuno-choledocostomy. Patient went into shock at end of op. Resp. poor
22	30 F	3	General	20	26	26	20	Thyroidectomy
23	38 M	4	General	28	42	30	21	Atrial appendectomy
24	68 M	1½	Spinal	10	10	17	19	Bilateral sympathectomy for arteriosclerosis
25	42 M	3	General	19	21	17	35	Thyroidectomy
26a	68 F	1¼	Pentothal and NO₂	18	10	10	20	After skin incision pt. went into shock. Bleeding peptic ulcer. Operation stopped
26b	68 F	5	Pentothal and NO₂	46	55	66	40	Gastric resection. BP low throughout the procedure
27	72 M	1	Spinal	31	26	24	20	Suprapubic prostatectomy
28	56 F	3	General	41	35	34	18	Excision of large abdominal cyst
29	56 F	2½	Spinal and pentothal	25	36	40	32	Smith-Peterson nailing
30	60 F	4	General	19	27	38	40	Cholecystectomy
31	37 F	2½	General	20	30	24	31	Splenectomy
32	57 F	6¼	General	28	32	34	36	Cholecystectomy
33	55 M	4	Spinal	12	19	22	23	Open reduction and internal fixation of hip
34	60 F	5	Spinal	28	30	26	18	Cholecystectomy. Patient jaundiced
35	38 M	2½	Spinal	6	16	28	35	Intramedullary nailing of left femur
36	60 M	5	Cyclo propa. and NO₂	13	22	47	33	Cholecystectomy and duct exploration
37	62 F	7	Pentothal and cyclo	36	53	60	54	Thyroidectomy
38	62 F	2½	Spinal and cyclo	29	25	29	28	Bilateral sympathectomy
39	60 F	3	Spinal	25	40	35	15	Right colectomy
40	62 M	4½	General	26				Gastrectomy
41	25 F	4½	General	42				Ligation of patent ductus
42	60 M	5¼	General	34				Thyroidectomy (substernal)
43	42 F	3	General	30	36	34	34	Removal of cyst of pericardium
44	60 M	4	General	30	33	40	20	Removal of diverticulum of esophagus

values during the period studied. The rise in 17-hydroxycorticosteroid levels both during and after operations lasting more than two hours was more striking.

The details of the operative procedures in a few of these patients may help to throw light on the significance of the steroid rises. One patient (No. 26) was a 68-year-old white female with auricular fibrillation and severe hemorrhage from a peptic ulcer. The patient had slight persistent bleeding from the ulcer at the time of surgery. On the first occasion, after she had been anesthetized with pentothal and nitrous oxide, her blood pressure fell

moderately, immediately following superficial incision. The latter was closed and the patient was returned to the ward where she recovered uneventfully. The 17-hydroxycorticosteroids showed little change following the closure of the incision (lower curve in Figure 3). Without additional blood transfusion or other specific therapy the patient underwent a gastric resection the following day under general anesthesia. In spite of a similar hypotensive reaction an operation lasting five hours was completed successfully. As can be seen in Figure 3 (upper curve) there was a striking rise in 17-hydroxycorticosteroid levels
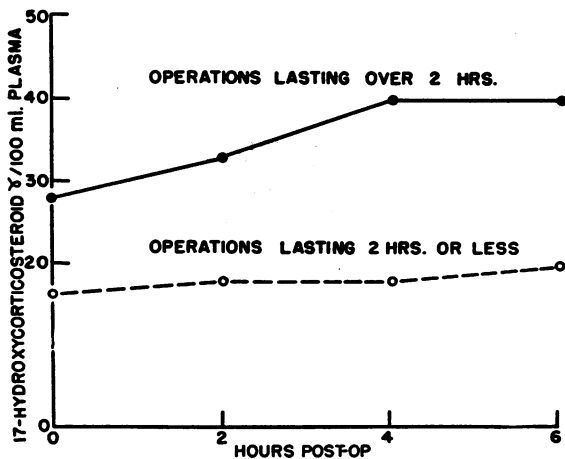
FIG. 2. AVERAGE PLASMA 17-HYDROXYCORTICOSTEROIDS
FOLLOWING SURGERY

after the second operation. This case suggests
that the magnitude of the rise in the 17-hydroxy-
corticosteroid levels in plasma is related to the
severity of the surgical procedure and its duration.

In Figure 4 the changes in 17-hydroxycorti-
costeroids in a 57-year-old female following a cho-
lecystectomy lasting four and one-half hours are
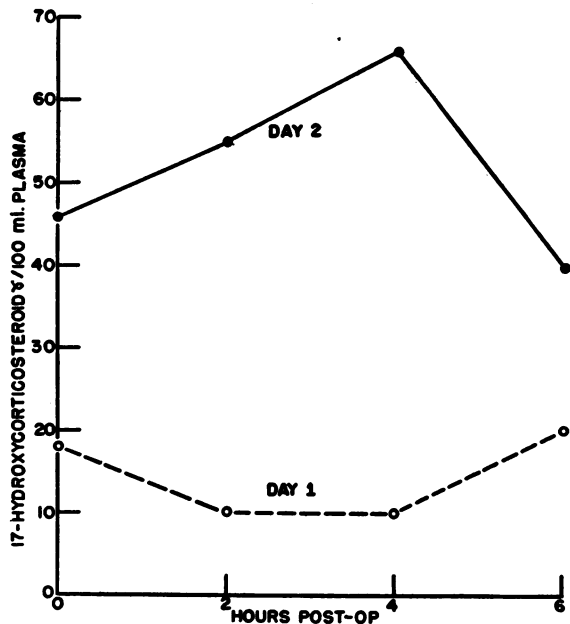shown. After the operation this patient's 17-hy-

FIG. 3. PLASMA 17-HYDROXYCORTICOSTEROIDS IN A PA-
TIENT IN WHOM ANESTHESIA WAS GIVEN AND ONLY A
SUPERFICIAL INCISION WAS MADE ON ONE DAY (LOWER
CURVE) AND A SUBTOTAL GASTRECTOMY THE FOLLOWING
DAY (UPPER CURVE)

droxycorticosteroid level reached 148 μg per 100
ml. of plasma. Such levels have not been ob-
served in other subjects not undergoing surgery
who were not moribund, even following the con-
tinuous intravenous administration of maximally
stimulating doses of ACTH over a period of 48
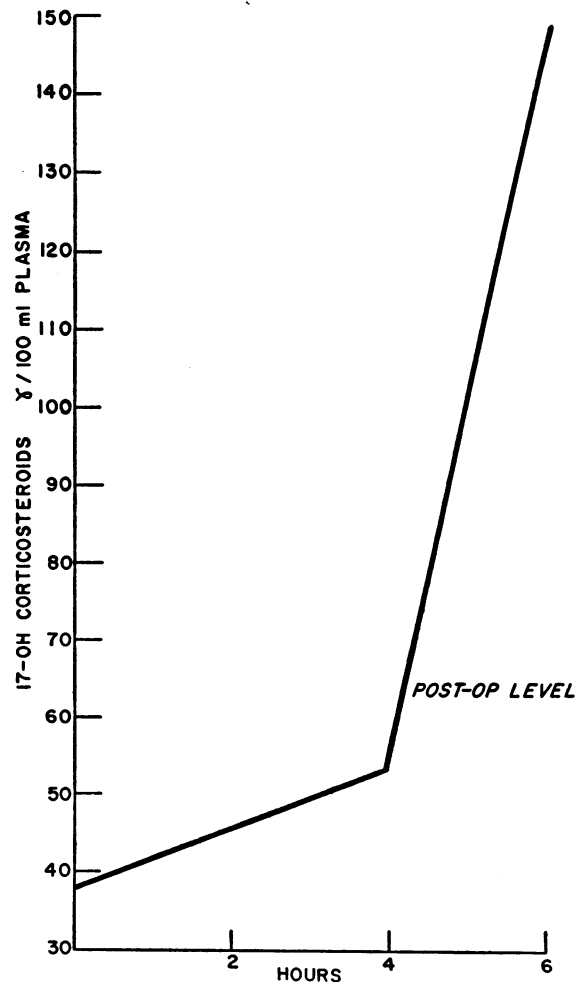hours. This patient died 36 hours following the
operation.

FIG. 4. PLASMA 17-HYDROXYCORTICOSTEROIDS IN A PA-
TIENT FOLLOWING CHOLECYSTECTOMY LASTING FOUR AND
ONE-HALF HOURS

ACTH response pre- and post-operatively

Standard ACTH response tests were performed
on six surgical patients at least one week before
the operation. In each case a normal rise in 17-
hydroxycorticosteroid levels occurred (Figure 5).
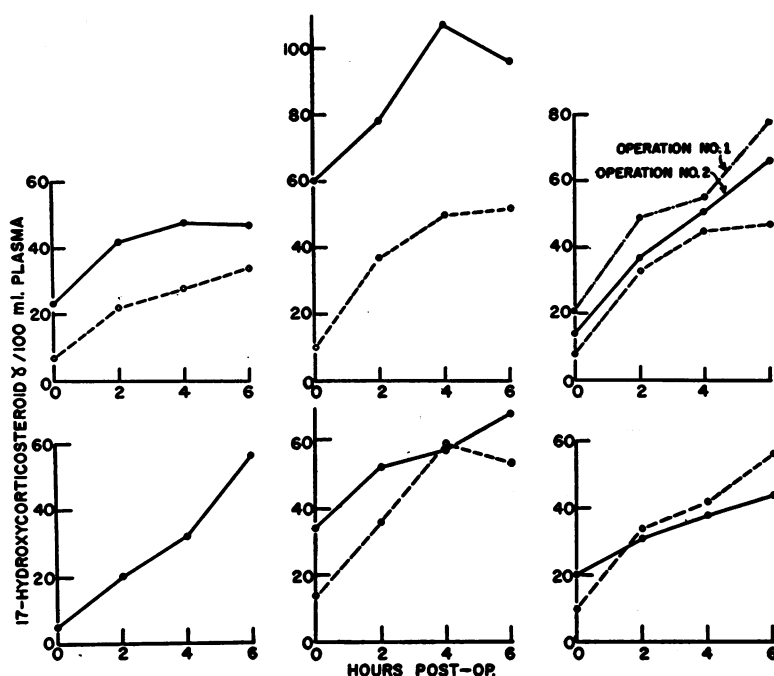After operation a similar rise was observed when

FIG. 5. RESPONSE OF PLASMA 17-HYDROXYCORTICOSTEROIDS TO 25 I.U.
ACTH INTRAVENOUSLY ON A CONTROL DAY (BROKEN LINES) AND FOLLOW-
ING MAJOR SURGERY (SOLID LINES)

ACTH was given intravenously regardless of the levels of the steroids at the end of the procedure. In one of these cases the postoperative 17-hydroxy-corticosteroid level was 60 μg per 100 ml. of plasma, a level compatible with maximal adrenal cortical stimulation. Interestingly enough, the administration of ACTH was associated with a further rise (up to 107 μg per 100 ml. of plasma) in the level of plasma 17-hydroxycorticosteroids; the magnitude of the rise was as great as that seen in the control curve in this patient or in normal unstressed individuals.

The effects of surgery on the blood levels produced by intravenously administered steroids

Each of five surgical patients was given hydrocortisone intravenously on two occasions. A control injection was given at least one week before or four weeks after the operation. The same patients received hydrocortisone during or following their operation. On each occasion the plasma 17-hydroxycorticosteroid levels were measured for a period of 8 hours (Figure 6). In three patients (G, H and I) the levels of 17-hydroxycorticosteroids reached higher values and were maintained

at higher levels after surgery than during the control periods. In two cases (J and K), the disappearance curves were not significantly different on the operative day than on the control day.

DISCUSSION

From the data presented here it appears that there are at least two factors associated with surgical procedures which affect the levels of adrenal steroids in the general circulation; induction of anesthesia and the actual handling of tissues. Spinal anesthesia had little effect on the plasma 17-hydroxycorticosteroid levels preoperatively, while general anesthesia produced a definite increase in most cases, even though the subsequent operation may have had little effect. The independence of these two effects is shown by the fact that the post-surgical rises were similar regardless of the type of anesthesia used.

The post-surgical rise would appear to be a continuation of the rise during surgery rather than a separate phenomenon. Both were correlated with the length of operation and the extent of tissue trauma. The post-operative rise probably is the result of the continued presence of damaged tis-

sues. Epinephrine apparently is not involved since the plasma 17-hydroxycorticosteroids fail to rise following its administration (9).

The adrenals of these patients were certainly not maximally stimulated, since the administration of ACTH was associated with an additional rise above the high levels of 17-hydroxycorticosteroids induced by the surgical procedures. It is of interest that in a few patients the rate of rise of the steroid level, either when ACTH was given or in its absence, exceeded that which we have observed in surgical patients or in normal individuals receiving amounts of ACTH which produce maximal rises in plasma 17-hydroxycorticosteroid levels under basal conditions. Thus, the data cannot be explained entirely by endogenous ACTH secretion. It must, therefore, be concluded that factors other than adrenal cortical stimulation play a part in raising the steroid concentrations during and subsequent to surgery. It follows that the removal of adrenal steroids from the circulation may be impaired. That this is a significant factor is suggested by the decreased rate of disappearance of injected hydrocortisone in three of the five patients in whom this type of study was performed during or immediately after surgery. There is evidence to suggest that the liver has an important role in these processes. Data concerning the importance of the liver in the metabolism of adrenal steroids is being presented in other papers of this series (18, 19).

It should be emphasized, however, that these data do not exclude the possibility that the adrenal cortex is stimulated submaximally by the surgical trauma. Indeed, if the spontaneous post-surgical rises in plasma 17-hydroxycorticosteroid level were entirely due to impaired extra-adrenal metabolism and excretion of these compounds, we should have observed supramaximal rises regularly when ACTH was administered in the presence of an already elevated level. The rate of disappearance of the additional steroid secreted by the stimulated adrenal would also presumably have been impaired, resulting in increments of considerably greater magnitude than those observed under basal circumstances. This was clearly not the case. Similarly *each* patient receiving exogenous steroid at a time when his level was elevated should have shown markedly impaired removal of the steroid if the elevation
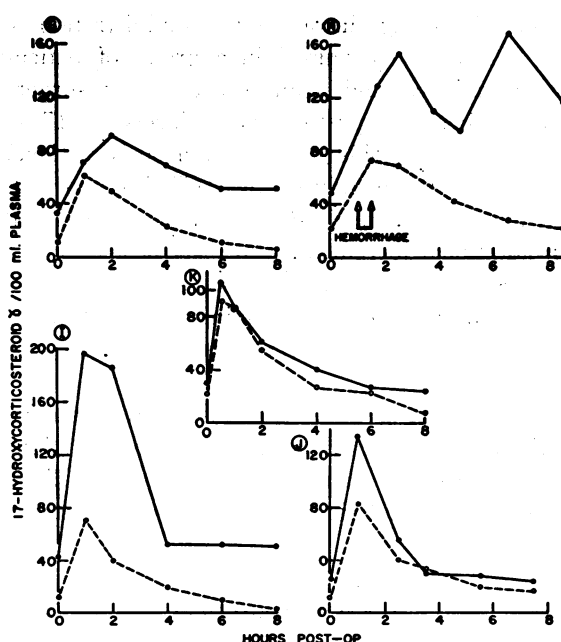

FIG. 6. PLASMA 17-HYDROXYCORTICOSTEROIDS FOLLOWING INTRAVENOUS ADMINISTRATION OF 50 MG. OF HYDROCORTISONE ON A CONTROL DAY (BROKEN LINE) AND FOLLOWING SURGERY (SOLID LINES)

resulted only from a decreased rate of removal. Thus these data suggest a combined effect of increased production and decreased removal.

Although the increased plasma 17-hydroxycorticosteroids in the post-surgical period probably are metabolically active, whether the higher levels are due to increased adrenal secretion or impaired disposition, for the reasons considered in the introduction, our finding that surgical trauma is associated with an increase in the levels of circulating adrenal steroids does not necessarily indicate that the entire adrenal-like metabolic response to surgery is mediated by these rises.

SUMMARY

1. The plasma levels of 17-hydroxycorticosteroids were determined in a group of surgical patients. They were found to be elevated following the induction of anesthesia and during and after surgery. Following surgery the increases were roughly proportional to the duration and severity of the operative procedure. This elevation usually persisted at least 6 hours following surgery.

2. In an attempt to measure adrenal cortical capacity, the changes in 17-hydroxycorticosteroid

levels following intravenous administration of ACTH were determined in a group of patients preoperatively, and again shortly after surgery. Even when the post-operative levels of 17-hydroxycorticosteroids rose spontaneously to levels as high as those induced by ACTH in normals, the administration of ACTH was associated with an additional increment.

3. Some patients undergoing surgery did not metabolize intravenously administered hydrocortisone as rapidly after surgery as they did on control days.

4. The data seem most consistent with the hypothesis that the adrenal is submaximally stimulated by surgical trauma but that impaired disappearance of circulating steroid also contributes to the rises observed.

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