The Adrenocortical Response in Surgical Patients *

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An increased activity of the adrenal cortex has been postulated to be an integral part of the reaction of the organism to situations involving stress.[16, 17] In past studies of clinical stress in man, non-specific indices of adrenocortical function have led to inconsistent conclusions concerning both the magnitude and temporal relations of adrenocortical responsiveness. Following the publication of the Porter-Silber reaction [13] several clinical investigators developed relatively specific methods for the determination of 17-hydrocorticosteroids in both blood and urine.[1, 6, 10] The present report deals with a study of spontaneous alterations in adrenocortical function based upon quantitative determination of both plasma and urinary 17-hydroxycorticosteroids in patients subjected to surgical operations.

MATERIALS AND METHODS

Eighteen male patients, varying in age from 26 to 70 years, were selected so that the series would include major and minor elective procedures and surgical emergencies. Four patients were studied during two operations performed at intervals of one to six weeks. All patients received the usual preoperative medications, consisting of sodium pentobarbital the night before and morphine and scopolamine on the morning of operation. All major operations were performed under ether or cyclopropane anesthesia. Spinal anesthesia was employed for the herniorrhaphies. Samples of peripheral blood were obtained before the operation; at two to 12, 24, and at 48 hours postoperatively in 17 patients, and also at 72 to 120 hours postoperatively in 11 patients. Each blood sample was heparinized and immediately centrifuged. The separated plasma was stored in the deep freeze until ready for analysis. All plasma samples in the series for one given operation were analyzed simultaneously. Free plasma 17-hydroxycorticosteroids (17-OHCS) were measured by a modification of the method of Nelson and Samuels.[10] The plasma extract after chromatography was dissolved in 0.5 ml. of ethanol, and two duplicates of 0.2 ml. were taken, one for reaction with 0.2 ml. of phenylhydrazine-sulfuric acid reagent and the other with 0.2 ml. of sulfuric acid. Recovery of 17-hydroxycorticosterone added to plasma varied from 70 to 90 per cent. Normal values for plasma 17-OHCS by the method described range from six to 32 γ per cent with a mean of $18 \pm 5\,\gamma$ per cent.

In 15 patients, 24 hour urine collections were made on the day of operation and for varying periods up to one week postoperatively. In 12 patients, preoperative 24 hour urine collections also were obtained. Urine samples were preserved in the frozen state until analyzed. Urinary 17-hydroxycorticosteroids (17-OHCS) were determined by two methods: 1) the method of Glenn and Nelson, employing β-glucuronidase hydroly-

* Submitted for publication October 22, 1956.

TABLE 1. *Peripheral Plasma 17-Hydroxycorticosteroids (γ%) in Patients Undergoing Surgery*

Case No.*	Pre-Oper.	2–10 Hr. P.O.**	24 Hr. P.O.	48 Hr. P.O.	72 Hr. P.O.	96 Hr. P.O.	120 Hr. P.O.
1. C. B., 42							
D.C., C.R.	18	77	40	11			
2. E. H., 61							
D.U., G.R.	26	49	66	58	36	21	
3. P. S., 27							
B.I.H., L.I.H.	21	36	27	20			
R.I.H.	22	39	25	20			
4. J. S., 60							
B.V., Te.L.	18	37	30	23			
Pc.S.	13	122	72	20	32	23	
5. W. H., 38							
B.V., Te.L.	45	86	78	64	62		
6. A. K., 57							
Gb., Ch.	32	97	41	49	42	40	33
7. G. L., 45							
P.U., D.	69	91	32	31	21	16	
8. J. C., 36							
P.U., D.	49	41	31	13			
9. F. W., 62							
P.U., D.	24	55	21	18			
10. H. M., 42							
B.I.H., L.H.	21	31	14	15			
R.H.	24	34	21	16			
11. K. W., 26							
D.U., G.R. #1	22	48	66	56	36	28	
G.R. #2	21	59	60	38	24	21	
12. J. M., 47							
D.U., G.R.	11	45	24	28			
13. J. F., 33							
D.U., G.R.	20	55	26	29	24	22	18
14. G. Q., 70							
CaC., C.R.	24	73	45	24	22	26	
15. R. F., 33							
M.P., C.R.	21	99	40	26	34	32	28
16. S. M., 55							
Gb., Ch.	14	53					
17. R. L., 48							
C.B.T., R.C.B.T.	24	63	17	45	23	28	
18. P. F., 41							
CaC., B.	31	48	44	34	28		

* The data after each case number refer to the patient's initials and age.

** Maximal value observed during this interval.

Key to the underlying abbreviations for diagnosis and operation is the following: D.C.—diverticulitis of colon; D.U.—duodenal ulcer; B.I.H.—bilateral inguinal herniae; B.V.—bleeding varices; Gb.—gall-bladder disease; P.U.—perforated ulcer; CaC.—carcinoma of colon; M.P.—multiple polyposis; C.B.T.—carotid body tumor; G.R., C.R.—gastric or colon resection; L. or R.I.H.—left or right inguinal herniorrhaphy; Te.L.—transesophageal ligation; Pc.S.—porta-caval shunt; Ch.—cholecystectomy; D.—duodenorrhaphy; R.C.B.T.—resection carotid body tumor; B.—biopsy during abdominal exploration.

TABLE 2. *Urinary 17-Hydroxycorticoid Excretion in Milligrams per 24 Hours*

Case No.*	GLENN-NELSON 17-OHCS							REDDY 17-OHCS						
	Pre-Oper.	Oper.	P.O. 1	P.O. 2	P.O. 3	P.O. 4	P.O. 5	Pre-Oper.	Oper.	P.O. 1	P.O. 2	P.O. 3	P.O. 4	P.O. 5
1. C. B.	4.5	14.8	7.5	5.0	4.5			7.0	18.3	23.0	14.2	10.1		
2. E. H.	3.5	10.7	14.6	9.1	10.2	6.8	5.1							
3. P. S.														
L.I.H.	3.5	6.1	5.3	3.4	3.1	3.8		6.1	12.0	10.0	2.7	6.3	6.5	
R.I.H.	3.2	8.6	7.5	3.0	3.6	2.3		7.0	15.5	0	12.1	12.2	8.9	
4. J. S.														
Te.L.		11.2	9.1	7.0	4.8				18.2	16.3	6.0	9.1		
Pc.S.	3.4	10.5	5.3	4.2	6.0			3.8	18.2	14.1	19.4	11.8		
5. W. H.		9.1	11.3	9.4	9.1				21.4	25.1	22.3	21.0		
6. A. K.	6.3	18.2	20.4	22.9	5.7	6.1	7.1	10.8	28.6	39.1	48.3	18.8	25.0	15.0
7. G. L.		20.8	6.9	3.6	3.1	3.5	5.3		73.7	42.2	59.3	10.2	0	8.3
9. F. W.		4.5	3.5	3.0	2.4	3.5	2.5		8.6	15.2	1.2	18.0	15.0	4.8
10. H. M.														
L.I.H.	3.8	6.6	7.2	4.1				5.2	9.1	12.1	8.5			
R.I.H.	3.7	6.5	6.8	3.1				3.9	12.7	14.5	9.2			
12. J. M.	4.7	10.2	7.5					8.4	17.6	15.1				
13. J. F.	5.7	14.7	3.4					10.1	31.2	17.6				
15. R. F.	4.1	9.3	6.3	4.2	8.1	5.2	3.4	7.2	35.4	24.2	15.3	20.0	16.1	11.2
16. S. M.	4.0	15.2	10.1					10.1	21.0	26.5				
**17. R. L.	4.1	15.8	14.0	12.1	10.4	9.1	7.7	8.4	41.3	77.4	63.2	45.1	57.7	56.8
18. P. F.	4.4	9.2	7.8					10.5	23.4	25.7				

* For key to abbreviations see Legend for Table 1.
** Potassium iodide was inadvertently administered on the day of operation and continued throughout the period of study[9].

sis and column chromatography on florisil; [6] 2) the method of Reddy *et al.*[14] The application of the Porter-Silber reaction in both methods employed four milliliters of phenylhydrazine sulfuric acid reagent or sulfuric acid to one milliliter of solvent containing the urine extract. In our laboratory, the normal daily excretion of 17-OHCS ranges from 2.5 to 6.5 mg. with the Glenn-Nelson method (G-N) and from 0 to 10 mg. with the Reddy method (R) in adult men. Urinary creatinine was measured by the method of Peters.[12]

RESULTS

In Tables 1 and 2 are recorded all of the data obtained in this study. In general, plasma 17-OHCS showed a prompt increase following surgical procedures. Urinary 17-OHCS showed more prolonged elevations than did plasma 17-OHCS. The following cases are presented in detail in an endeavor to correlate the clinical situation of the patient with the type of adrenocortical response observed.

A. *Adrenocortical Response to an Elective Major Operation in a Well-Nourished Individual.*

Case 1. Diverticulitis of sigmoid colon with resection (Fig. 1).

Clinical summary. This 42-year-old man, C. B., entered the hospital with a week's history of crampy abdominal pain and diarrhea. Barium enema revealed a large annular constriction in the sigmoid colon. At operation on March 2, 1955, diverticulitis of the sigmoid colon with a small perforation was discovered. A transverse colostomy was performed and an uneventful postoperative course ensued. Six weeks later, on April 19, 1955, an elective sigmoid resection was performed and the colostomy was closed. Postoperatively, the patient did well except for a slight temperature elevation for two days. The adrenocortical response to the latter operation is presented in Figure 1.

Endocrine summary. Plasma 17-OHCS increased promptly in response to surgical trauma and reached a peak value of 77 γ per cent eight hours postoperatively. Plasma 17-OHCS dropped abruptly in the next four hours and then gradually reached preoperative levels by 32 hours.

Urinary G-N 17-OHCS were elevated to 14.8 mg. per 24 hours on the day of operation and returned to preoperative levels two days later. Urinary R 17-OHCS reached

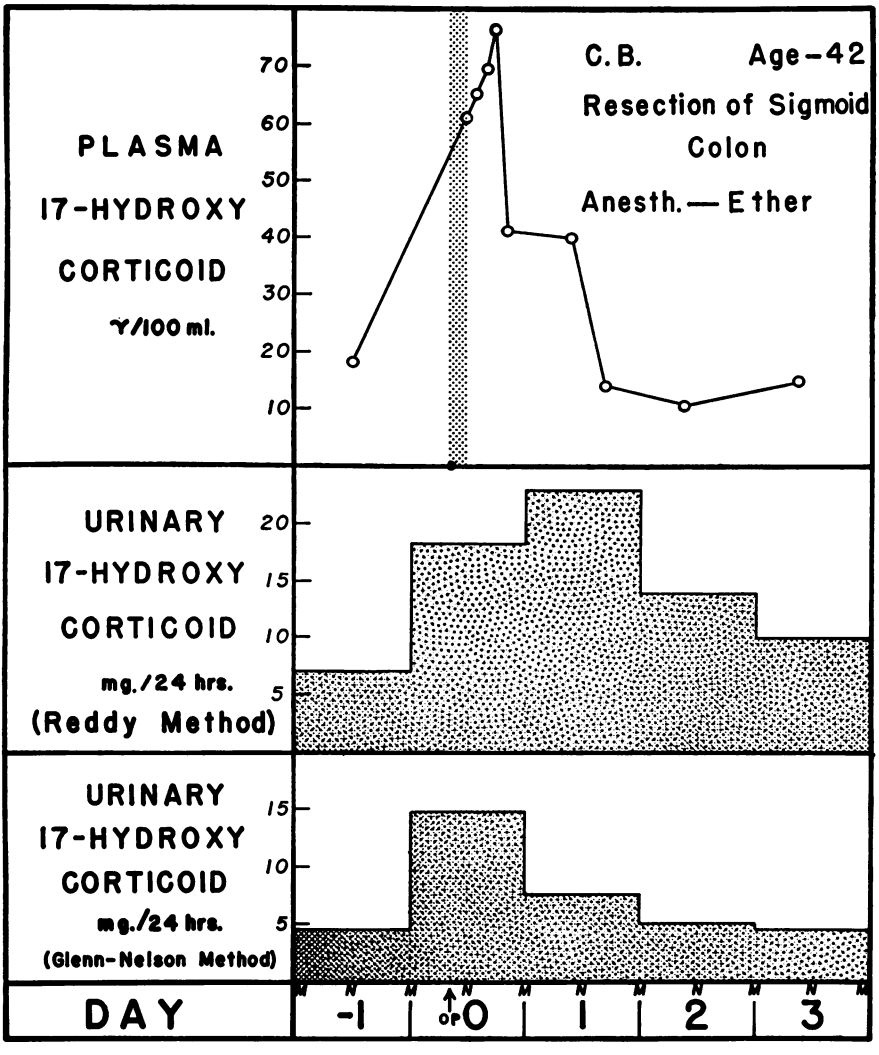

FIG. 1

a maximum value of 23 mg. per 24 hours on the first postoperative day and then returned to control values by the third postoperative day.

Comment. This type of adrenocortical response was commonly observed in well-nourished patients undergoing elective operations with uneventful postoperative convalescence. Elevated plasma 17-OHCS levels ordinarily were back to normal 48 hours postoperatively. Urinary R 17-OHCS reached higher absolute levels in response to operation and usually remained elevated for one to three days longer than urinary G-N 17-OHCS.

B. *Adrenocortical Response to an Operation in a Chronically Malnourished Anemic Individual.*

Case 2. Bleeding duodenal ulcer with subtotal gastric resection and gastroenteostomy (Fig. 2).

Clinical summary. This 61-year-old man, E. H., entered the hospital with a six months' history of tarry stools and weight loss. On admission the hemoglobin concen-

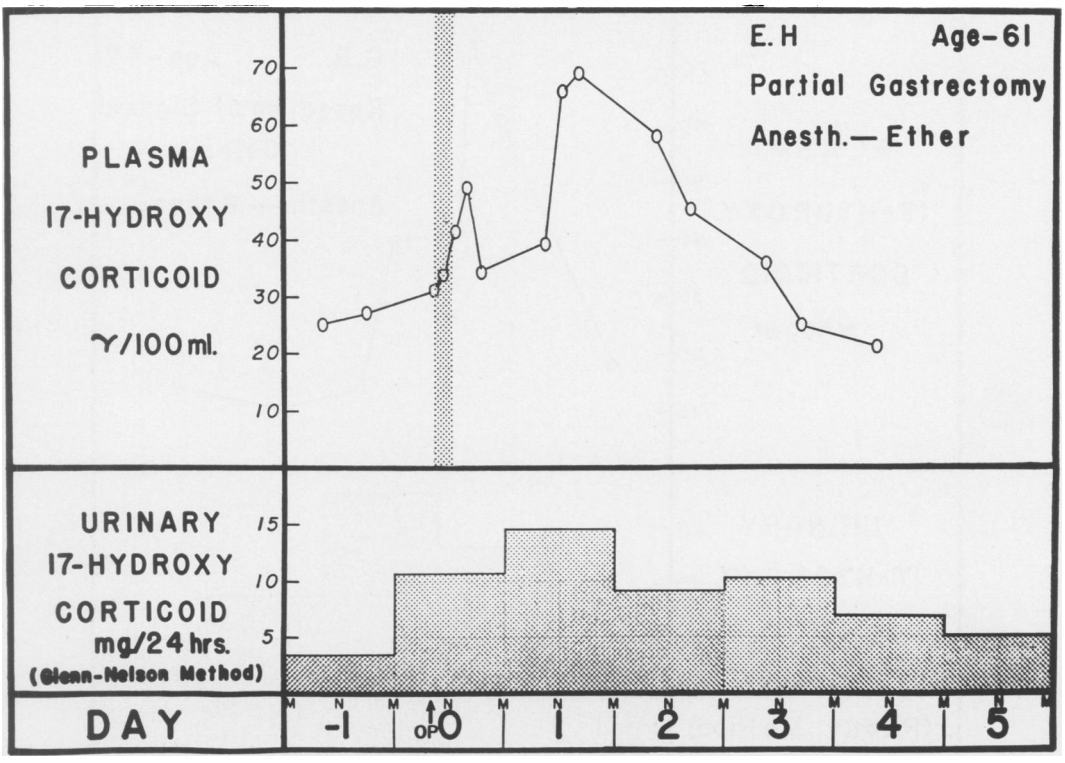

FIG. 2

tration was 8.6 Gm. per cent. The patient was placed on frequent liquid feedings and antacids and was transfused. A gastro-intestinal series revealed a. duodenal ulcer. Slow persistent bleeding continued for two weeks. Consequently, a subtotal gastrectomy and posterior gastroenterostomy were performed. The postoperative course was uneventful.

Endocrine summary. Plasma 17-OHCS increased promptly in response to general anesthesia and operation and reached a value of 49 γ per cent three hours postoperatively. Following a slight fall, plasma 17-OHCS showed a secondary rise up to 69 γ per cent on the first postoperative day, and gradually returned to control levels by the third postoperative day.

Urinary G-N 17-OHCS showed a maximum daily elevation of 14.6 mg. on the first postoperative day and remained elevated for the next three days.

Comment. This type of a somewhat delayed and prolonged adrenocortical response was seen in two patients, both of whom were suffering from complications of duodenal ulcers, namely bleeding and pyloric obstruction. Malnutrition and anemia were present in both patients. One patient, K. W. (Table 1), underwent two gastric operations six weeks apart and had a similar type of plamsa adrenocortical response to both operations.

C. *Adrenocortical Response to Bilateral Inguinal Herniorrhaphies.*

Case 3. Bilateral inguinal herniorrhaphies performed eight days apart (Fig. 3).

Clinical summary. This 27-year-old man, P. S., entered the hospital with bilateral inguinal hernias of several years' duration. Under spinal anesthesia, first the left and then, eight days later, the right inguinal

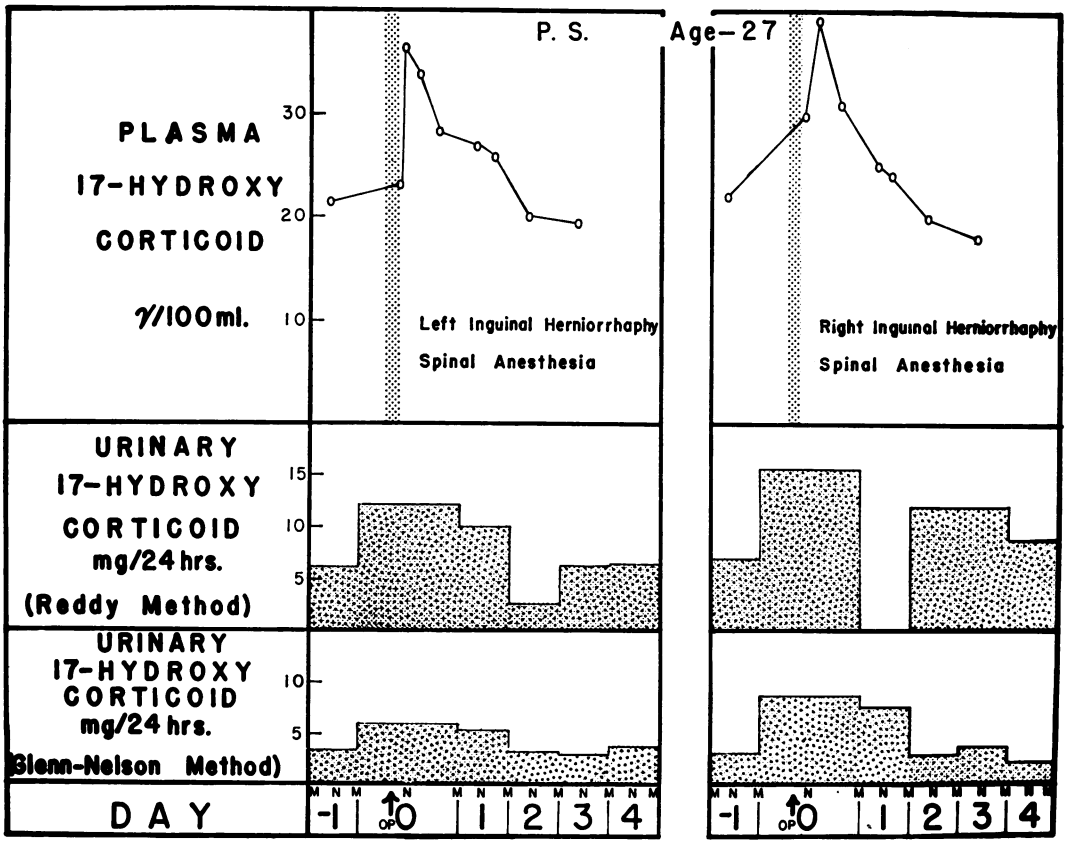

FIG. 3.

hernias were repaired. No postoperative complications were encountered.

Endocrine summary. The plasma 17-OHCS response to both operations was essentially the same, with peak levels being reached three to six hours postoperatively. Plasma 17-OHCS reached levels of 36 γ per cent and 39 γ per cent, respectively. Normal plasma 17-OHCS values were present 24 hours postoperatively.

Urinary G-N 17-OHCS were elevated for two days in both studies. Urinary G-N 17-OHCS reached levels of 6.1 and 5.3 mg. in response to the first operation and daily levels of 8.6 and 7.5 mg. in response to the second. Urinary R 17-OHCS remained slightly elevated two days longer than did urinary G-N 17-OHCS in response to the second operation.

Comment. In two patients (Table 1) undergoing two stage bilateral herniorrhaphies one week apart, plasma 17-OHCS response to both operations was identical. In patient P. S. urinary 17-OHCS excretion was greater in response to the second operation than to the first. In patient H. M. (Table 2), urinary 17-OHCS excretion was similar in response to both operations. These studies demonstrate that the adrenal cortex can respond as well, if not better, to the second of two minor operations spaced one week apart.

D. *Adrenocortical Response to a Major Operation in Patients with Hepatic Disease.*

Case 4. Bleeding esophageal varices; transthoracic transesophageal ligation as an

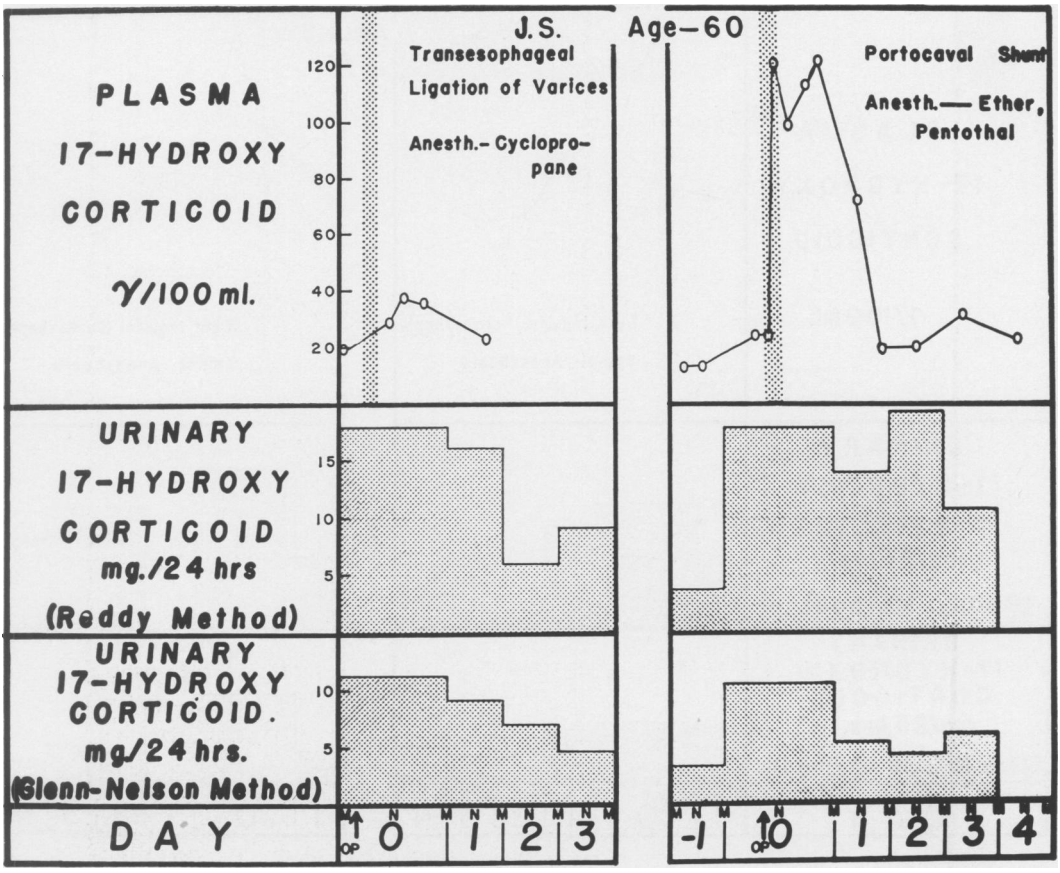

FIG. 4

emergency procedure followed by a porta-caval shunt one month later (Fig. 4).

Clinical summary. This 60-year-old man, J. S., with Laennec's cirrhosis of the liver entered the hospital with severely bleeding esophageal varices and a hemoglobin concentration of 8 Gm. per cent. Despite the passage and inflation of a Sangstaken tube, four liters of whole blood had to be administered over a 24 hour period in order to maintain a normal blood pressure. Because of continued bleeding, an emergency transthoracic transesophageal ligation of the esophageal varices was performed. Postoperatively, the bleeding ceased and the patient did well. Interim studies revealed a low serum albumin, a slightly prolonged prothrombin time, and an increased BSP retention. One month following the first operation a porta-caval shunt was performed. The patient tolerated this procedure well and had no postoperative complications.

Endocrine summary. No plasma 17-OHCS levels were obtained during the first operative procedure until eight hours postoperatively. The peak plasma 17-OHCS response to the first operation occurred ten hours postoperatively at a level of 37 γ per cent. Plasma 17-OHCS returned to normal 48 hours postoperatively.

Plasma 17-OHCS reached a level of 122 γ per cent nine hours following the second operation. Normal plasma 17-OHCS values were observed 33 hours postoperatively. On the third postoperative day, a secondary rise in plasma 17-OHCS to 32 γ per cent

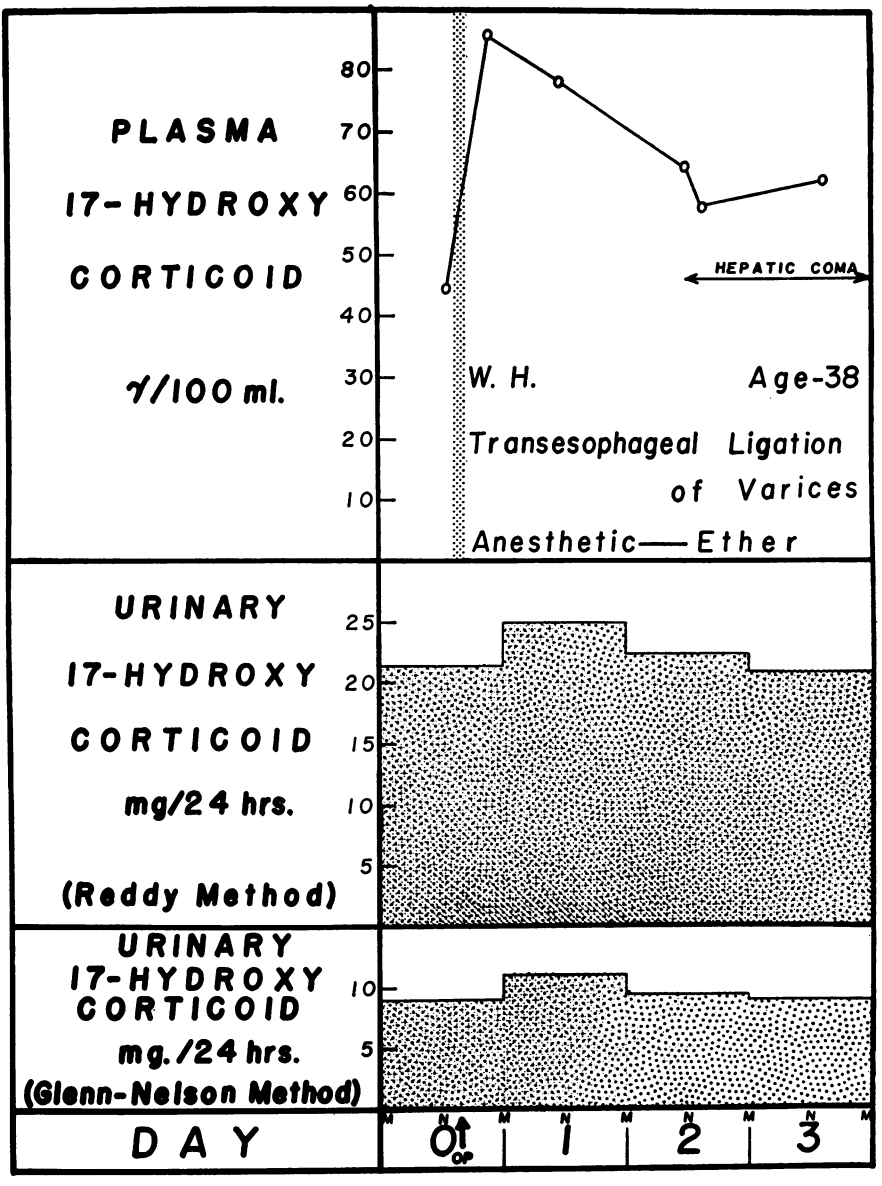

FIG. 5

was observed unassociated with any complications.

Urinary G-N 17-OHCS excretion was similar following both procedures. The urinary R 17-OHCS response to the second operation appeared to last two days longer than did the urinary G-N 17-OHCS response.

Case 5. Bleeding esophageal varices with emergency transthoracic transesophageal ligation (Fig. 5).

Clinical summary. This 38-year-old man, W. H., with decompensated Laennec's cirrhosis of the liver entered the hospital immediately following a profuse hematemesis. Transfusions were administered as bleeding continued. An emergency transesophageal ligation of the bleeding esophageal

varices was performed. On the second postoperative day, the patient went into hepatic coma and died one week later.

Endocrine summary. A high preoperative plasma 17-OHCS level of 45 γ per cent was observed in association with severe hemorrhage. Following the surgical procedure, the plasma 17-OHCS rose to a peak of 86 γ per cent four hours postoperatively. The plasma 17-OHCS remained markedly elevated postoperatively as the patient went into hepatic coma.

Urinary 17-OHCS remained elevated postoperatively as long as observations were recorded. Urinary R 17-OHCS were approximately twice urinary G-N 17-OHCS.

Comment. The plasma 17-OHCS response to a transthoracic ligation of bleeding esophageal varices was substantially less than to a porta-caval shunt in the same patient. This difference may be related to the greater tissue trauma and longer duration of the latter operation. The urinary 17-OHCS excretion was similar following both surgical procedures despite the difference in the plasma 17-OHCS response.

The adrenocortical response to operation in W. H. was prolonged and associated with the development of hepatic coma postoperatively. This suggests that the persistent elevation of plasma 17-OHCS postoperatively in patients with hepatic disease may be associated with a poor prognosis.

E. *Adrenocortical Response to Operation in an Individual with a Postoperative Psychotic Episode.*

Case 6. Cholelithiasis and choledocholithiasis with cholecystectomy and common bile duct exploration (Fig. 6).

Clinical summary. This 57-year-old man, A. K., entered the hospital with a three-day history of upper abdominal pain, fever and jaundice. Following seven days of antibiotic therapy, the patient's fever disappeared and the jaundice decreased. On the tenth hospital day, a cholecystectomy and common bile duct exploration were performed for cholelithiasis and choledocholithiasis. On the first postoperative day, acute urinary retention developed and an indwelling Foley catheter was inserted. On the second postoperative day, the patient became grossly psychotic and had to be restrained. This psychosis lasted for two days and then abruptly disappeared.

Endocrine summary. Plasma 17-OHCS rose to a peak level of 97 γ per cent five hours postoperatively and then dropped abruptly to 51 γ per cent three hours later. A secondary rise to 62 γ per cent was observed 30 hours postoperatively followed by a very gradual fall to 24 γ per cent by the sixth postoperative day.

Urinary G-N 17-OHCS reached daily levels of 18.2 to 22.9 mg. and fell sharply on the third postoperative day. Urinary R 17-OHCS reached daily levels of 28.6 to 48.3 mg. and remained elevated for five postoperative days.

Comment. The plasma 17-OHCS response to operation in this patient was one of the most prolonged of any patient studied. Urinary 17-OHCS elevations were marked with both methods. This intense adrenocortical response was associated with the development of a transient postoperative psychosis. It is of interest to emphasize that the adrenocortical response to operation was marked for two days before the appearance of the psychotic state.

F. *Adrenocortical Response in Patients with Perforated Duodenal Ulcers.*

Case 7. Perforated duodenal ulcer with shock and duodenorrhaphy (Fig. 7).

Clinical summary. This 45-year-old man, G. L., entered the hospital with severe generalized abdominal pain of 16 hours' duration and tarry stools of two days' duration. On admission, the temperature was 103° F. and the blood pressure was unobtainable. The abdomen was diffusely tender and rigid. Following the administration of one liter of dextran, the blood pressure returned to normal levels. At operation, diffuse peri-

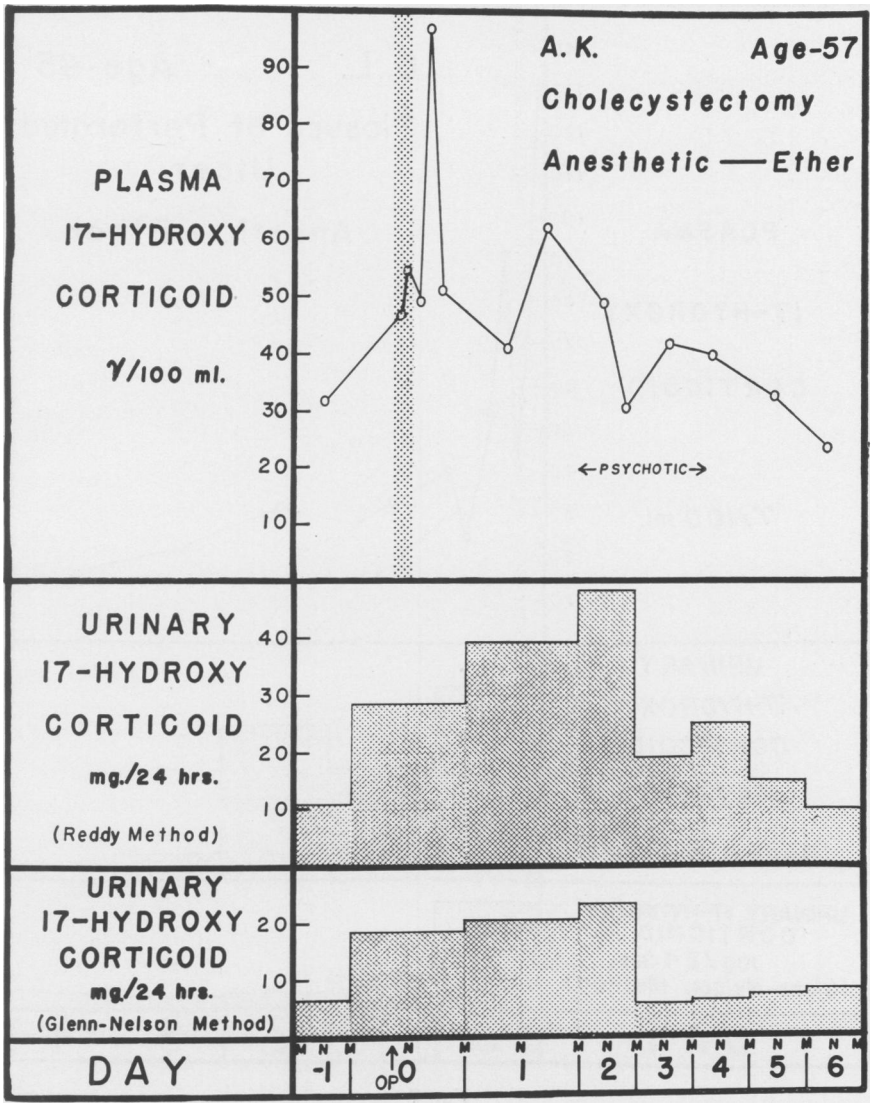

FIG. 6

tonitis was present secondary to a perforated ulcer of the duodenum. A duodenorrhaphy was performed. Postoperatively, the patient was transfused and placed on antibiotics. He remained febrile for the first three postoperative days and then gradually recovered.

Endocrine summary. Preoperatively a plasma 17-OHCS level of 131 γ per cent was observed while the patient was in shock. Following recovery from shock, the plasma 17-OHCS fell to 69 γ per cent. This fall continued following general anesthesia and during the operation. After the operation was completed, the plasma 17-OHCS rose to 91 γ per cent four hours postoperatively. Following an abrupt fall to 24 γ per cent, the plasma 17-OHCS rose to 40 γ per cent 16 hours postoperatively. A gradual return to 21 γ per cent occurred by the third postoperative day.

Urinary G-N 17-OHCS reached a value

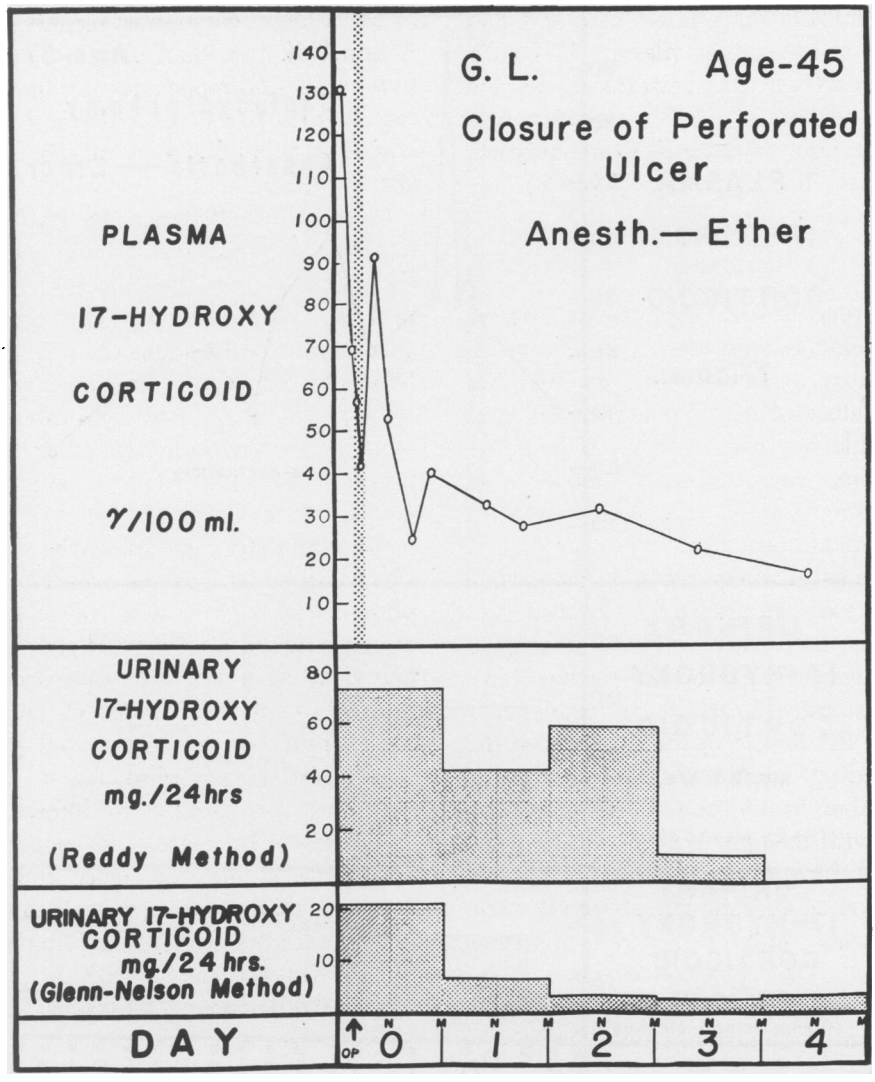

FIG. 7

of 20.8 mg. per 24 hours on the day of operation with a rapid return to normal within 48 hours. Corresponding urinary R 17-OHCS excretion reached a value of 73.7 mg. on the day of operation and remained elevated 72 hours.

Comment. In three patients studied with perforated duodenal ulcers, the intensity of the adrenocortical response to both the disease and to the operation correlated well with the severity of the clinical status of the patient at the time of admission. Patient G. L. entered in a state of peripheral vascular collapse and had a markedly elevated plasma 17-OHCS level. Restoration of plasma volume resulted in a rapid decrease in plasma 17-OHCS which continued during anesthesia with a secondary rise occurring after operation. Patient J. C. (Table 1) was in severe pain on admission, but had a well maintained peripheral circulation. The plasma 17-OHCS response to his disease process was similar to that of G. L., but of less magnitude. Patient F. W. (Table

1) was clinically the mildest case and had a normal preoperative plasma 17-OHCS level. This patient demonstrated a definite transient plasma 17-OHCS elevation following operation in contrast to an equivocal urinary 17-OHCS response (Table 2).

DISCUSSION

The adrenocortical response in surgical patients must be considered in relation to many factors. It is evident from our data that the nature of the clinical problem is of considerable importance. Pain, shock, psychic tension, drugs, and anesthesia have all been shown to affect the plasma level of adrenocortical hormones.

In acute surgical emergencies free plasma 17-OHCS may be markedly elevated preoperatively in response to both severe pain and/or shock.[8] Franksson and Gemzel have shown that free 17-OHCS are significantly higher on the day of operation than on the day preceding operation.[5] This increase has been ascribed to intense psychic tension associated with the approach of an operation. Siker et al. have demonstrated that the administration of sodium pentobarbital intravenously may result in a decrease in plasma 17-OHCS.[18] The induction of general anesthesia has been shown to result in a definite increase in plasma 17-OHCS although spinal anesthesia has little effect.[15, 19]

During the operative procedure and in the immediate postoperative period, the actual height to which free plasma 17-OHCS may rise should be considered as a balance between adrenocortical secretion and peripheral and hepatic utilization.[19] Brown *et al.* have shown that hepatic impairment definitely slows the disappearance rate of intravenously administered hydrocortisone.[2] Tyler and associates have presented convincing evidence that impaired hepatic removal of free plasma 17-OHCS may be an important factor in maintaining an elevated 17-OHCS level in the immediate postoperative period.[20] The fact that the duration of elevation of conjugated urinary 17-OHCS is usually longer than plasma elevations of free adrenal hormone suggests that circulating hydrocortisone is rapidly and efficiently conjugated by the liver in the postoperative period.[19]

Urinary 17-OHCS excretion rises promptly in response to surgical trauma and remains elevated several days longer than free plasma 17-OHCS levels before returning to preoperative values. No exact temporal relationship between plasma and urinary corticosteroids has been demonstrated. The methods employed in this study measured primarily free 17-OHCS in the plasma and conjugated metabolites of 17-OHCS in the urine. The determination of the conjugated 17-OHCS as well as the free 17 OHCS in plasma would give a more complete picture of spontaneous adrenocortical alterations occurring during or after operation.

Analysis of the results of the present study indicates that the actual pattern of adrenocortical response to an operation may vary considerably in different clinical situations. The usual adrenocortical response to an elective major surgical procedure consists of a prompt elevation in free plasma 17-OHCS following the onset of general anesthesia with a peak level within the first 12 postoperative hours. Following this peak rise, there is a more or less abrupt descent to normal plasma levels within 36 to 48 hours postoperatively.[19] Small secondary elevations of free plasma 17-OHCS unassociated with clinical complications may be seen within the first 96 hours, particularly in patients who have undergone extensive and prolonged surgical procedures.[3]

Variations in this pattern of response have been observed. Two patients suffering from malnutrition and anemia demonstrated a delayed peak plasma 17-OHCS response following gastric resections for duodenal ulcers. Pareira *et al.*[11] have suggested that patients on a subcaloric diet may have a more prolonged plasma 17-

OHCS response to intravenous ACTH than patients on a normal diet.

The association of postoperative complications with the persistent elevation of free plasma 17-OHCS levels has been emphasized in the study of Franksson *et al.*[4] One patient in our study had a pronounced adrenocortical response associated with the appearance of a transient postoperative psychosis following biliary surgery. This association suggests that both the endocrine and emotional components of this patient were quite responsive to surgical stress.

The adrenocortical response to operation in patients with hepatic disease has been variable. One patient with compensated cirrhosis of the liver had a normal pattern of adrenocortical response to a porta-caval shunt operation. However, a plasma 17-OHCS level of 122 γ per cent in this patient was the highest postoperative value observed in our study. In a patient with severe hepatic impairment, the precipitation of hepatic coma by transthoracic ligation of bleeding esophageal varices was associated with a prolonged period of adrenocortical stimulation.

The importance of pain and/or peripheral vascular collapse as potent adrenocortical stimulants is clearly demonstrated in our study of patients with perforated duodenal ulcers. In the two most seriously ill patients, the preoperative plasma 17-OHCS values were higher than those following anesthesia and operation. Hume and Nelson have shown in dogs that hemorrhagic shock evokes a marked adrenocortical response, and that as soon as circulating blood volume is restored adrenocortical secretion diminishes.[7]

Four patients in this study underwent two operations spaced one to six weeks apart. In every patient, the adrenocortical response to the second operation was equal to or greater than to the first. These observations suggest that a previous surgical operation does not exhaust the capacity of the adrenal cortex to respond to a second similar or more extensive surgical procedure.

SUMMARY

1. Free plasma 17-hydroxycorticosteroids and urinary 17-hydroxycorticosteroids have been measured before and after surgical procedures in a wide variety of surgical patients.

2. Free plasma 17-hydroxycorticosteroids rose promptly in response to both minor and major surgical procedures, reaching a peak in most cases four to 12 hours postoperatively and falling to preoperative levels between 24 and 72 hours. Specific exceptions to this pattern have been demonstrated.

3. Urinary 17-hydroxycorticosteroids are elevated in response to operation for one to four days postoperatively. Urinary 17-hydroxycorticosteroids determined by the Reddy method are usually considerably higher in response to operation than those determined by the Glenn-Nelson method.

4. In evaluating the adrenocortical response to operation, general anesthesia, pain, and shock are as important to recognize as stimuli as actual tissue trauma.

5. The relationship of the observed changes in free plasma 17-hydroxycorticosteroids following operation to the intermediary metabolism and renal excretion of these steroids is discussed.

BIBLIOGRAPHY

1. Bayliss, R. I. S. and A. W. Steinbeck: A Modified Method for Eestimating 17-Hydroxycorticosteroids in Plasma. Biochem. J., **54**: 523, 1953.
2. Brown, H., D. G. Willardson, L. T. Samuels and F. H. Tyler: 17-Hydroxycorticosteroids Metabolism in Liver Disease. J. Clin. Invest., **33**: 1524, 1954.
3. Elman, R., T. E. Weichselbaum, J. C. Moncrief and H. W. Margraf: Adrenal Cortical Steroids Following Elective Operations. A. M. A. Arch. Surg., **71**: 697, 1955.
4. Franksson, C., C. A. Genzell and U. S. Von Euler: Cortical and Medullary Adrenal Ac-

tivity in Surgical and Allied Conditions. J. Clin. Endocrinol. & Metab., 14: 608, 1954.
5. Franksson, C. and C. A. Genzell: Adrenocortical Activity in the Preoperation Period. J. Clin. Endocrinol. & Metab., 15: 1069, 1955.
6. Glenn, E. M. and D. H. Nelson: Chemical Method for the Determination of 17-Hydroxycorticosteroids and 17-Ketosteroids in Urine Following Hydrolysis with β-Glucuronidase. J. Clin. Endocrinol. & Metab., 13: 911, 1953.
7. Hume, D. M. and D. J. Nelson: Adrenal Cortical Function in Surgical Shock. Surgical Forum, Am. College of Surgeons, 1954. W. B. Saunders, 1955, p. 568.
8. MacGillivray, D. and L. J. Marks: Free Plasma 17-Hydroxycorticoids in Surgical Emergencies. Unpublished data.
9. Marks, L. J. and J. H. Leftin: Note of Caution on the Lack of Specificity of the Porter-Silber Reaction for 17,21-Dihydroxy-20-Ketosteroids. J. Clin. Endocrinol. & Metab., 14: 1263, 1954.
10. Nelson, D. H. and L. T. Samuels: A Method for the Determination of 17-Hydroxycorticosteroids in Blood, 17-Hydroxycorticosterone in the Peripheral Circulation. J. Clin. Endocrinol. & Metab., 12: 519, 1952.
11. Pareira, M. D., W. Hicks, T. E. Weichselbaum and R. Elman: The Influence of Nutrition on the Response to Intravenous ACTH. Surgical Forum, Am. College of Surgeons, 1953. W. B. Saunders, 1954, p. 531.
12. Peters, J. H.: The Determination of Creatinine and Creatine in Blood and Urine with the Photoelectric Colorimeter. J. Biol. Chem., 146: 179, 1942.
13. Porter, C. C. and R. H. Silber: A Quantitative Color Reaction for Cortisone and Related 17, 21-Dihydroxy-20-Ketosteroids. J. Biol. Chem., 185: 201, 1950.
14. Reddy, W. J.: Modification of the Reddy-Jenkins-Thorn Method for the Eestimation of 17-Hydroxycorticoids in Urine. Metabolism, 3: 489, 1954.
15. Sandberg, A. A., K. Eik-Nes, L. T. Samuels and F. H. Tyler: The Effects of Surgery on the Blood Levels and Metabolism of 17-Hydroxycorticosteroids in Man. J. Clin. Invest., 33: 1509, 1954.
16. Sayers, G.: The Adrenal Cortex and Homeostasis. Physiol. Rev., 30: 241, 1950.
17. Selye, H.: The General Adaptation Syndrome and the Diseases of Adaptation. J. Clin. Endocrinol., 6: 117, 1946.
18. Siker, E. S., E. Lipschitz and R. Klein: The Effect of Preanesthetic Medications on the Blood Level of 17-Hydroxycorticosteroids. Ann. Surg., 143: 88, 1956.
19. Steenburg, R. W., R. Lennihan and F. D. Moore: Studies in Surgical Endocrinology. II. The Free Blood 17-Hydroxycorticoids in Surgical Patients; Their Relation to Urine Steroids, Metabolism and Convalescence. Ann. Surg., 143: 180, 1956.
20. Tyler, F. H., C. D. Schmidt, K. Eik-Nes, H. Brown and L. T. Samuels: The Role of the Liver and the Adrenal in Producing Elevated Plasma 17-Hydroxycorticosteroid Levels in Surgery. J. Clin. Invest., 33: 1517, 1954.