

# Studies in Surgical Endocrinology

## II. The Free Blood 17-Hydroxycorticoids in Surgical Patients; Their Relation to Urine Steroids, Metabolism and Convalescence\*

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### I. INTRODUCTION

IN THE PREVIOUS paper of this series<sup>24</sup> a group of 11 surgical cases was reported in which metabolic balance studies were combined with observations of the urinary 17-hydroxycorticoid excretion. It was noted that, although diminished sodium excretion and certain eosinophile changes did not correlate with any of the endocrine indices measured, there was a good correlation of endocrine, metabolic and clinical events in most (but not all) instances as follows: (1) During the first four days after trauma, the excretion of 17-hydroxycorticoids correlated well with the total nitrogen loss; (2) the four-day nitrogen loss correlated well with the clinical magnitude of the trauma, and (3) the four-day excretion of 17-hydroxycorticoids correlated well with the clinical magnitude of the trauma.

Although there were many instances of variability, and a clear difference between fractures, primary soft-tissue trauma and secondary trauma, the above important cor-

relations might be interpreted as lending further support to the hypothesis that the early metabolic changes after injury (the "catabolic phase" of Browne and Albright, "shock phase of the alarm reaction" of Selye, "adrenergic-corticoid phase") are produced (initiated) by an increased secretion of carbohydrate-active adrenal steroids. On the other hand, there has been evidence that trauma may affect metabolism through some other pathways, the adrenal steroids playing a permissive role only.<sup>4, 5, 9, 16-18, 20, 33, 34</sup> It is therefore of importance to determine the changes in blood steroid concentration which underlie the alterations in urine excretion and in body metabolism, moving one step closer to a valid interpretation of post-traumatic endocrinology and metabolism.

The present study was undertaken in an attempt to corroborate the work of others who have studied the blood steroids,<sup>10, 11, 23, 31, 35</sup> and to make such observations on surgical patients within the framework of our other metabolic and endocrine methods.

In addition, there are technical reasons for looking beyond the urinary excretion to other data on postsurgical endocrinology. These are as follows: The urine 17-hydroxycorticoid method will recover only about 30 per cent of the administered dose of compound F.<sup>32</sup> Variations in this quantity depend not only upon total adrenal activity but upon the rate at which these compounds are conjugated in the liver and excreted by

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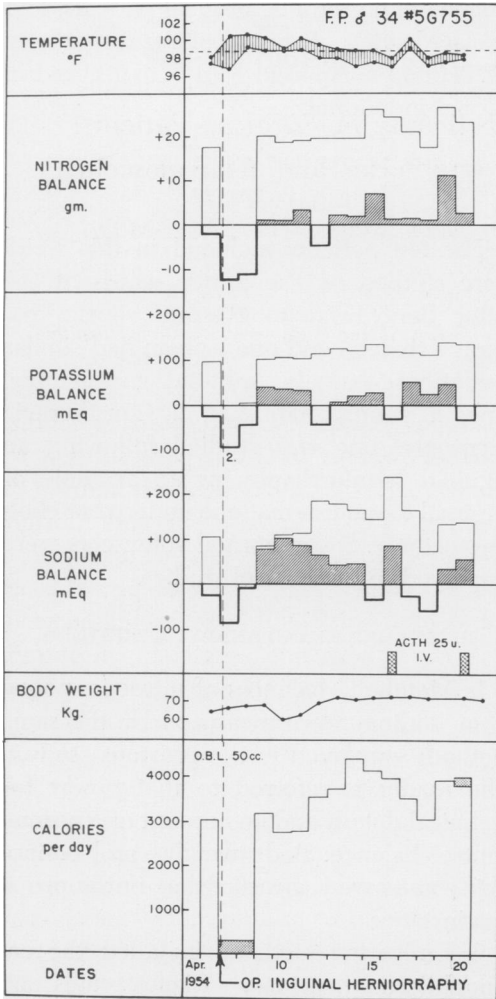


FIG. 1 (Case 12). Metabolic Chart. In this and in the other metabolic charts the metabolic balances are charted as previously described.<sup>25</sup> In this instance balance of N and K showed a transient negativity; sodium conservation began the first postoperative day and was marked for several days.

the kidney.<sup>1</sup> Marks and Leaf<sup>21</sup> have demonstrated a direct correlation between the rate of excretion of 17-hydroxycorticoids and the glomerular filtration rate in dogs. Alterations in glomerular filtration rate following anesthesia and operation are well documented. Furthermore, the largest fraction of the 17-hydroxycorticoids measured in the urine exists as conjugates which in themselves are biologically inactive, although

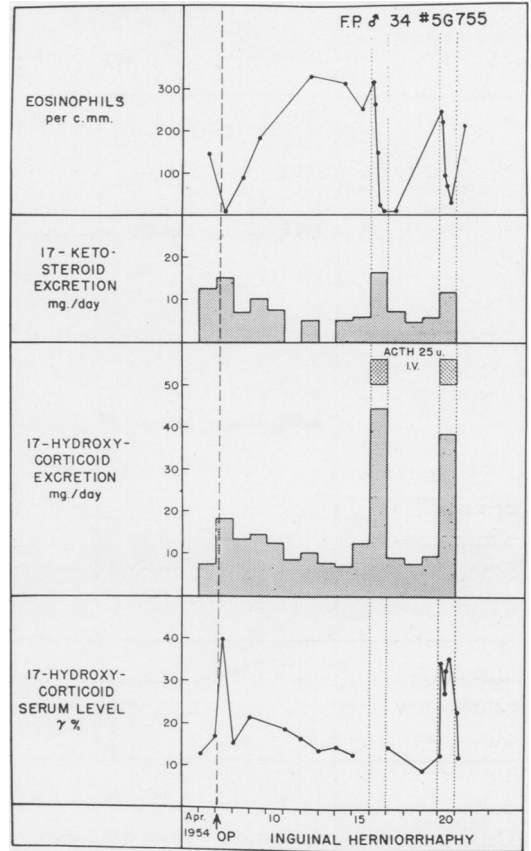


FIG. 2 (Case 12). Endocrine Chart. In this and in the other endocrine charts the eosinophil counts and urine steroids are charted together with the free serum 17-hydroxycorticoids. Here the operative trauma produced transient eosinophil and urine steroid changes; the blood curve showed a sharp operative peak. Postoperative ACTH on the thirteenth postoperative day did not produce a higher rise in the blood curve, a change characteristic of more severe trauma. The increase in urinary steroid excretion is evident.

they undoubtedly were produced as active free steroids. Although little is known of the mechanisms which alter the conjugation of these steroids with glucuronic acid in the liver, any change in the relative rate at which this reaction occurs in the postoperative patient would alter the biologic effect of a given quantity of adrenal steroid secreted. Alteration in other metabolic pathways (sulfate ester formation, side-chain oxidation and reduction, and reduction in ring "A") may also influence the blood

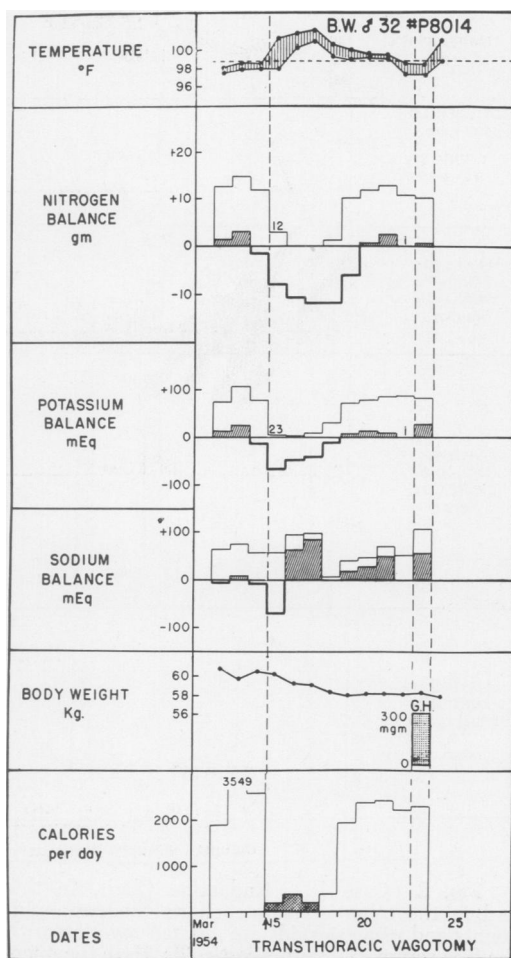


FIG. 3 (Case 13). Metabolic Chart.

level of hormone and the total amount excreted. Since the tissues respond to hormone concentrations in the fluids bathing them, whatever the forces affecting those levels, it clearly becomes important to study blood steroid concentrations in surgical patients.

Following the work of Nelson and Samuels,<sup>28</sup> it became possible to add to our previous studies of urinary hormones a measurement of the free 17-hydroxycorticoids in the peripheral blood of patients following injury and operation. The present paper describes the measurement of free serum corticoids, total urine corticoids, and metabolic

balance in a group of surgical patients, and a related series of studies of the response to ACTH and compound F in patients, and in normal individuals.

## II. MATERIALS AND METHODS

### A. PATIENTS

The ten patients included in this series were studied on the public wards of the Peter Bent Brigham Hospital. Seven patients (six men and one woman had similar operations: namely, subtotal gastrectomy. One, a young man, had a transthoracic vagotomy; one was studied following an inguinal herniorrhaphy as an example of minimal tissue trauma; one underwent cholecystectomy. Seven normal volunteers were employed in the control studies.

### B. METABOLIC AND ANALYTIC METHODS

1. Metabolic balances of nitrogen, potassium, sodium were measured by the same methods employed in the previous study.<sup>24</sup> The reader is referred to that report for technical details and an account of a normal control balance. Body weights and eosinophil counts were measured, as in the previous instance.

2. Endocrine methods included the eosinophil count, urinary 17-ketosteroids and 17-hydroxycorticoid excretion<sup>29</sup> as in the previous study.

The blood levels of free 17-hydroxycorticoids were measured by the method of Nelson and Samuels.<sup>28\*</sup> In our hands, this method has been found to give results which are generally reproducible to within 10 per cent. The normal range in this laboratory coincides with that previously published by Nelson *et al.*<sup>3</sup> (5-18 gamma per cent, mean 12 gamma per cent). Within the

\* Analyses have been carried out on serum rather than plasma. We have changed the final reaction as follows: to the final residue 0.1 ml. of methyl alcohol is added, followed by 0.4 ml. of a reagent containing 65 mg. phenylhydrazine HCl and 100 ml. of 62 per cent H<sub>2</sub>SO<sub>4</sub>.

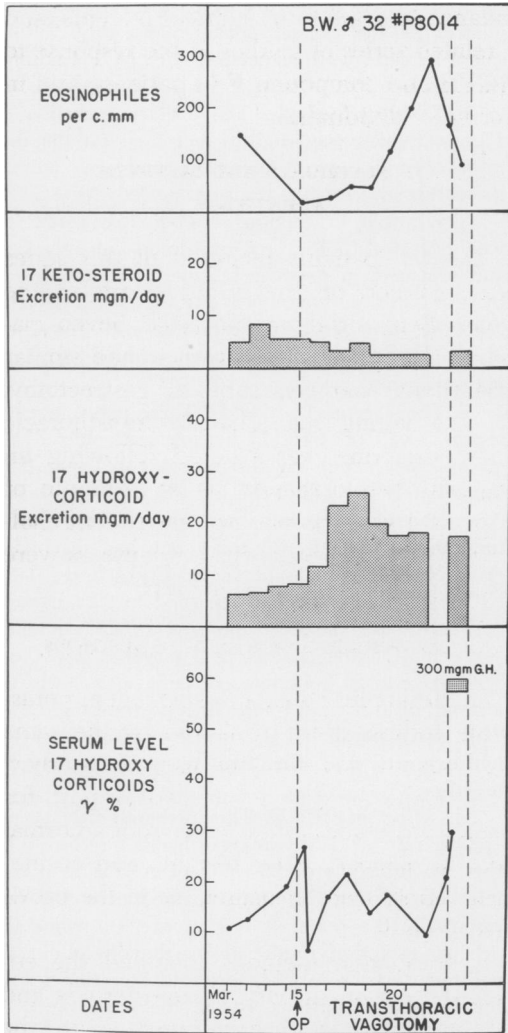


FIG. 4 (Case 13). Endocrine Chart. There was a normal eosinophil response with a very low blood peak and no immediate increase in urine steroid excretion. The increase in apparent urinary 17-hydroxycorticoid excretion starting on the second postoperative day was associated with the administration of potassium by mouth.

normal range of concentration the variation is  $\pm 1.5$  gamma per cent, or 12 per cent of the mean. When the blood concentration is over 20 gamma per cent, this same variability becomes a lesser fraction of the mean. Recoveries in concentrations between 20 and 50 gamma per cent have been complete within 8 per cent.<sup>36</sup>

3. Charting and interpretation follows the graphic convention of Moore and Ball,<sup>25</sup>

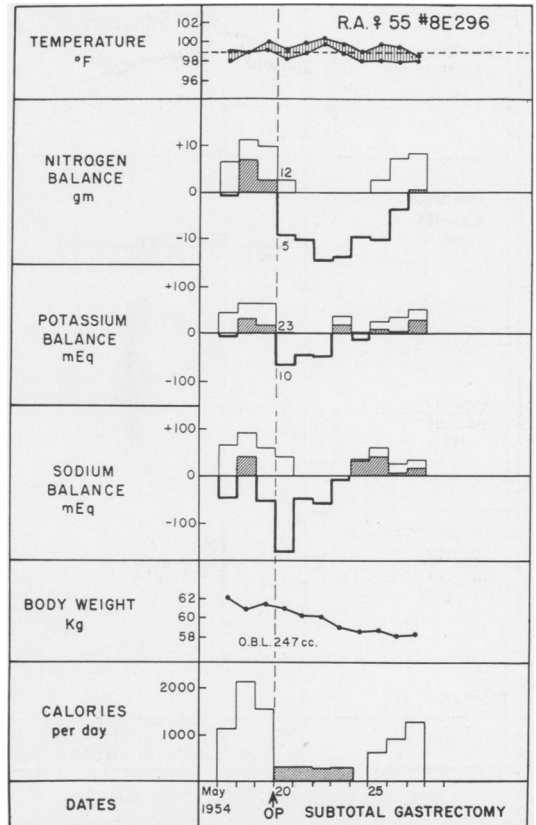


FIG. 5 (Case 14). Metabolic Chart. The large postoperative urinary sodium loss (270 mEq. in three days) was remarkable.

and the case reports follow the same pattern as that of the previous paper. The charts present the data in detail; the written account is condensed.

### III. RESULTS

#### A. SURGICAL PATIENTS; RESPONSES TO OPERATION AND ACTH

**Case 12.\*** *Inguinal Hernia. Herniorrhaphy (Pentothal-Ether Anesthesia).* Patient F. P., male, age 34, Unit No. 5G755. Admitted April 5, 1954. Discharged April 21, 1954 (Figs. 1 and 2).

##### Clinical Summary

This man, moderately obese, was admitted for the repair of an inguinal hernia which he had first noted 8 months prior to admission. At operation a combined direct and indirect right inguinal hernia was repaired. Postoperatively, the patient was am-

\* These cases are numbered in sequence with those of the previous paper, for ease of reference in the discussion.

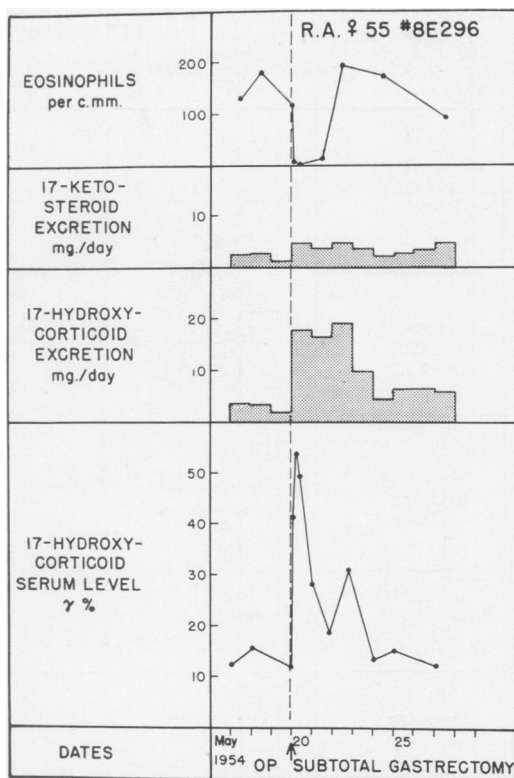


FIG. 6 (Case 14). Endocrine Chart.

bulatory from the first day. His clinical convalescence was uneventful. On his ninth and thirteenth postoperative days test doses of ACTH were given. **Metabolic Summary**

Nitrogen balance became negative (11 Gm. a day) for 2 days, and then became positive with feeding; essentially a starvation phenomenon. Potassium balance paralleled nitrogen, with negative balance at a high K:N ratio (6.0 mEq. per Gm.) on the day of operation. Subsequent K loading was also at a high K:N ratio. Renal sodium excretion the day of operation (operation at noon) was 88 mEq. For the next 4 days excretion was markedly reduced (average 11.2 mEq. per day); with re-feeding there was a positive sodium phase followed later by diuresis on the eighth, tenth and eleventh days; this diuresis was interrupted by ACTH. Twenty-five units of ACTH given intravenously over an 8 hour period on the ninth and thirteenth postoperative days had a marked effect, increasing potassium loss and decreasing renal sodium excretion. There was a slight weight gain over the whole period of study. There was hyponatremia (134 mEq./l.) the first postoperative day.

#### Endocrine Summary

a. *Eosinophil Count.* With operation, the eosinophil count dropped to 3/mm.<sup>3</sup> from a normal

preoperative value, returning to a level above the control by the second postoperative day. Subsequent changes were associated with ACTH administration.

b. *Urinary Steroids.* The urinary excretion of 17-ketosteroids was slightly increased on the day prior to and day of operation, and was normal thereafter save for two transient peaks with ACTH.

The urinary excretion of 17-hydroxycorticoids was increased to 18.3 mg. on the day of operation and returned, in stepwise fashion, to control levels by the sixth postoperative day. It is noteworthy that the urine corticoid excretion rate remained elevated as the eosinophil count climbed to high normal levels.

c. *Free Serum Corticoids.* There was a normal serum level of free 17-hydroxycorticoids (16.9 gamma per cent) on the morning of operation, immediately preceding the induction of anesthesia. After the close of the operation (3 hours after induction of anesthesia) this value had reached a peak of 40.2 gamma per cent. Eight hours later (10 P.M.) this value had returned to 22.4 gamma per cent, and the next morning to 15.5 gamma per cent. On the second postoperative day there was a rise to 21.6 gamma per cent, and thereafter a slow fall to normal by the fifth postoperative day. This curve paralleled the urinary excretion of 17-hydroxycorticoids; the two returned to normal together.

d. *Effect of ACTH.* The increased urinary excretion rate of 17-hydroxycorticoids produced by the two infusions of 25 units of ACTH at 4 day intervals starting the ninth postoperative day was essentially the same. It was more than twice the urinary excretion produced by the operation. By contrast, the rise in 17-ketosteroid excretion resulting from the infusions was in the same range as the day of operation.

The blood corticoid response to the first ACTH infusion was lost as a laboratory accident. On the second occasion the blood steroids rose to around 35 gamma per cent (34.2, 27.2, 32.6, and 34.6 gamma per cent recorded at 2 hour intervals during the infusion). This was not significantly different from the operative value of 40 gamma per cent; it was 13 days after a comparatively trivial trauma.

*Case 13. Duodenal Ulcer (Subtotal Gastrectomy.) Transthoracic Vagotomy (Pentothal-Ether Anesthesia).* Patient B. W., male, age 32, Unit No. P8014. Admitted February 25, 1954. Discharged March 24, 1954 (Figs. 3 and 4).

#### Clinical Summary

This patient had experienced the onset of ulcer symptoms in his late teens. At the age of 20, he

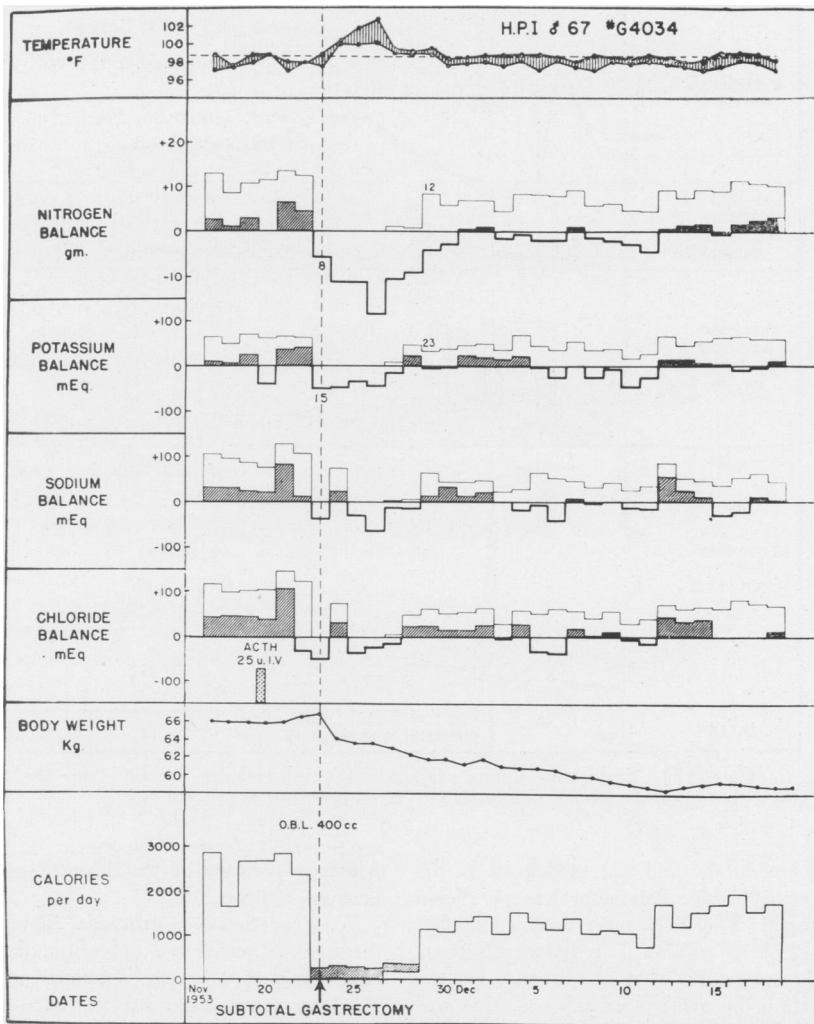


FIG. 7 (Case 15). Metabolic Chart. The prolonged weight loss was associated with a prolonged period of calorie intakes below 1500.

was hospitalized with an episode of massive gastrointestinal bleeding. Thereafter he had followed a dietary regimen and remained symptom-free until 1950, when his symptoms recurred with such severity that he underwent subtotal gastrectomy. Following gastrectomy, he experienced mild "dumping" which was readily controlled. He had no further ulcer symptoms until 2 months prior to this admission when he noted recurrence of typical postprandial distress. On the morning of admission he noted melena associated with weakness and faintness. In the hospital, bleeding subsided and the hematocrit stabilized in a normal range with 2 transfusions.

A transthoracic vagotomy was carried out on the eighteenth hospital day under Pentothal-ether anesthesia. The patient was ambulatory the first postoperative day. Aspiration of a left hemothorax on the second postoperative day resulted in prompt subsidence of temperature. His course thereafter was uneventful. At the time of discharge, 9 days postoperatively, he was asymptomatic on a 6 meal bland diet.

#### Metabolic Summary

The period of negative nitrogen balance lasted 5 days. Positive balance resulted from an absolute decrease in the nitrogen excretion rate with re-

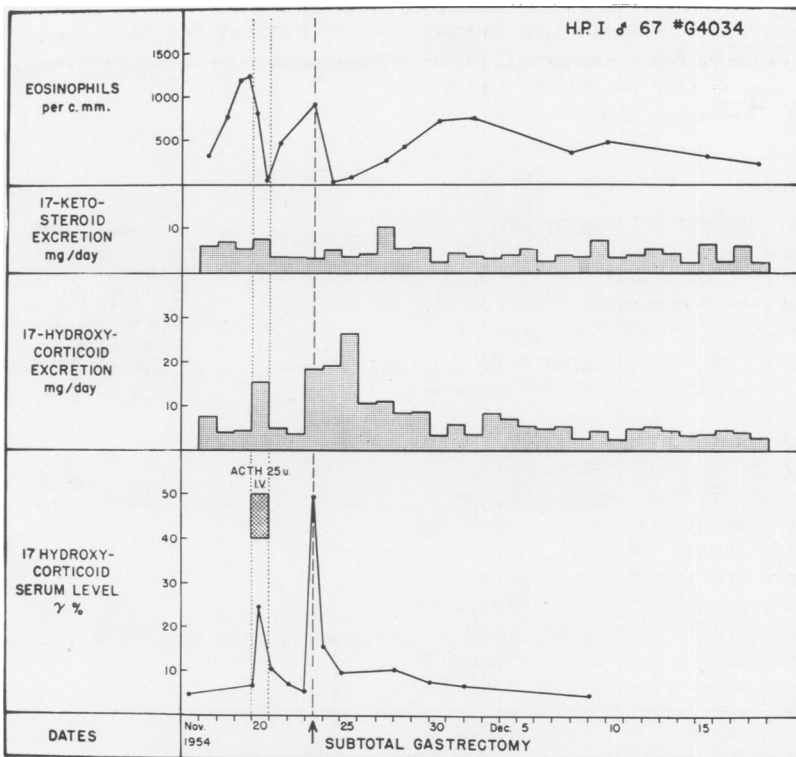


FIG. 8 (Case 15). Endocrine Chart. Operation produced an increase in blood steroid almost twice that produced by a maximal ACTH stimulation preoperatively.

sumption of oral intake and was evidenced on the sixth postoperative day. Potassium loss paralleled that of nitrogen. The K:N ratio during the first 4 days was 2.25 mEq./Gm. This balance became positive 1 day preceding that of nitrogen. On the day of operation the urinary sodium excretion was 79 mEq. For the next 6 days it averaged 18 mEq. per day. Sodium balance was a net positive for the period of study. There was hyponatremia (133 mEq./l.) the second postoperative day. Weight fell 2.0 Kg. in the first 5 days.

#### Endocrine Summary

a. *Eosinophil Count.* The eosinophil count fell abruptly to 18/mm.<sup>3</sup> with operation. Low counts (from 28 to 50/mm.<sup>3</sup>) were observed for the subsequent 3 days. The upswing thereafter was rapid, with return to a level significantly above that observed in the preoperative period.

b. *Urinary Steroids.* The 17-ketosteroid excretion showed no significant response to operation.

There was an interesting lack of response in the 17-hydroxycorticoid excretion rate on the day of operation and the first postoperative day. Thereafter, this value rose to elevated levels (over 20 mg./day) where it remained during the period of study. This rise may have resulted from KI therapy

which was started on the second postoperative day because of bronchitis.\*

c. *Free Serum Corticoids.* Three hours after the completion of the operation, the serum level rose to a peak value of 27 gamma per cent. This is the least pronounced rise we have observed in a patient undergoing operation under general anesthesia, and is correlated with the lack of urine steroid excretion in the early postoperative period. There was a pronounced "dip" in the blood level on the following morning; then a secondary rise to high normal values on the second and third postoperative days following a febrile episode. Whereas the administration of KI may have distorted the urinary excretion data, there is no apparent effect in the blood curve.

b. *Growth Hormone.* A single infusion of Armour's Growth Hormone (300 mg.) given for study purposes on the ninth postoperative day produced a rise in blood steroid as described more fully elsewhere.<sup>27</sup>

\* The pattern is reminiscent of Case 6 of the preceding paper<sup>24</sup> save for the fact that in that case no KI or other medication known to confuse this determination were given.<sup>22</sup>

**Case 14. Carcinoma of the Stomach. Subtotal Gastrectomy (Pentothal-Ether Anesthesia).** Patient R. A., female, age 55, Unit No. 8E266. Admitted May 16, 1954. Discharged May 30, 1954 (Figs. 5 and 6).

**Clinical Summary**

This patient had first noted epigastric distress and postprandial vomiting 2 years prior to admission. Fluoroscopic examination revealed a prepyloric ulcer crater which seemed benign on gastroscopy and healed under a medical regimen. With renewal of symptoms and radiographic evidence of recurrence, the patient was admitted for surgical therapy.

A subtotal gastrectomy was carried out for what appeared grossly to be a benign prepyloric ulcer. Permanent pathologic sections revealed a microscopic focus of malignancy at the edge of the ulcer crater, with minute metastases to two lesser curvature nodes. The patient's clinical course was satisfactory. Nasogastric suction was discontinued on the second postoperative day; the patient was ambulatory thereafter. At the time of discharge on the tenth postoperative day, she was taking a 6-meal bland diet without difficulty.

**Metabolic Summary**

Following operation, there was a stepwise increase in the absolute nitrogen excretion rate which, in the face of no intake, resulted in an appreciable negative balance reaching a maximum of 14.3 Gm. on the second postoperative day. An absolute decrease in excretion rate and resumption of intake resulted in a weakly positive balance immediately prior to discharge. Potassium balance followed nitrogen, returning to positive more rapidly. The early loss (first 4 days) was at a K:N ratio of 3.5 mEq./Gm. Sodium balance was remarkable in that an excretion rate of 182.0 mEq. per day was maintained the day of operation; in the first 3 days 270 mEq. was lost. Renal excretion then dropped to 3.0 and 6.0 mEq./day during the third and fourth days, a rather delayed sodium conservation, evident only after establishment of a significant bodily deficit. There was hyponatremia (130 mEq./l.) on the fourth postoperative day.

The patient lost 2.0 Kg. of weight in the first week.

**Endocrine Summary**

a. *Eosinophil Counts.* With operation the eosinophil count showed an abrupt fall to near zero levels, where it remained during the first postoperative day. By the second day there had occurred a rapid rise to levels above the control; a gradual decline was seen during the remainder of the study period.

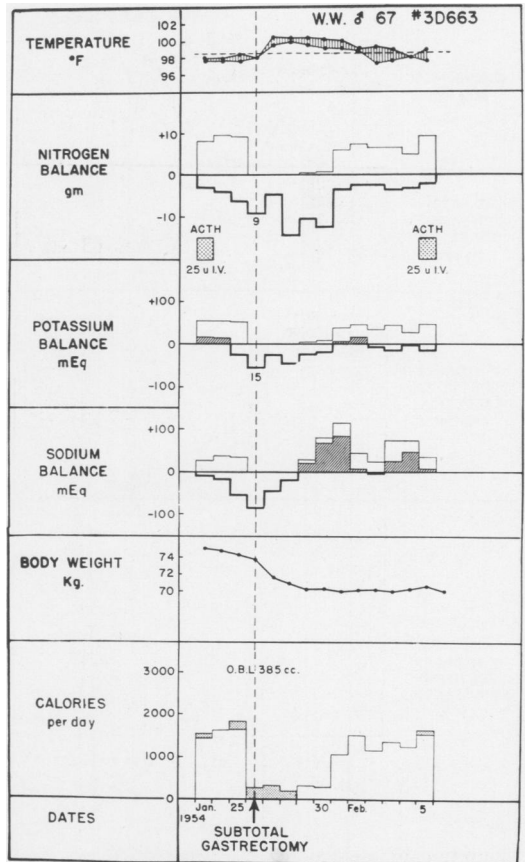


FIG. 9 (Case 16). Metabolic Chart. Failure to load nitrogen at any time was noteworthy.

b. *Urinary Steroids.* The 17-ketosteroid excretion rate was not significantly altered during the period of study.

The 17-hydroxycorticoid excretion rate rose promptly on the day of operation from normal values to 17.7 mg./day, in which range it remained for the subsequent two days, after which it fell abruptly to the normal range and remained there.

c. *Free Serum Corticoids.* The blood levels of free 17-hydroxycorticoids rose suddenly during operation. A level of 43.1 gamma per cent was reached during the operation, only 3 hours after the control reading of 12.0 gamma per cent. This value then rose to 54 gamma per cent in the next three hours, and dropped rapidly to 28.2 gamma per cent, reaching the normal range on the fourth postoperative day. In this case both urine and blood steroid measurements reached normal together on the fourth postoperative day.

**Case 15. Duodenal Ulcer. Subtotal Gastrectomy (Pentothal-Ether Anesthesia).** Patient H. P.,



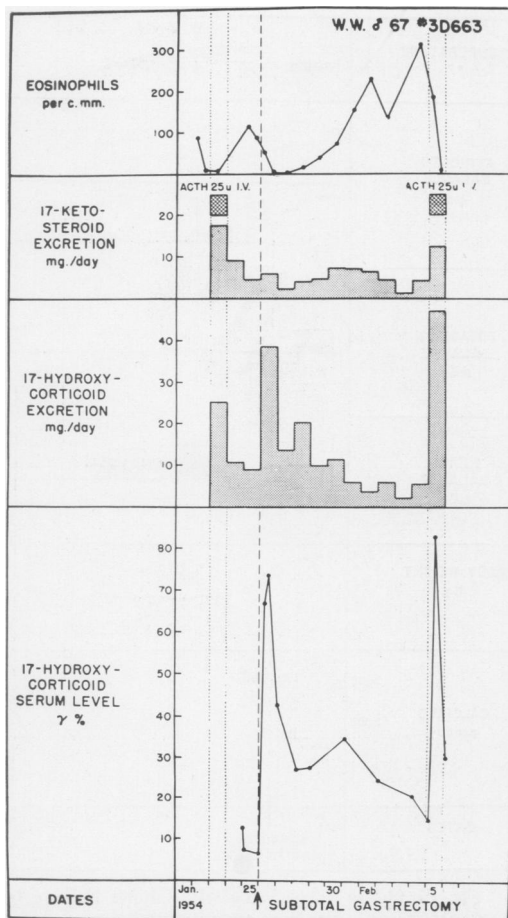


FIG. 10 (Case 16). Endocrine Chart. The administration of a maximal ACTH stimulus on the tenth postoperative day producing a rise in blood and urine steroids significantly greater than the operative rise or the preoperative ACTH.

male, age 67, Unit No. G4034. Admitted October 29, 1953. Discharged December 19, 1953 (Figs. 7 and 8).

#### Clinical Summary

This patient had an "ulcer history" going back 30 years. He was admitted because of epigastric pain and tenderness associated with anorexia and occasional vomiting.

A preoperative ACTH study was carried out 3 days before abdominal exploration, which revealed an active duodenal ulcer adherent to the pancreas. Subtotal gastrectomy was uneventful; he was ambulatory from the first day. Nasogastric suction was discontinued on that day. At no time was there a demonstrable gastric residual. During his convalescence, the patient complained of anorexia and repeated bouts of cramping epigastric pain. His temperature remained normal after the

fourth postoperative day. At the time of discharge on the twenty-sixth day, appetite had improved and these abdominal complaints, for which no cause was found, had subsided.

#### Metabolic Summary

A stepwise increase in the nitrogen excretion rate in the face of zero intake resulted in a net negative balance reaching a maximum of 18.6 Gm./day on the third postoperative day. Thereafter there was a decrease in the absolute rate of nitrogen excretion, to a relatively stable level of 7-10 Gm./day with resultant positive balance as soon as nitrogen intake exceeded 9 Gm./day, which did not occur until the nineteenth postoperative day because of the prolonged anorexia. Between the fifth and sixth postoperative days there was a decrease in urinary nitrogen rate despite increase in intake, leading to a zero balance by the eighth day, even though positive balance was long delayed. Potassium balance during the early postoperative period followed nitrogen closely with a K:N ratio of 3.2 mEq./Gm. Positive balance of potassium was observed earlier than was nitrogen gain. Urinary sodium excretion was reduced only moderately, and quite slowly, after operation. On the days of zero intake the excretion was 24, 22 and 62 mEq. There was no well-defined period of loading. Serum sodium was low throughout, with a further fall to 130 mEq./l. on the 3rd postoperative day. Chloride balance paralleled sodium.

The patient lost a total of 7.0 Kg., losing weight steadily until nitrogen balance became positive.

#### Endocrine Summary

a. *Eosinophil Counts.* The eosinophilia observed preoperatively (500 to 1000/mm.<sup>3</sup>) remained unexplained. The count responded promptly in the usual fashion to ACTH and to the stress of operation. The return to normal levels was gradual, and occurred over the first 4 postoperative days. There was no "overswing."

b. *Urinary Steroids.* There was no significant increase in the 17-ketosteroid excretion rate after ACTH or operation. The 17-hydroxycorticoid excretion rose promptly after ACTH to 15.5 mg./day, and with operation to a maximum of 26.2 mg. on the second postoperative day. After this delayed peak, the excretion rate remained within normal limits for the rest of the study period.

c. *Free Serum Corticoids.* An ACTH infusion (25 units given intravenously over an 8 hour period) 3 days preoperatively produced a rise in the circulating free 17-hydroxycorticoids from normal levels to 24.8 gamma per cent. This is to be contrasted with the level of 49.1 gamma per cent observed 9 hours after the surgical incision. This latter concentration fell rapidly to the normal range, and remained there after the second post-

operative day. This occurred 48 hours before the urinary excretion rate of the total corticoids had reached normal values.

**Case 16. Duodenal Ulcer. Subtotal Gastrectomy (Pentothal-Ether Anesthesia).** Patient W. W., male, age 67, Unit No. 3D663. Admitted January 22, 1954. Discharged February 6, 1954 (Figs. 9 and 10).

**Clinical Summary**

This patient was first admitted to the hospital in October 1953 with an acute perforation of a duodenal ulcer. His first ulcer symptoms dated back to 1948, when he similarly had experienced a perforation. In the interim, he had followed a dietary regimen and was asymptomatic until 2 weeks prior to this second episode, when he noted the return of postprandial distress.

Following closure of the second perforation, his course was uneventful. He returned home on a full diet, and experienced no untoward symptoms. Because of this history, he was re-admitted for subtotal gastrectomy. There was no complicating disease, the patient was active, and in a good nutritional state.

Two days prior to operation a test dose of ACTH was given.

A subtotal gastrectomy was carried out on the patient's fourth hospital day under Pentothal-ether anesthesia. The nasogastric tube was removed on the second postoperative day and oral intake increased in stepwise fashion. At the time of discharge, the patient was taking a 6 meal bland diet. His postoperative course was uneventful.

**Metabolic Summary**

Nitrogen balance was remarkable in that the patient was not observed to be in spontaneous anabolism during the entire study. There was a sharp increase in nitrogen excretion on the second postoperative day, with a negative balance of 14.6 Gm. Potassium balance paralleled nitrogen balance with no clearcut differential loss: the K:N ratio for the first 4 postoperative days was 3.34 mEq. per Gm. There was marked renal conservation of sodium lasting for the first 5 postoperative days, with resultant positive balance as oral intake was resumed. The average urinary sodium excretion for the day of operation and the next 5 days was 13.9 mEq./day, despite intakes approaching 100 mEq. on the third, fourth and fifth days. There was no hyponatremia. Weight fell 4.0 Kg. in 3 days; of this 750 Gm. was resected stomach.

**Endocrine Summary**

a. *Eosinophil Count.* The eosinophil count had started to drop before the induction of anesthesia,

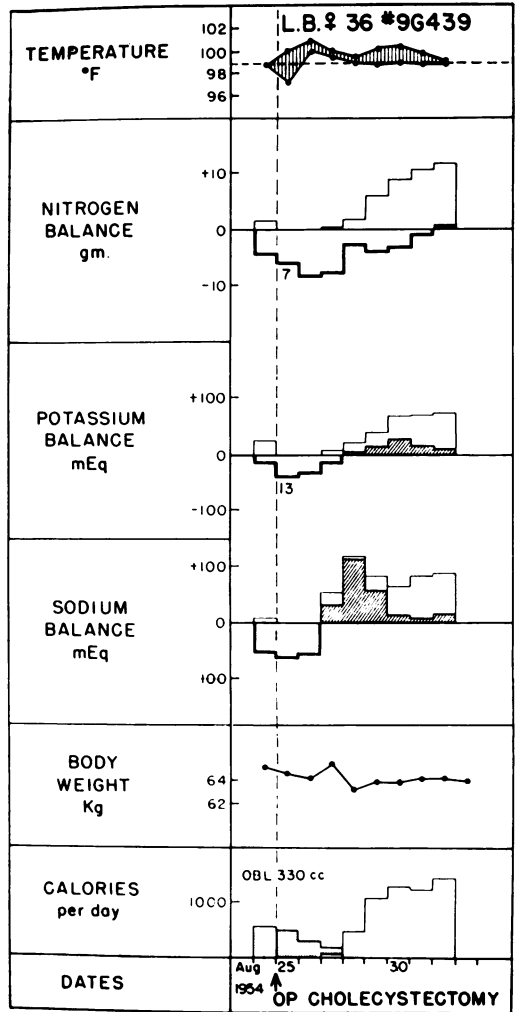


FIG. 11 (Case 17). Metabolism Chart.

and fell to zero with operation. The gradual upswing reached preoperative values on the fourth postoperative day, and proceeded to levels considerably above those seen before the operation.

b. *Urinary Steroids.* The 17-ketosteroid excretion rates showed no change with operation.

There was an inverse correlation of eosinophil count and 17-hydroxycorticoid excretion, the latter showing a peak rate of 38.7 mg. on the day of operation. The corticoid excretion returned to a normal value on the third postoperative day.

c. *Free Serum Corticoids.* No rise in the free 17-hydroxycorticoids in the peripheral blood was observed preceding anesthesia. At the close of the operative procedure (8 hours after the preoperative normal control value), this value had reached

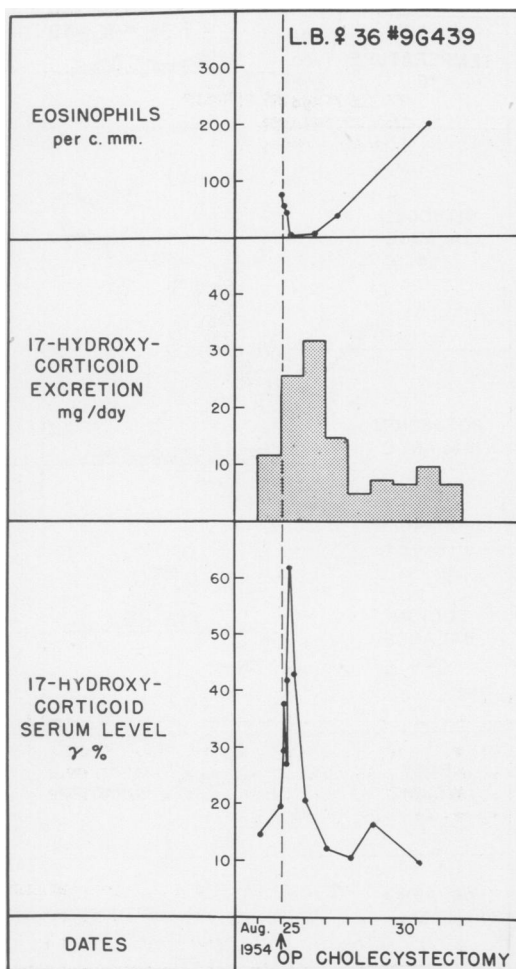


FIG. 12 (Case 17). Endocrine Chart.

66.8 gamma per cent, and 6 hours thereafter a peak value of 73.8 gamma per cent was measured. This fell rapidly to the range of 25 to 35 gamma per cent, reaching normal on the ninth postoperative day. The blood steroids remained elevated while the eosinophils started up; blood and urine steroids returned to normal together.

d. *ACTH Studies.* In contrast to operation, 25 units of ACTH given by intravenous infusion over an 8 hour period produced a significant rise in 17-ketosteroid excretion both pre- and postoperatively. This produced little effect on the metabolic balance in either instance.

The urinary 17-hydroxycorticoid excretion was increased to 26 mg. on the day of ACTH infusion prior to operation. By contrast, an identical infusion on the tenth postoperative day produced an increase in the urine corticoid excretion to 48 mg., an extremely high value.

The blood steroid response to ACTH preoperatively was not recorded. Postoperatively (tenth day) a blood level of 82.9 gamma per cent was observed after ACTH, the highest measured in this series. In this instance, both blood and urine steroids during ACTH administration were higher postoperatively than in response to operation alone; the urine steroid elevation was particularly striking.

**Case 17. Cholecystitis and Cholelithiasis. Cholecystectomy and Appendectomy (Pentothal-Ether Anesthesia).** Patient L. B., female, age 36, Unit No. 9G439. Admitted August 23, 1954. Discharged September 2, 1954 (Figs. 11, 12 and 13).

### Clinical Summary

This patient was admitted with a characteristic story of abdominal pain and fatty food intolerance. On the third hospital day a cholecystectomy was carried out under Pentothal-ether anesthesia. Convalescence was entirely uneventful, and the patient was discharged home on the eighth postoperative day.

To study the metabolic stimulus of anesthesia alone, the anesthesia was induced and the patient maintained under surgical anesthesia (ether) for approximately 2 hours prior to the incision. Multiple blood steroid samples were taken at this time.

### Metabolic Summary

Nitrogen balance became negative with lower excretion rates (7 to 9 Gm. per day) than are usually seen in the male after comparable trauma. Positive balance was not attained in the 8 days of the study. Potassium balance followed an analogous course, becoming positive on the third postoperative day. Urine sodium excretion the day of operation was 24 mEq. (the rest of the loss being extra-renal), the next day 59 mEq.; there then followed a 3-day period of conservation with rising intake, producing a positive sodium balance. Weight fell 2 Kg., the slope being interrupted by a small gain during the sodium-positive period. Serum sodium concentration fell to 134 mEq. per liter, and remained low until the eighth day.

### Endocrine Summary

a. *Eosinophil Count.* The eosinophil count fell during the administration of the anesthetic from 75 to 56 mm.;<sup>3</sup> its fall to zero did not occur until the end of the operation. The return upwards was rapid, and by the fifth postoperative day, the count was 200/mm.<sup>3</sup>

b. *Urinary Steroids.* The urinary excretion of 17-hydroxycorticoids rose on the day of operation to 25 mg. per 24 hours, and on the next day to 32, thereafter falling to normal amounts.

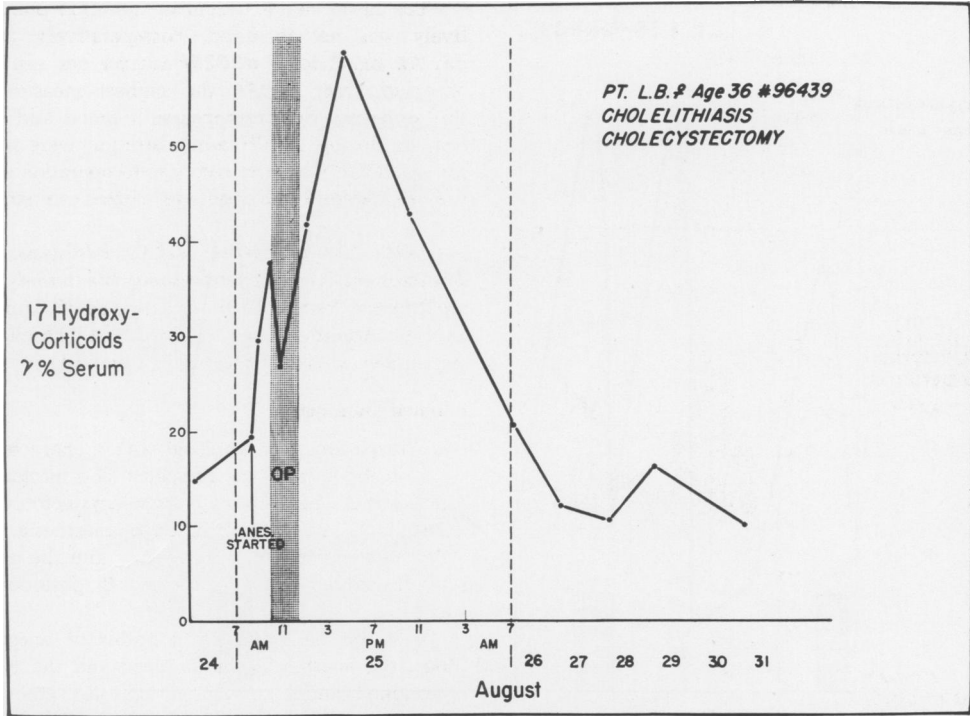


FIG. 13 (Case 17). Blood Steroid Chart. In this and Figures 14 and 15, the blood steroid values are charted alone. In several instances, as above, the operative day is allotted additional space on the abscissa. In this instance the administration of a Pentothal-ether anesthesia produced a distinct rise in the blood steroid prior to the surgical incision.

c. *Free Serum Corticoids.* With induction of deep ether anesthesia and with no other stimulus (save the preoperative medication), the serum steroid level rose to 38 gamma per cent; there was then a slight fall coincident with the start of operation, followed by a rise to 62 gamma per cent, this being observed at 4:30 P.M. (anesthesia started at 8:00 A.M., operation at 10, completed at 11:30 A.M.). That evening (10:10 P.M.) the level fell to 43 gamma per cent, and the next morning to 20 gamma per cent, with normal values thereafter.

**Case 18. Duodenal Ulcer. Subtotal Gastrectomy (Pentothal-Ether Anesthesia).** Patient J. E., male, age 21, Unit No. 9C781. Admitted April 20, 1954. Discharged May 4, 1954 (Fig. 14).

**Clinical Summary**

The first admission for this patient was almost exactly 1 year previously for a perforation of a duodenal ulcer. Ulcer symptoms had started at the age of 14, with recurrent difficulties annually. It had been noted that some of his recurrent bouts of pain were associated with difficulties either in his college work or in his employment. Three days after the present admission subtotal gastrectomy was carried out. The operation was uneventful, and

required approximately 2½ hours. The patient's postoperative convalescence was satisfactory.

ACTH infusions were given at intervals for the purpose of comparing the endocrine pattern after ACTH with that produced by operation. These infusions were given 2 days prior to operation, and on the first and seventh postoperative days. In each instance the infusion consisted of 25 units of ACTH administered intravenously in 500 cc. of 5 per cent glucose in water, over an 8 hour period. The patient was not on metabolic balance study.

**Endocrine Summary**

a. *Free Serum Corticoids.* The preoperative ACTH infusion produced a rise to 44 gamma per cent, the operation itself a rise to 60 gamma per cent. ACTH on the first postoperative day produced a rise to 58 gamma per cent, and on the seventh postoperative day the ACTH infusion produced a value of 50 gamma per cent.

**Case 19. Duodenal Ulcer; Postoperative Pancreatitis; Subtotal Gastrectomy (Pentothal-Ether Anesthesia).** Patient F. M., male, age 64, Unit No. 9F85. Admitted April 6, 1954. Discharged May 17, 1954 (Fig. 15).

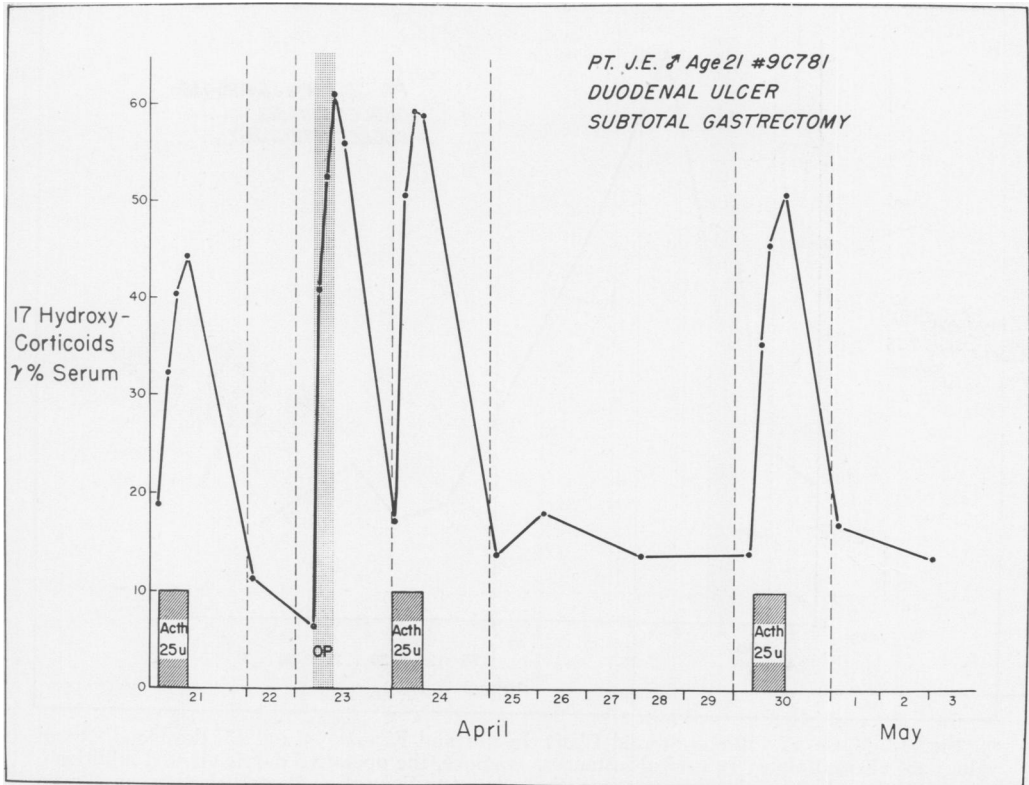


FIG. 14 (Case 18). Blood Steroid Chart. The operative rise is greater than preoperative maximal ACTH stimulation; postoperative ACTH rise is greater than preoperative. To obtain additional evidence regarding this phenomenon the patient returned 10 months later for an exactly similar series of ACTH injections, but without anesthesia or surgery. There was slight "potentiation" as in Figure 22; no values were over 40 gamma per cent; there was no "peaking" as here on the operative day.

#### Clinical Summary

This was the second hospital admission of this man, who had an ulcer history of 43 years' duration. A heavy drinker, he had never followed a medical regimen adequately. His most recent bout of difficulty had involved severe ulcer pain, suggesting acute penetration. After suitable preparation, a subtotal gastrectomy was carried out, without event. Fever was elevated for 4 days after the operation, and the patient was slow to commence peristaltic activity. He had more than the usual abdominal discomfort and spasm, and his serum amylase was on the upper limits of normal, but this relented by the sixth postoperative day, and his course appeared to straighten out. But by the fourteenth day, localization was evident, fever again became apparent, and a subhepatic abscess was drained. This material showed a high amylase content; there was no duodenal fistula. The wound soon closed and the patient was discharged. Metabolic balance was not measured.

#### Endocrine Summary

a. *Free Serum Corticoids.* Operation was associated with a rise in free serum corticoids to a level of 54 gamma per cent, this level being achieved by 3:00 P.M. the day of operation. The familiar drop to normal by the following day did not occur. Instead, the level remained high throughout the period of observation (thirteenth postoperative day); there was a gradual fall, however, from the postoperative high to a value of 20 gamma per cent on the thirteenth day.

*Case 20. Gastric Ulcer. Subtotal Gastrectomy (Pentothal-Ether Anesthesia).* Patient H. F., male, age 69, Unit No. 1B674. Admitted October 9, 1954. Discharged November 10, 1954 (Figs. 16 and 17).

#### Clinical Summary

This patient was admitted with a history of gradual change in digestive habits, of 2 years' duration. His appetite remained good. He had lost 25 pounds in weight. Other than evidence of recent weight loss and benign prostatic hypertrophy, physical examination was negative. Appro-

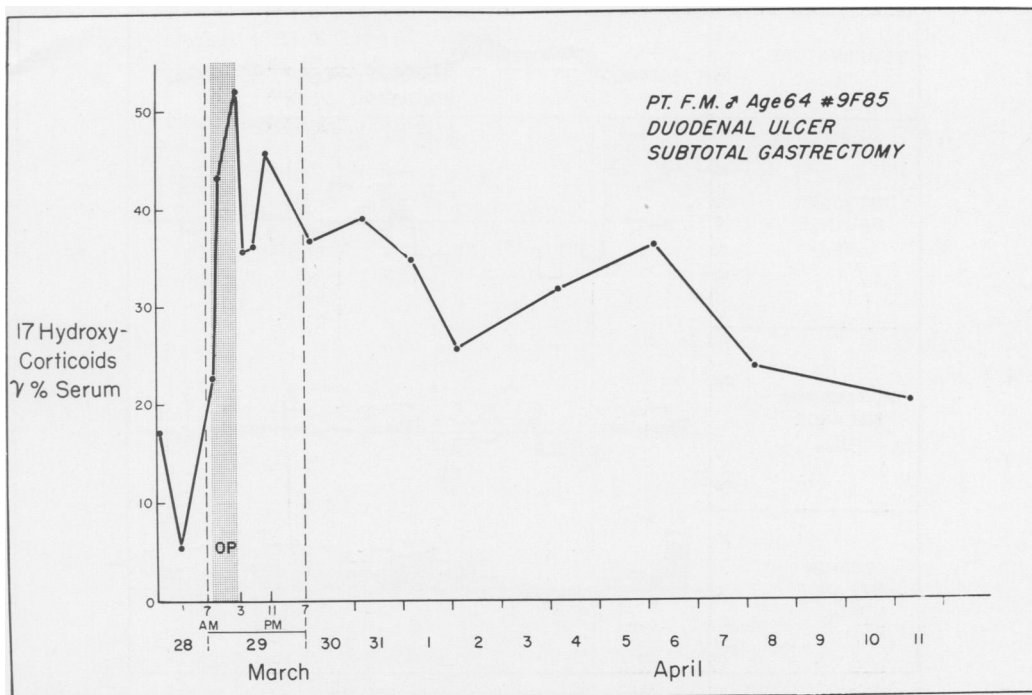


FIG. 15 (Case 19). Blood Steroid Chart. The prolonged elevation was associated with a stormy postoperative course.

appropriate studies were carried out, all of which pointed to carcinoma of the stomach (anacidity, roentgenographic and gastroscopic appearances).

A subtotal gastrectomy was carried out. The gross findings were most suggestive of a benign ulcer, and this was corroborated at the pathology laboratory. The patient's postoperative convalescence was characterized by "lack of response" clinically, as one sometimes sees in elderly depleted patients. There was bladder neck obstruction, requiring constant drainage for 10 days postoperatively. No completely satisfactory cause for the preoperative weight loss was found. There was no obstruction.

#### Metabolic Summary

Nitrogen balance was zero preoperatively. With operation there was not an increase in the urinary nitrogen excretion rate; on zero intake a negative balance, of course, resulted. As intake was increased, losses were lessened, but positive balance was not achieved until the fourteenth postoperative day despite caloric intake in the 1200 to 1500 range, and a calorie:nitrogen ratio of about 200. We have no explanation of the prolonged catabolism in this rather depleted man. There were urinary complications, and his eosinophil count remained low until the fourteenth to fifteenth day. Potassium balance showed loss of 100 mEq. in the

first 3 days after operation (a K:N ratio of 5). Thereafter balance was intermittently positive, with a net of close to zero for the period. His intake was low; he did not eat much meat. Sodium excretion was at a low level throughout; preoperatively he was in strongly positive balance, with urine excretions in the range of 20 to 35 mEq. per day on an intake of 50 to 110. On the day of operation his urine sodium excretion remained at 25 mEq., then dropping about 50 per cent for an 8-day average of 15.3 mEq.; as intake rose there was therefore a prolonged period of positive balance (566 mEq.) from the fifth day to the end of the study, and during this time a gain of 4 Kg. of weight despite a nitrogen loss of 18 Gm. This is an example of lean tissue loss (on the basis of nitrogen) persisting during a period of sodium-retention weight gain, as a postoperative manifestation in a depleted man whose lowering of eosinophil count and sodium retention were very prolonged. There was hyponatremia (126 mEq./l.) on the twenty-second postoperative day.

Weight fell 3.75 Kg. during the first 5 days postoperative, thereafter rising as mentioned above.

Urinary creatinine data show that some of the urine of the first postoperative day found its way into the pool for the second postoperative day. The corticoid data must be evaluated in the light of these findings.

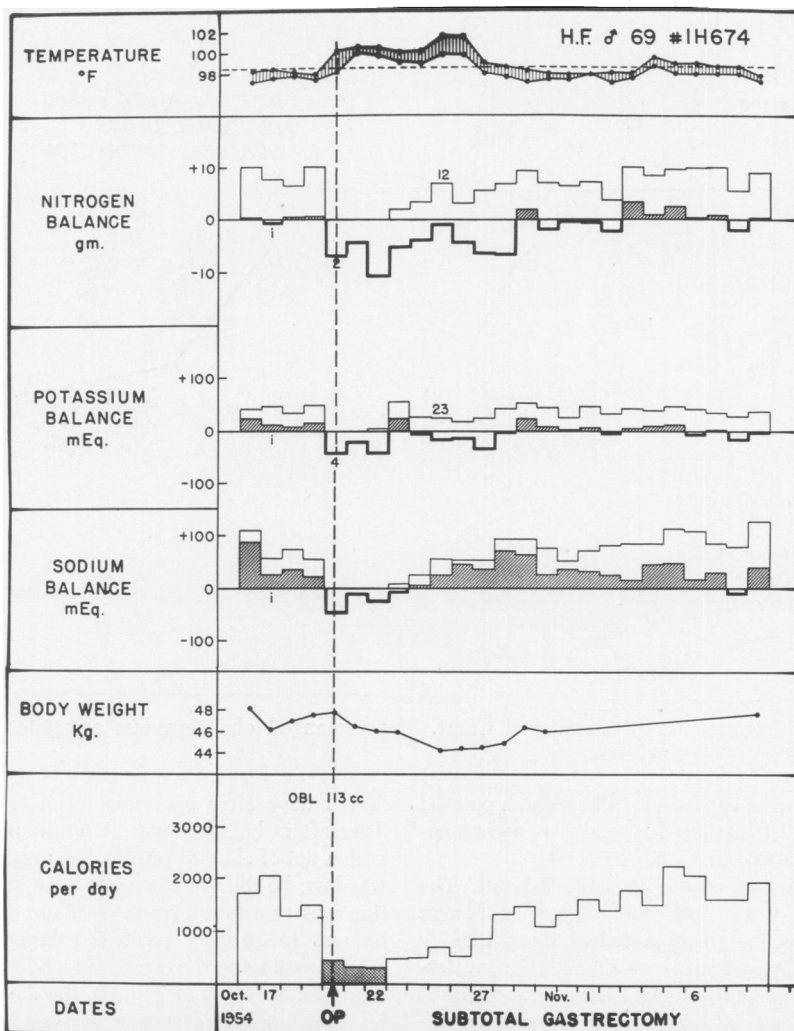


FIG. 16 (Case 20). Metabolic Chart. The prolonged nitrogen negativity was exceptional in view of the patient's age and preoperative weight loss, as well as intake levels observed.

#### Endocrine Summary

a. *Eosinophil Count.* On the day of operation the counts fell from preoperative values near 100/mm.<sup>3</sup> to zero. The return to normal was slow, not being complete until the sixteenth postoperative day.

b. *Urinary Steroids.* At no time was the urinary 17-hydroxycorticoid excretion increased over 18 mg. per day. The excretion on the day of operation and the second postoperative day were significantly higher than any others for a 2-week period (at 15 and 18 mg. respectively). This is one of the most minimal urinary steroid responses we have seen.

c. *Free Serum Corticoids.* Operation was followed by a rise in free serum corticoids to 30 gamma per cent. This low peak was observed at 11:00 A.M., as the incision was being closed. The

values returned to normal the second postoperative day.

**Case 21. Duodenal Ulcer; Subtotal Gastrectomy (Pentothal-Ether Anesthesia).** Patient C. T., male, age 38, Unit No. 1B888. Admitted October 8, 1954. Discharged November 13, 1954 (Figs. 18 and 19).

#### Clinical Summary

This patient was admitted to the hospital with a history of duodenal ulcer symptoms going back to the age of 16. Ten days prior to admission he had had a marked exacerbation of pain. Previous bleeding had been noted, and there had been episodes of faintness and tarry stools.

After approximately 12 days in the hospital the patient was operated upon, a subtotal gastrectomy being carried out without event save for a rather

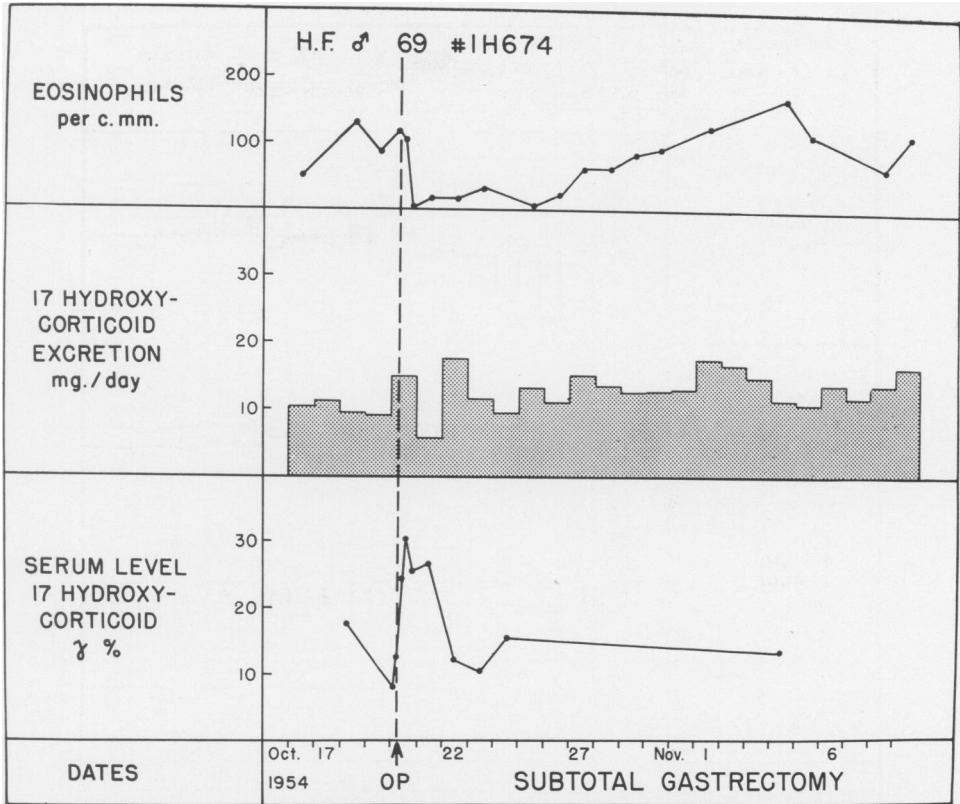


FIG. 17 (Case 20). Endocrine Chart. There is a prolonged eosinopenia despite a lack of elevation of urine 17-hydroxycorticoid excretion, and only a minimal rise in the blood steroid concentration.

acutely inflamed duodenum which presented some problems in closure. Convalescence was entirely uneventful. The patient remained in the hospital for approximately 10 days longer than would be routine, to permit completion of metabolic studies, and after that time he was discharged.

On several occasions infusions of ACTH were given to study their effect on the blood steroids and contrast that effect with the procedure itself and with similar studies done in Case 18 (J. E.). These infusions were given 2 days prior to operation, and on the first and seventh postoperative days, and again on the twentieth postoperative day.

**Metabolic Summary**

Nitrogen balance became negative postoperatively with, on the second postoperative day, a marked increase in urinary nitrogen excretion (20 Gm.). Excretion remained high (12 to 15 Gm.) with increasing intakes (10 Gm. N, 2000 cal.; Cal:N = 200) until, on the sixteenth postoperative day he achieved consistently positive nitrogen balance. The administration of ACTH increased nitro-

gen excretion on the twentieth postoperative day; otherwise the nitrogen effects were small. Potassium balance showed a loss of 154 mEq. on the first 3 postoperative days (a K:N ratio of 4.4). Consistently positive potassium balance was achieved by the eighth postoperative day. ACTH given on the twentieth postoperative day resulted in an increased excretion. Sodium balance showed an excretion of 63 mEq. on the day of operation, followed the next day (ACTH) by an excretion of only 14 mEq., then 61.4 mEq.; starting on the third postoperative day there was an 8-day period of conservation in which 307 mEq. was gained, and there was a transient weight gain at this time. There was hyponatremia (131 mEq./l.) on the first postoperative day.

Weight fell 4 Kg. during the first 3 days after operation, thereafter staying constant save for the sodium-engendered rise mentioned above.

Urinary creatinine data showed some urine from the third postoperative day in the pool for the second day. The chart has not been "smoothed" as a correction for this; the nitrogen and steroid curves,



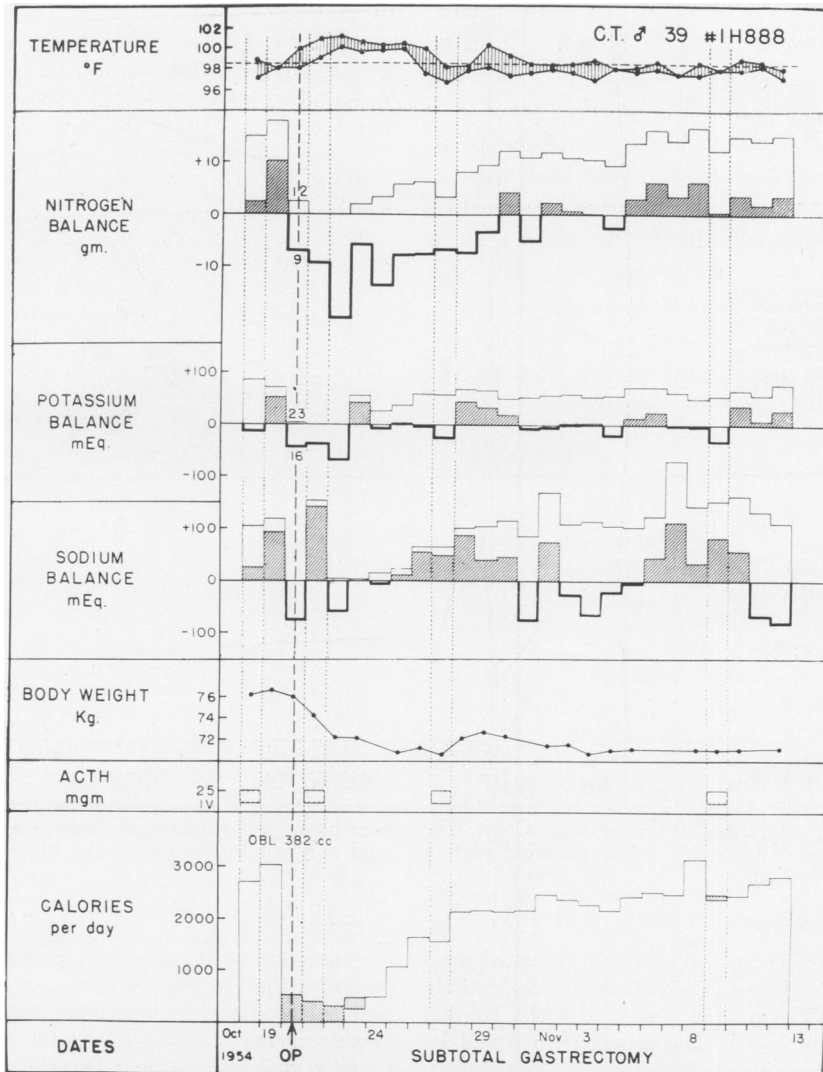


FIG. 18 (Case 21). Metabolic Chart.

particularly, must be interpreted with this in mind.  
**Endocrine Summary**

a. *Eosinophil Count.* The operative eosinopenia occurred; the count was again zero the next day following ACTH. On the seventh postoperative day the count was not lowered to zero by ACTH, nor was it on the twentieth day.

b. *Urinary Steroids.* For any "stimulated" day, the urinary steroid excretion was least (18 mg.) the day of operation and greatest (57 mg.) on the day following the ACTH administration on the first postoperative day.

c. *Free Serum Corticoids.* The preoperative ACTH rise and that of the twentieth postoperative day are about normal and equal, near 40 gamma

per cent. The operation produced a rise to 49 gamma per cent. The following day a single intravenous dose of 25 units of ACTH produced a further rise to 77 gamma per cent. On the seventh postoperative day the same infusion produced a rise to 72 gamma per cent, also a remarkably high level.

#### B. RESPONSES TO ACTH AND COMPOUND F WITHOUT TRAUMA

##### 1. *Grouped Normals.*

In Figure 20 are shown two families of curves, representing ACTH tests on four normal young men carried out by identical technics save for the dose of ACTH. The

four subjects, all volunteer college students, were not hospitalized. They were given an intravenous infusion of ACTH\* over an eight-hour period. The ACTH was dissolved in 500 ml. of 5 per cent glucose in water. On one occasion the dose was 25 units; on the second occasion (from two days to two weeks later) the dose was 50 units. The blood steroid concentration rose to similar levels in both instances, suggesting, as found by others<sup>6, 13, 30</sup> that the 25-unit dose given in this manner constitutes a substantially maximum stimulus to the adrenal.

## 2. Individual Studies.

**Case 22. Normal Control. ACTH Studies.** Patient J. C., male, age 20, Unit No. 9G516. Admitted September 8, 1954. Discharged September 15, 1954 (Figs. 21 and 22).

### Clinical Summary

J. C. was admitted in excellent health as a normal volunteer for metabolic study. The experimental protocol called for an initial 2 days of observation, followed by a third day in which 25 units of ACTH was infused intravenously over an 8-hour period. On the subsequent day the same procedure was carried out, using 50 units of ACTH, and on the third day it was again repeated, using 25 units of ACTH. There was then a one-day period of stabilization, followed by a single infusion of 25 units of ACTH.

The infusions were without effect clinically. Each was given in 500 ml. of 5 per cent glucose in water. There were no changes in vital signs during the procedure. Over the total of 3 days in which the infusions were given, the patient gained 2.2 Kg. in body weight.

The purpose of this study was to discern whether or not repeated administrations of ACTH would produce a progressive increase in the peak serum 17-hydroxycorticoid concentration and urinary excretion rate.

### Metabolic Summary

Nitrogen balance was positive throughout except on the last day of the study. Potassium balance was likewise positive, most marked on the day between the ACTH infusions. Sodium balance was strongly positive (200 mEq.) on the first 3 days of ACTH infusions. The weight gain of 2.2 Kg. is correlated with that predicted from a gain of 200 mEq. of sodium, and 15 Gm. of nitrogen.

### Endocrine Summary

a. *Eosinophil Count.* Eosinopenia was observed on each day of ACTH administration. Between injections there was a tendency to higher counts. But no counts over 100 were observed.

b. *Urinary Steroids.* There was a stepwise increase in urinary 17-hydroxycorticoid excretion as successive infusions of ACTH were given; a normal value was then observed on the next day. The day of final infusion the response was slightly greater than on any previous day.

c. *Free Serum Corticoids.* On the second day of ACTH (50 units) the serum corticoid values rose higher (40 gamma per cent) than on the previous day (30 gamma per cent), an unusual finding when the infusions are isolated with a rest period between. The third day, although the dose returned to 25 units, the blood peak remained at 40 gamma per cent. The final infusion (25 units) produced a blood peak slightly higher than any previously (43 gamma per cent). The conclusion is inescapable (both on blood and urine data) that there was some tendency to potentiation when 4 ACTH infusions were given so close together, and in the absence of trauma. This may be due to adrenal hypertrophy. It must be emphasized that these values all lie between 29 and 43 gamma per cent, a fairly narrow range. Any "potentiation" of the blood peak is of a mild sort when compared with that produced by operation after which peaks as high as 70 gamma per cent are produced by the same infusion.

**Case 23. Normal volunteer. Study of ACTH and Starvation.** Patient C. J., male, age 22, Unit No. 8G224. Admitted September 9, 1954. Discharged September 18, 1954 (Figs. 23 and 24).

### Clinical Summary

C. J. was admitted for metabolic study.

Study protocol called for a 2-day equilibrium period, followed by 2 days of starvation. On the first day of starvation, ACTH was given in the amount of 25 units intravenously over an 8-hour period. The starvation regimen called for no food by mouth but the administration of a total of 1000 ml. of 5 per cent glucose in water. After 2 days on a routine of this type ("dummy operation"), including 1000 ml. of oral water the second day, the diet was increased in stepwise fashion. The purpose here was to compare the response (metabolic and steroidal) to a single dose of ACTH in the starving man, with those recorded in the surgical patients. After 3 days of stabilization, the patient was given potassium iodide by mouth, 15 drops 3 times a day. This was done for the purpose of studying the effect on the urinary excretion pattern of 17-hydroxycorticoids.

\* Parke-Davis ACTH was used throughout.

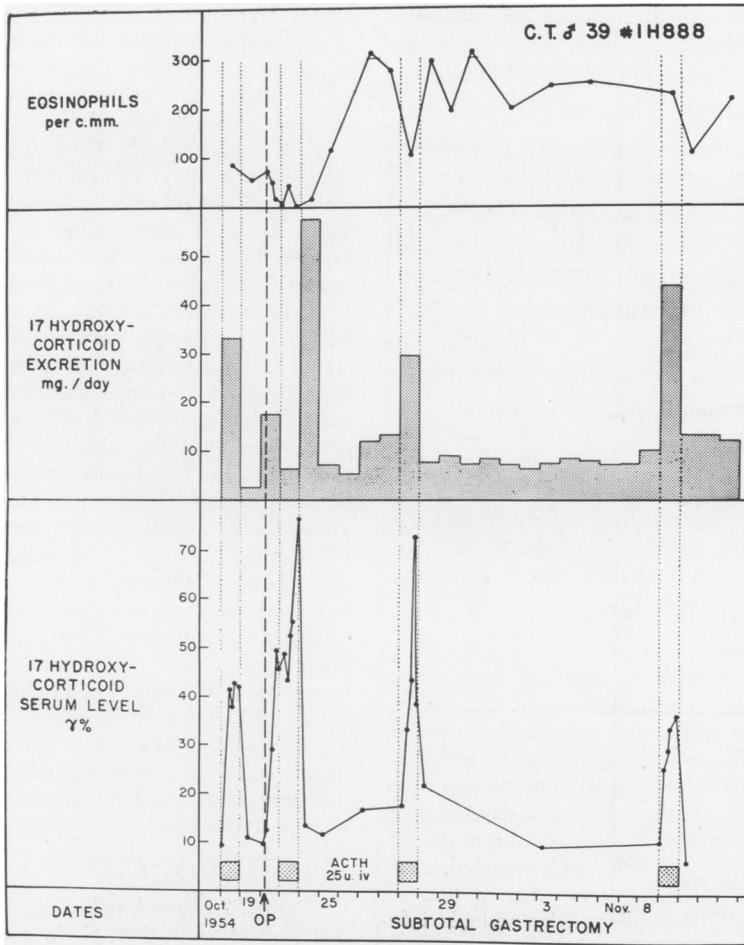


FIG. 19 (Case 21). Endocrine Chart. The postoperative administration of ACTH, as in Case 18, produced an excessive (77 per cent) rise in blood steroid and a marked increase in urine 17-hydroxycorticoid excretion the following day. On the twentieth postoperative day the rise in blood steroid produced by ACTH has returned to the normal range.

The clinical and study procedures produced very little reaction on the part of the patient. As is characteristic in such experiments, there was virtually no sensation of hunger. The patient lost 2 Kg. of weight during his acute starvation phase, but gained this back during the recovery phase.

**Metabolic Summary**

The loss of nitrogen (16.5 Gm.) on the first day of starvation plus ACTH was significantly greater than that to be expected from starvation alone; the following day the loss was less, and thereafter there was a return towards positive balance. Potassium balance closely followed nitrogen; the K:N ratio the first day was 7 mEq. per Gm. Sodium balance was negative on the first day

of ACTH; there was then a transient positive balance. The weight loss of 2 Kg. is greater than that predicted from nitrogen or sodium balance. Fat oxidation or intracellular water loss (high K:N ratio) must be invoked to explain the observed facts.

**Endocrine Summary**

a. *Eosinophil Count.* The expected eosinopenia occurred with ACTH. There was no backswing overshoot.

b. *Urinary Steroids.* The urinary 17-hydroxycorticoid excretion rose sharply with ACTH to 33 mg. per day, thereafter falling to normal. On the second and third day of potassium iodide therapy the excretion rose again to 18 and 20 mg. per day respectively.

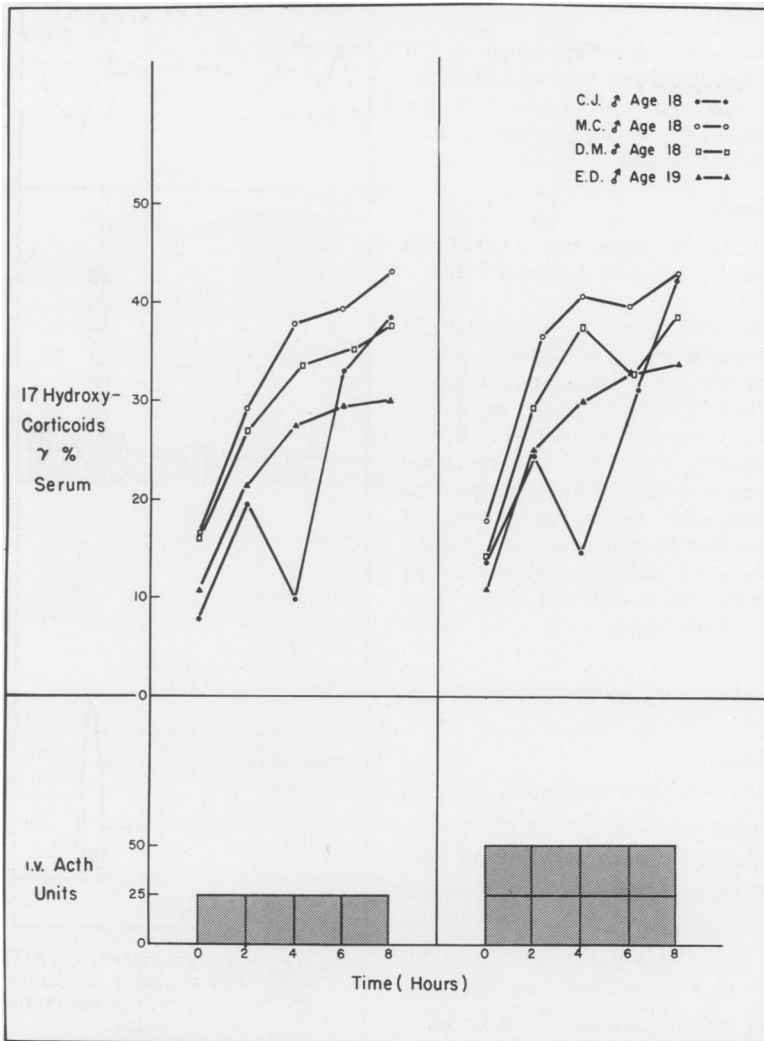


FIG. 20. Response of four normal individuals to intravenous ACTH at dose levels of 25 and 50u. per 8 hours. The rise in blood steroids is of the same magnitude in all instances.

c. *Free Serum Corticoids.* Upon administration of 25 units of ACTH, the serum corticoid level rose sharply to 54 gamma per cent, falling as abruptly the next day to normal. This was a level substantially higher than that seen with most surgical operations of moderate trauma.

**Case 24. Normal Subject. Compound F. Infusions, Followed by ACTH.** Patient R. J., male, age 20, Unit No. 9G517. Admitted September 8, 1954. Discharged September 15, 1954 (Figs. 25 and 26).

**Clinical Summary**

R. J. was admitted to the hospital for metabolic study. His physical examination was normal. Ex-

perimental protocol consisted of an initial 2-day period of stabilization followed by 3 successive days of compound F infusion intravenously, 20 mg. the first day, 40 the second, and 60 the third. On the fourth day an infusion of 25 units of ACTH was given. The purpose here was to study the blood level produced by these infusions, and to compare these with the rises produced by surgery, and secondly to discern if 3 days of hydrocortisone produces any inhibition of adrenal response to standard ACTH infusions. There was no clinical change or alteration of vital signs. There was a weight gain of 1.3 Kg. over the period of the infusion. Following 2 days of stabilization, the patient was discharged.

**Metabolic Summary**

Nitrogen balance was positive throughout (20 Gm. total), potassium balance was unremarkable. Sodium balance was positive (110 mEq.) for the period. The sum of nitrogen and sodium balance approximates the weight-gain.

**Endocrine Summary**

a. *Eosinophil Count.* There was a consistent eosinopenia, save for transient intervals between injections.

b. *Urinary Steroids.* The urinary excretion of 17-hydroxycorticoids increases in stepwise fashion from 7 to 15 mg./day on hydrocortisone; then, on the day of ACTH it increases to 21 mg. per day.

c. *Free Serum Corticoids.* The serum corticoids rose progressively (33, "over 40," 48 gamma per cent) on the successive days of hydrocortisone infusion. The exact value the second day is not available but was over 40 gamma per cent. On the day of ACTH the level reached was 40 gamma per cent, a normal value for the infusion given. There was no evidence of inhibition.

**C. SUMMARY OF OBSERVATIONS**

**1. Metabolism.**

*Postoperative nitrogen* excretion rates in the surgical cases are in the range previously reported: 8 to 15 Gm. per day on zero intake during the first two to five postoperative days, depending on the severity of the trauma. The loss in Case 17 (female, cholecystectomy) was somewhat less than we would predict for this trauma in a male.

*Potassium* losses are less marked than some previous series,<sup>25</sup> although none of these patients suffered trauma more than scale 5 to 6 (subtotal gastrectomy). The K:N ratios of the early period are over 2.5 mEq. per gram in seven out of eight of the surgical cases on balance measurement, but none is over 7.5 mEq. per gram; the highest being 6.0 mEq. per gram.

*Sodium* metabolism in these eight cases shows certain features of interest. In four of the eight the sodium excretion the day of operation was over 50 mEq. per day; restricted sodium excretion was slow to start. In all save Case 14 there was a period of four to six days when excretion averaged

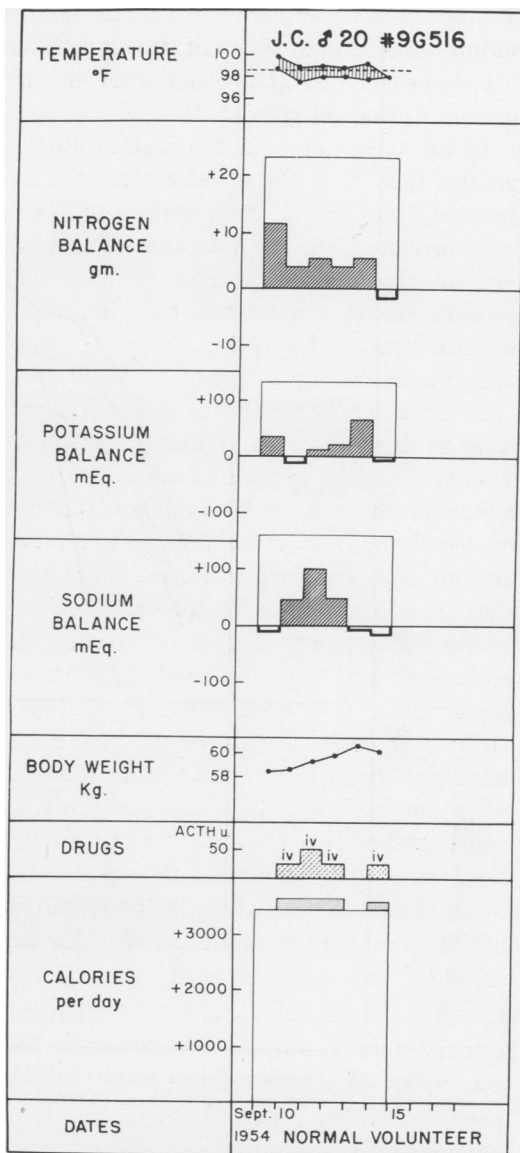


FIG. 21 (Case 22). Metabolic Chart. Sodium conservation with weight gain on ACTH is evident.

from 11 to 30 mEq. per day, and in many individual instances was less than 10 mEq. per day. Case 14 showed the loss of 270 mEq. of sodium in the first three days, following which restricted sodium excretion became evident. In all instances restricted sodium excretion outlasted nitrogen loss, potassium loss, and eosinophil depression.

Steroid values returned to normal before sodium excretion in seven of the eight. This "dissociation" resembles that seen in the previous group of patients.<sup>24</sup>

In all save Case 12, the weight loss is greater than  $N \times 30$  corrected for sodium. In one (Case 15) the weight loss of 7.0 Kg. was correlated with considerable body wasting, and by calculation from nitrogen and sodium changes indicated the disappearance of over 5.0 Kg. of fat.

2. Endocrinology.

a. *Eosinophil counts.* The eosinophil patterns in these cases are similar to those previously reported in surgical patients. In all instances, the eosinophil count was reduced to very low levels at the time of operation. In four instances (Cases 13, 15, 16 and 21) there was a period of postoperative eosinophilia ("backswing overshoot") when the eosinophil count rose to levels significantly higher than that observed preoperatively. In all instances the eosinophil fall correlated closely with the rise in serum steroids. As a general rule, the eosinophil upswing bears a much closer inverse correlation with the reduction in urinary excretion curve of total 17-hydroxycorticoids<sup>24</sup> than with the fall in blood concentration curve of the free steroids. This is particularly noticeable in Cases 14, 15, 16 and 17. In Case 13, the high urinary steroid values (evidently an artefact caused by the administration of iodides) persisted during a period when the eosinophils returned to normal values. In Case 12 the eosinophils were well back towards normal while the urinary 17-hydroxycorticoid excretion was still slightly elevated. In Case 20 an atypical urinary 17-hydroxycorticoid curve (no clearcut rise) and a very low but sharp serum rise to 31 gamma per cent was associated with a prolonged low eosinophil count.

b. *Urinary Steroids.* The urinary excretion of 17-ketosteroids shows no significant changes as a result of operation in any cases, save that of Case 12, where there is an eleva-

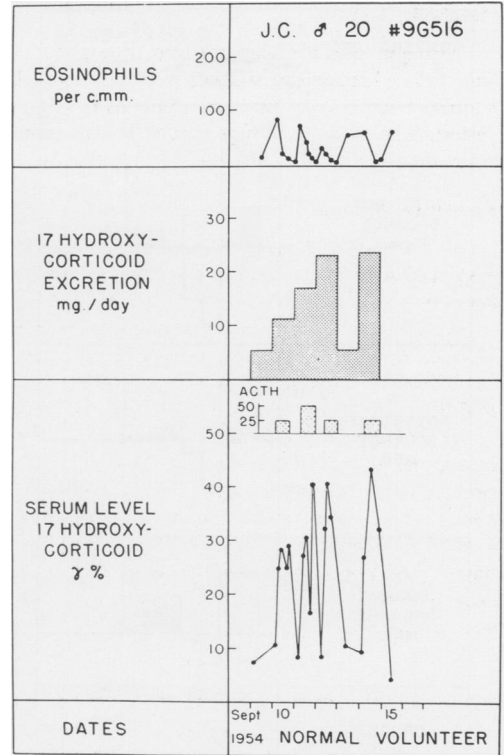


FIG. 22 (Case 22). Endocrine Chart. The rise in blood and urine steroid produced by successive doses of ACTH was materially less than that in postoperative patients. All the blood peaks lie in the range of 30 to 45 gamma per cent. There is some suggestion that three days of ACTH infusion has increased the response on the final day.

tion of borderline significance on the day of operation.

The urinary total 17-hydroxycorticoid excretion in these cases bears out the pattern previously described. There is an elevation on the day of operation in four of the five cases, Case 13 being the only exception. An elevation of urinary 17-hydroxycorticoid excretion is usually evident for the first two postoperative days, and in Case 16 the urinary excretion remains elevated for four days. In Case 13, we see an apparent elevation of urine excretion associated with the administration of iodides.

c. *Free Serum 17-Hydroxycorticoids Following Surgical Trauma.* The most noteworthy characteristics of the concentration

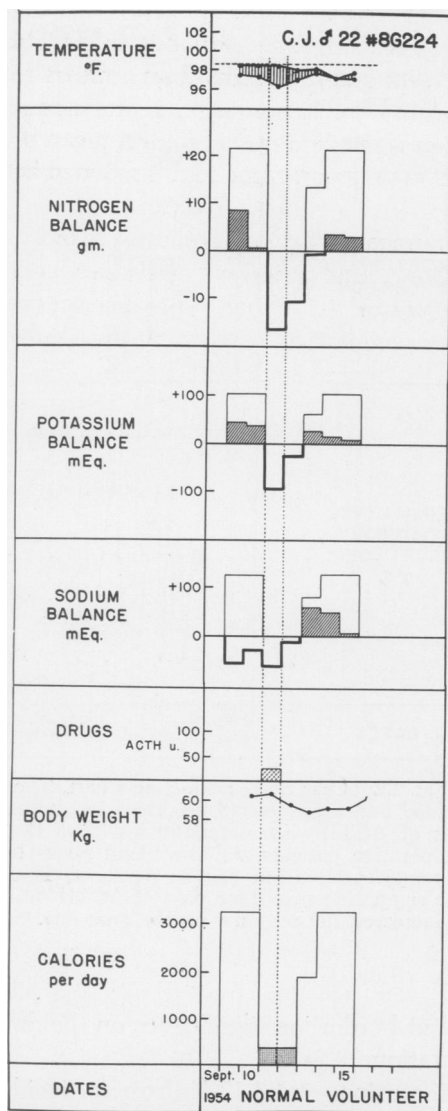


FIG. 23 (Case 23). Metabolic Chart. "Dummy operation" consisting of starvation and ACTH.

curves of the free 17-hydroxycorticoids in these cases may be summarized as follows:

1. *The rise is early and steep.* In all instances, a peak is seen on the day of operation which is not exceeded subsequently. In Case 14 the maximum value is observed four hours after starting the anesthesia, and in Case 16 a level of 66.8 gamma per cent is seen within two hours of the completion of

the operation, reaching a peak value of 73.8 gamma per cent approximately 12 hours after commencing the incision.

2. *The steep rise is then followed by a steep fall.* The steepness of the fall is particularly evident in Cases 12, 14, 15 and 16, where the operative peak has been reduced by one half or more within the subsequent 24 hours. As a general statement, in trauma of the magnitude observed here, the blood free 17-hydroxycorticoid values may be expected to rise from preoperative values in the range of 5 to 15 gamma per cent to values immediately after operation in the range of 50 to 70 gamma per cent with a return to normal within 48 hours.

3. *The absolute level attained in these cases is variable.* The postoperative maxima range all the way from 27 gamma per cent (Case 13) to 73.8 gamma per cent (Case 16). The range of traumas here is not wide, encompassing cases of magnitude subtotal gastrectomy or less. The maximum concentration of 17-hydroxycorticoids reached in the blood is not correlated with the intensity of nitrogen loss or with the duration of eosinophil depression.

4. *There is not a phase of preliminary depression of the steroid concentration prior to the rise.* We have not seen in any of these instances an example of a preliminary depression of the blood steroid values prior to the rise, even though sampling was quite frequent in several of the cases, and in all of them a preoperative value was taken.

5. *The relationship of the blood free steroid value to the urine excretion of total steroids is not predictable.* In one (Case 15) the urine excretion continues elevated for two days after the peak in the blood steroids. In three cases (Cases 12, 14 and 16) the blood steroid value returns more gradually to its normal range, although the initial fall after the high peak is very sudden. In these cases the blood and urine values reach normal at approximately the same time, although the fall in blood values is initially

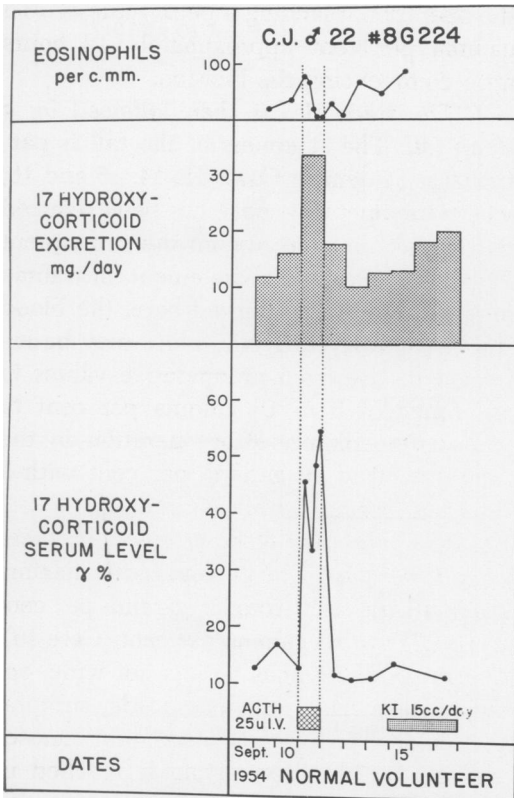


FIG. 24 (Case 23). Endocrine Chart. "Dummy operation" with starvation and ACTH has produced a sharp rise in blood and urine steroids. The blood peak is significantly higher than the normal (Fig. 20).

steeper. In one instance (Case 16) the blood value remains elevated two days longer than the increase in excretion of urine total 17-hydroxycorticoids. And in Case 20, as mentioned above, there is no distinct change in urine steroid excretion despite a low-normal serum steroid response.

*d. Free Serum 17-Hydroxycorticoids Following ACTH.*

1. *In Surgical Patients.* The surgical patient undergoing trauma of moderate magnitude responds to ACTH postoperatively by a higher blood level of steroid than was produced by ACTH preoperatively. The operative response, in turn, is greater than that produced by ACTH in the preoperative period or in the resting normal individual.

2. *In Normal Individuals.*

(a) ACTH. The response to ACTH in the resting normal individual appears to be maximum for an eight-hours intravenous infusion when 25 units is given. A mean blood level of 40 gamma per cent is reached at the end of the infusion (Fig. 20).

(b) Compound F. The infusion of 20 mg. of Compound F intravenously produces an increase in the blood 17-hydroxycorticoid to 32 gamma per cent; of 60 mg., a rise to 48 gamma per cent.

IV. DISCUSSION AND INTERPRETATION

1. *Meaning of the Blood Curve in Surgical Trauma.*

The early occurrence and high peak in free serum 17-hydroxycorticoids suggests that there is an early and significant increase in adrenal secretion after trauma. The concept that the adrenal responds gradually to trauma seems untenable in the light of these findings.

We have not seen any lowering of the serum steroid level with the onset of trauma. We therefore have no evidence that peripheral utilization or "transient hypoadrenalism" is responsible for increased pituitary activity following operation.

The rising limb of the curve correlates in point of time with the fall in eosinophil count, although the eosinophil count often reaches zero values before the blood steroid concentration is at its peak. The rising limb of the curve also correlates loosely with the onset of increased nitrogen excretion in the urine; our urine collections have not been subdivided sufficiently to permit any closer correlation than to indicate that nitrogen excretion increases characteristically on the day of operation. We thus have no evidence to support the concept<sup>12</sup> that changes in nitrogen metabolism are initiated by some other agency, and that adrenal cortical effects then occur to "compensate" or "normalize" the metabolism.<sup>8</sup> The blood steroid change occurs so early that it does not ap-



pear to be "secondary" or "compensatory" but rather "primary" in point of time.

The onset of sodium conservation after trauma is variable in time and may or may not be correlated with the blood 17-hydroxysteroid alteration. In some instances the onset is late, occurring 24 to 72 hours after the injury.

The descending limb of the blood curve antedates any other endocrine or metabolic reversion which we have measured. It characteristically occurs from one to four days prior to the eosinophil rise or reduction in nitrogen excretion rate. In several instances, as mentioned above, it has returned towards normal 24 to 48 hours before the urinary excretion of total corticoids has returned to normal.

It has been our tentative interpretation that the rising curve (a four-fold increase in four hours) is due in large part to a true change in secretory rate, an impression substantiated by data from the adrenal vein in the experimental animal.<sup>15</sup> By contrast we have interpreted the absolute peak attained (see below), and the descending limb of the curve (a return to normal in 24 to 48 hours) as functions of more gradual conjugation, destruction and excretion as well as decreased secretion.

The method for determination of urinary 17-hydroxycorticoids measures almost entirely conjugated steroids. The fact that this urinary excretion of conjugates may remain elevated one to three days after the return of blood values to normal constitutes further evidence that the descending limb of the curve occurs at least in part by the mechanism of conjugation, as well as excretion and decreased secretion.

## 2. Significance of the ACTH Responses.

The normal person (or the preoperative patient) responds to the standard maximal stimulus of ACTH with a predictable increase in the blood steroid. The fact that the operation itself—or the early postoperative administration of ACTH—produces a

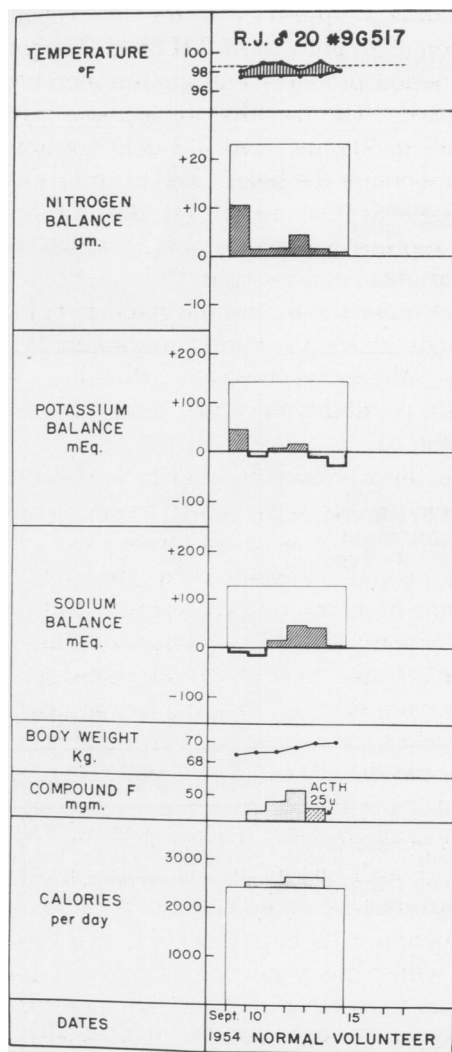


FIG. 25 (Case 24). Metabolism Chart.

significantly higher rise suggests either: (1) that the 25-unit ACTH infusion in the resting person is not a maximal stimulus, or (2) that trauma alters the adrenal so that it can produce more steroid in response to the same stimulus, or (3) that there is less excreted and therefore more retained, or (4) that there is a metabolic alteration which results in a less rapid rate of conjugation in the post-traumatic patient.

Dealing with these possibilities in order, we come first to the matter of maximum ACTH stimulation. Both from blood and

urine data it appears that the intravenous infusion of 25 units of ACTH over an eight-hour period produces a maximum secretion of steroids. The fact that an increase from 25 units to 50 units of ACTH does not ordinarily increase the blood level or urine output suggests that an ACTH dose of this order represents the maximum to which the normal gland can respond.

That trauma sensitizes the gland so that it responds above its resting maximum to a given adrenocorticotrophic stimulus remains a possibility on which these data cast no light.

The third possibility, that less steroid is excreted in the urine after trauma (thus producing a higher blood level) has certainly not been borne out by observations on urine excretion in these cases. There has been an early increase in urine excretion in all save Cases 13 and 20, in whom blood levels were elevated to a subnormal extent. A decrease in renal clearance of hormone *relative* to the increased secretion rate could still play a role in determining (a) the height of the peak, and (b) the speed of fall.

The fourth possibility, that trauma alters the inactivation, conjugation and metabolic destruction so as to produce a higher blood level with a given adrenal output of steroid appears to us the most likely explanation of the observed phenomenon. The continued excretion of the urinary (conjugated) steroid in some of the cases for a day or two after the return of the blood level to or near normal indicates clearly the importance of conjugation in clearing the blood. It is quite conceivable that alteration in hepatic function following trauma may be responsible for the higher blood levels seen.<sup>37</sup>

The pattern of blood 17-hydroxycorticosteroid changes discussed here has also been reported by Tyler and his group.<sup>7, 31, 37</sup> They also found that 25 units of ACTH intravenously gave a maximum rise in blood levels, though they used a 6-hour infusion time. Normals showed a four-to-five-fold increase,

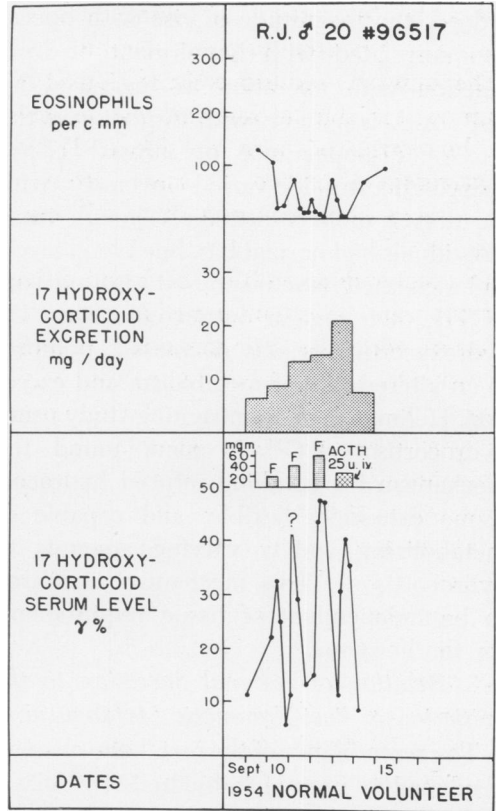


FIG. 26 (Case 24). Endocrine Chart. The infusion of Compound F in doses ranging from 20 to 60 mg. produced no significant increase in urine steroids, with blood peaks of 35 to 48 gamma per cent. Thereafter a maximal ACTH stimulus produced a normal blood and urine steroid response.

from averages of 8 gamma to 38 gamma per 100 ml. plasma. Similarly, blood steroids taken before, during and after operation revealed prompt increases to levels higher than obtained from 25 units of ACTH intravenously. The concentration of plasma 17-hydroxysteroid seemed to correlate with the duration and severity of operation, while the urinary 17-hydroxysteroids did not reflect the sharp changes in plasma levels. Since intravenous ACTH following major surgery brought out further increases in plasma 17-hydroxy levels, Samuels<sup>37</sup> hypothesized that the levels after operation are the result of both increased adrenal secretion and impaired hepatic removal of the steroid.

Indeed, the magnitude of rise with operation correlated with impairment of liver function with operation as measured by BSP. In their patients with liver disease the rate of disappearance of infused 17-hydroxycorticosteroid varied inversely with the degree of liver damage. Though these individuals had normal baseline blood levels and a characteristic response to intravenous ACTH, their regular output of urinary 17-hydroxycorticoids was decreased, pointing to an altered rate of metabolism and excretion. Hellman,<sup>14</sup> in an intriguing study using hydrocortisone-4-C<sup>14</sup> in man, found the mechanism for handling infused hydrocortisone extremely flexible, and capable of metabolizing widely varying amounts of hydrocortisone. This mechanism appeared to be independent of tissue requirements for the hormone.

### 3. Relation of Adrenal Secretion to the Initiation of Post-Traumatic Metabolism.

The resemblance of the metabolic changes produced in normal individuals by ACTH and cortisone to those seen after surgical operations has been one basis for the opinion that an increased secretion of adrenal steroids is responsible for that metabolism. The findings herein, of a very rapid change in the concentration of steroids in the blood after operation, might be interpreted as further evidence for this view.

On the other hand, the observations of Ingle,<sup>16-18</sup> and of Engle,<sup>8, 9</sup> suggest that the association of an increased excretion of corticoids with a certain metabolic pattern after injury may not be cause and effect. This is based on the observation that an adrenalectomized rat on a constant dose of adrenal cortical extract shows a "normal" nitrogen excretion pattern after injury, suggesting that increased adrenal steroid production is not essential to this metabolic change. Instead, some other as yet unspecified agency is considered by these authors to initiate the metabolic response to injury, while the presence of adequate corticoster-

oid in the body fluids permits this reaction to occur; in the absence of hormone it cannot occur. In addition, there is evidence that as the severity of the trauma increases, there is a need for a correspondingly greater amount of cortical hormones to "support" the metabolic needs of the organism.<sup>20</sup> This concept therefore allows also for quantitative changes in corticoid concentration in association with variations in the magnitude of the trauma. Hence the term "permissive" action of adrenal steroids, and the concept that the adrenal discharge after stress does not initiate the metabolic alterations which are contemporaneous with it even though adrenal secretion may vary with the intensity of the trauma.

All of these interpretations hypothesize that when the exogenous dose of hormone is constant, the concentration in body fluids is also constant. The changes in blood steroid level after ACTH reported here suggests that blood levels of hormone may change after trauma even though the steroid input be constant. The fact that operation itself and postoperative ACTH produce a level of free steroid higher than that produced by a maximal ACTH stimulus preoperatively suggests that anesthesia and operation induce some alteration in hormone production or conjugation which results in the increased blood level of the free steroid. Such an explanation is supported by findings in adrenalectomized dogs wherein the blood level of free steroid on a constant dose of Compound F is increased by anesthesia and surgery.<sup>36</sup>

These facts taken together make a reinterpretation necessary for the previously mentioned experiments in which a trauma has produced metabolic changes in the adrenalectomized animal on a constant dose of adrenal hormones. It is apparent that the blood level may rise even though dose be constant. The tissues will then respond to this change in their endocrine milieu despite its nonsecretory origin.

Therefore, we return again to the likelihood that early post-traumatic metabolism may indeed be initiated by alterations in the blood level of adrenal hormones. Such blood level changes are early and profound. The blood level of free hormone is the resultant of changes in secretion and conjugation, and the blood level may change even with constant exogenous dose, after adrenalectomy, when trauma is added.

In considering surgical trauma as a stimulus to endocrine activity it is of course important to recognize the multiplicity of stimuli involved. These include not only tissue trauma but also anesthetic agents, other drugs, pain, fear, blood loss and starvation. Final proof that early post-traumatic metabolism is adrenal in origin must await further study. We know that other forces—vascular, hemodynamic, hepatic, antidiuretic—are also at work. Our studies here merely indicate that the timing, magnitude and nature of the curve of free 17-hydroxycorticoid levels in the blood of surgical patients is such as to suggest that it is of primary importance in those endocrine and metabolic adjustments which follow injury.

#### 4. *Relationship of Adrenal and Extra-adrenal Factors to the Duration, Depth and Details of the Metabolic Sequence.*

When we turn from the initiation of metabolic changes to their depth, duration and details, we find many evidences that other factors than the Compound E-F (11-oxy, 17-hydroxy) hormones are of great importance in surgical metabolism.<sup>26</sup> The pertinent facts, in brief outline, are as follows:

1. In closed soft tissue trauma, the extent and duration of nitrogen loss correlates well with glucocorticoid activity. But in *fractures*, a long period of nitrogen loss follows a very intense but brief adrenal discharge. In *burns*, prolonged increase in urinary nitrogen excretion likewise occurs long after evidences of increased glucocorticoid activity have ceased. The nature of the wound

and the length of time required for it to resume tensile integrity is apparently of importance in the duration and extent of catabolism of lean tissue after trauma.

2. The onset, intensity and duration of sodium conservation bears virtually no relation to increases in glucocorticoid activity in many instances. It is to be hoped that aldosterone (electrocortin) assay in surgical patients may provide a measurable endocrine counterpart to metabolic sodium conservation.

3. Depletion or previous surgical procedures diminish metabolic responsiveness as regards the nitrogen-potassium-eosinophil complex (occasionally producing a post-operative eosinophilia), while sodium conservation, hyponatremia and antidiuresis may be accentuated.

4. The eosinophil count itself, well known to be affected by epinephrine as well as glucocorticoids of the adrenal cortex, frequently departs from any correlation with the blood or urine steroids. Its fall initially correlates well with the timing of the rise in serum corticoids, but the eosinophil count quite regularly remains depressed for long periods after blood and urine 17-hydroxycorticoids have returned to normal.

#### V. SUMMARY

1. Measurement of the metabolic balances of nitrogen, potassium and sodium has been accompanied by measurements of the blood and urine 17-hydroxycorticoids in a group of surgical patients. An additional group of patients, and normal control individuals, has been studied with respect to endocrine responses by these and other indices.

2. The increase in free serum 17-hydroxycorticoids which occurs after operation is early, steep and massive, being of the order of a four-fold increase in four hours.

3. This is a greater increase than that produced by maximal doses of ACTH over similar periods of time. Furthermore,

ACTH given during the early postoperative period produces higher levels than in the normal or resting state.

4. This suggests that trauma alters the metabolism or conjugation of 17-hydroxycorticoids.

5. Measurement of the free serum 17-hydroxycorticoids provides an index of the timing and intensity of adrenal response to injury. The urine excretion of the total steroid provides a better measurement of the total duration and magnitude of this response.

6. The endocrine-metabolic response to trauma includes certain common denominators in all patients who have an intact neuro-humoral system. But the details of the response are manifold in their variations; clinical variables such as the nature of the wound itself, the age and nutrition of the patient introduce marked and important variations in the metabolic response to injury. These clinical variables may operate by changes in the intermediary metabolism, as well as in the secretory pattern, of adrenal steroids.

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