

## POSTOPERATIVE SALT RETENTION AND ITS RELATION TO INCREASED ADRENAL CORTICAL FUNCTION\*

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TEMPORARY DISTURBANCES of electrolyte and protein metabolism in the period immediately following a major surgical operation long have been recognized and investigated. The usual alterations in electrolyte metabolism include marked reduction in urinary excretion of sodium and chloride and a transient increase in the output of potassium. As a consequence of these electrolyte changes, water retention occurs. Because of this postoperative salt retention, saline solutions no longer are given routinely in the immediate postoperative period.<sup>1</sup> Moyer has summarized the electrolyte disturbances after operation and states that these changes cannot be attributed to alterations in renal blood flow, water deficit, sodium or chloride lack, blood loss or action of the anesthetic agent.<sup>2</sup>

A negative nitrogen balance independent of protein intake is also commonly encountered after operation. Amino acid solutions administered parenterally to counteract the excessive nitrogen excretion do not usually change the nitrogen balance significantly until about three or four days after operation.

It has been demonstrated that a major surgical procedure elicits a sharp increase in adrenal cortical function, as indicated by increased amounts of urinary excretory products which reflect steroids of the 11-oxysteroid and androgenic types.<sup>3, 4</sup> Actions of the 11-oxysteroids include, among other things, catabolism of body protein and depression of circulating lymphocytes and eosinophilic polymorphonuclear leukocytes. The fall in the number of circulating eosinophils provides a simple index of increased elaboration of these 11-oxysteroids.<sup>5</sup>

Since it might be expected that increased production of desoxycorticosterone-like steroids would occur simultaneously, it was decided to evaluate such activity. No direct measurement of changes in endogenous production of such electrolyte-regulating steroids is available. However, it has been demonstrated that the electrolyte composition of thermal sweat offers a reliable index of changes in the activity of these salt-active corticosteroids.<sup>6</sup> Analyses of sweat in various clinical and experimental conditions have shown an

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inverse relationship between desoxycorticosterone-like activity and the concentration of sodium and chloride in the sweat.<sup>7</sup> In the experiments described below, the electrolyte concentrations of serially obtained samples of sweat were used as an index of changes in the activity of the salt-active adrenal steroids.

#### METHOD

This method involves the collection of sweat from hands and forearms during a one-hour exposure of the entire body to humid heat (98° F. and 90 per cent relative humidity). Sweat samples were obtained from 14 patients before operation and at two- to three-day intervals after operation. In addition, a follow-up determination of sweat composition was obtained several weeks later on most subjects. Sweat tests are not performed at shorter intervals because of the possibility of inducing heat acclimatization, which is in itself a stimulus to adrenal cortical activity.<sup>8</sup> Electrolyte concentrations of sweat were determined by standard methods.<sup>9</sup> Some sodium and potassium determinations were also made with the flame photometer. Periodic eosinophil counts before and after operation were done by the method of Randolph.<sup>10</sup>

Twelve men and two women patients were studied by multiple sweat tests and eosinophil counts before and after operation. Ages ranged from 16 to 45 years, and the operations varied in severity from varicose vein ligations to subtotal gastric resections for chronic duodenal ulcer. Included were five gastric resections, three cholecystectomies, three herniorrhaphies, one splenectomy, one closure of colostomy and one varicose vein ligation. All subjects were excellent surgical risks, in good nutritional state, and none had malignant disease. Most received at least 5 Gm. of sodium chloride per day orally or parenterally during the postoperative period. Ether with nitrous oxide induction was the anesthetic usually used. Uneventful recovery followed in every case.

#### RESULTS

The results of sweat analyses before and following surgical operation are shown in Figures 1, 2, 3 and 4, and indicate increased endogenous production of salt-active corticosteroids after operation, as manifested by decreasing sodium and chloride concentrations of thermal sweat. The lowest values occurred five to eight days after operation, and represented average falls of 38.1 per cent in sodium (Fig. 1) and 39.0 per cent in chloride (Fig. 2). A gradual rise to the preoperative level then followed. A sharp rise averaging 73.3 per cent in the concentration of sweat potassium (Fig. 3) and 58.1 per cent in sweat nitrogen (Fig. 4) began on the first or second day and lasted for one or two days.

Quantitative determinations of circulating eosinophils on the same patients demonstrated increased 11-oxysteroid production, as indicated by a sharp decrease or complete disappearance of these cells within 12 hours after operation (Fig. 5). Between the second and fifth postoperative days the eosino-

FIG. 1

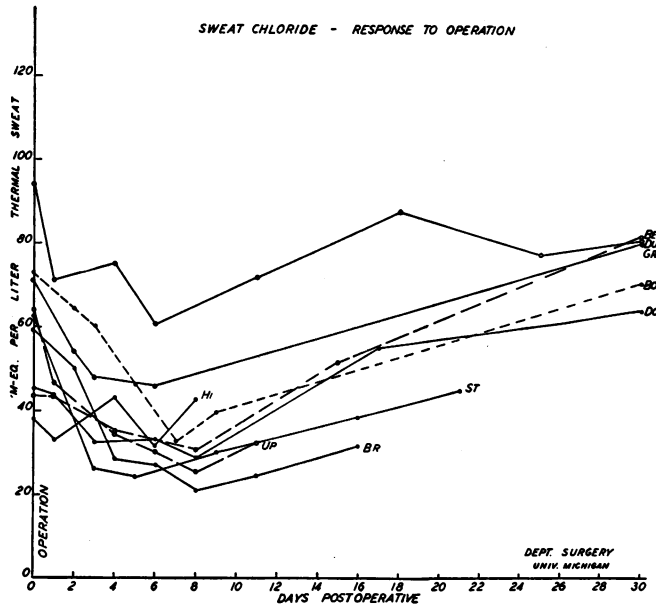
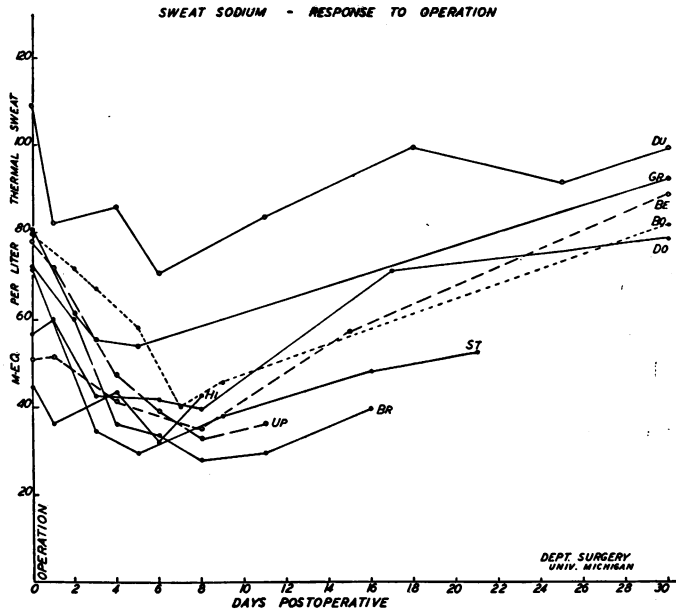


FIG. 2

FIG. 1.—Response to major operation of sodium concentration of thermal sweat.

FIG. 2.—Response to major operation of chloride concentration of thermal sweat.

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FIG. 3

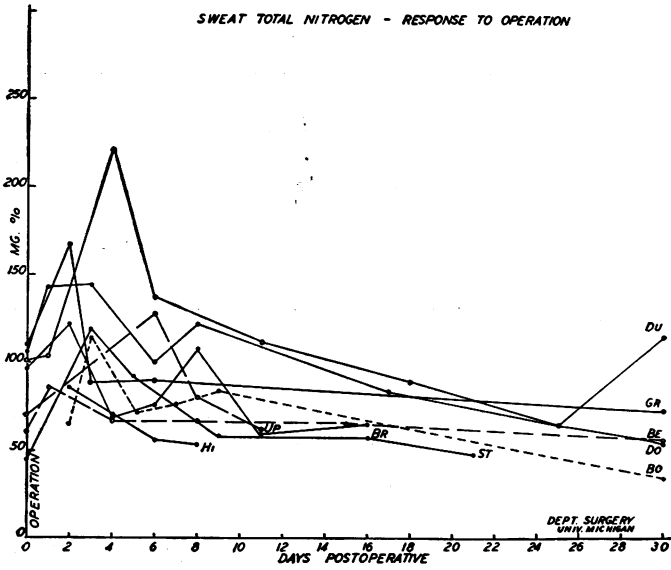
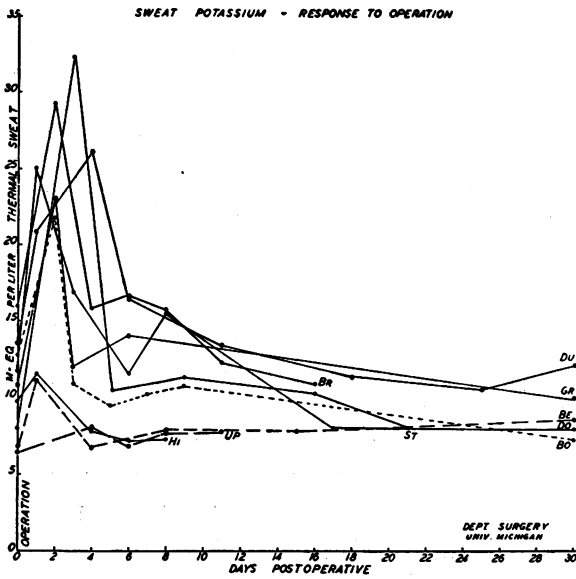


FIG. 4

FIG. 3.—Response to major operation of potassium concentration of thermal sweat.

FIG. 4.—Response to major operation of total nitrogen concentration of thermal sweat.

phils returned to the peripheral blood in numbers approximating or greater than the preoperative levels.

Figure 6 shows the typical changes in the composition of sweat as well as the changes in eosinophil and total leukocyte counts after operation. Characteristic of the desoxycorticosterone effect is the decrease in sweat sodium concentration of 30 per cent and a fall in sweat chloride concentration of 36 per cent.<sup>8</sup> An immediate but transient increase (114 per cent) in sweat potassium concentration occurs at the same time. With respect to the kidney, these two phenomena, sodium chloride retention and rise in potassium excretion, are now well established accompaniments of the postoperative state. They are equally well established effects of administered desoxycorticosterone.

Eosinophils disappear completely from the blood stream six hours after beginning the operation, and return to above preoperative levels five days after operation. An immediate rise in total leukocytes of the blood occurs as promptly but returns to the preoperative level gradually over many days.

Thirteen of the 14 patients studied demonstrated a significant fall in sodium and chloride concentrations of thermal sweat. One subject, a 42-year-old male, who underwent repair of a recurrent inguinal hernia, failed to show the characteristic electrolyte changes and maintained relatively constant sweat composition. His eosinophil response also was one of the least marked of the group. His postoperative course, however, was uneventful.

#### DISCUSSION

Recently it has been shown<sup>6</sup> that stimulation of the adrenal cortices of normal people results in the appearance of metabolic changes which reflect increased activities of three main types of adrenocorticosteroids, namely, electrolyte-regulating or 11-desoxycorticosterone-like steroids, 11-oxysteroids, and steroids having activities and end-products characteristic of sex hormones. The latter two groups already have been shown to be increased following operation.

1. *Effects of 11-Desoxycorticosterone-like Steroids.* Desoxycorticosterone administration to normal persons produces marked reduction in urinary excretion of sodium, chloride and water.<sup>11</sup> This effect continues only for two or three days, and is followed by a rebound of urinary sodium and chloride output to levels even higher than normal, despite continued desoxycorticosterone administration.<sup>8</sup> Increased extracellular fluid and plasma volume accompany this retention. This steroid also causes increased renal excretion of potassium, but has little or no effect upon protein or carbohydrate metabolism or upon circulating leukocytes. While the electrolyte composition of the urine may be a good measurement of deficiency of salt-retaining corticosteroids, it is a poor indicator of increased activity of these desoxycorticosterone-like compounds because of the renal "rebound" phenomenon.

The electrolyte composition of sweat reflects activity of electrolyte-regulating steroids. Changes in the composition of sweat have been followed in

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FIG. 5

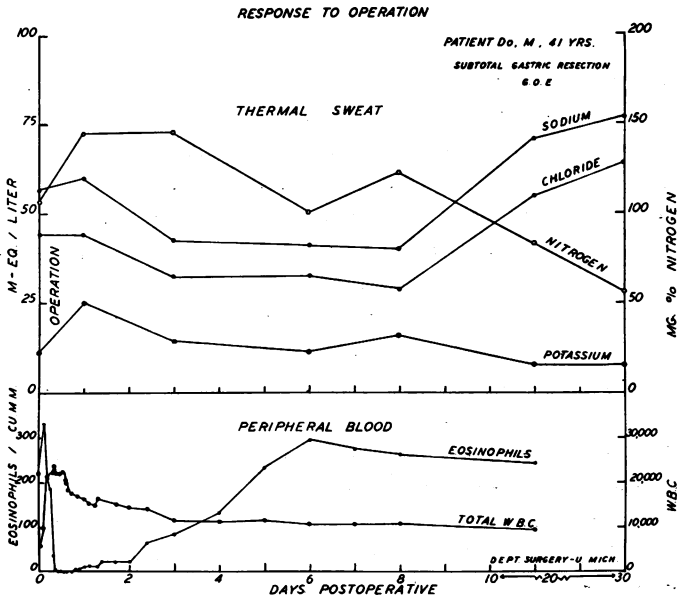
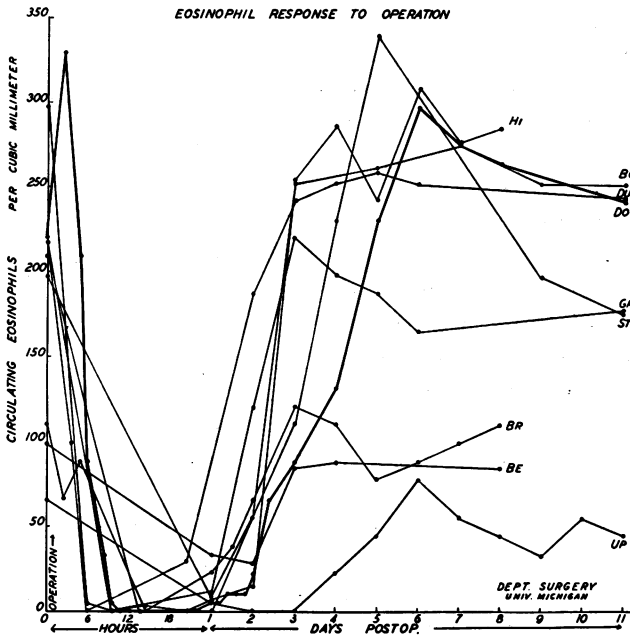


FIG. 6

FIG. 5.—Response to major operation of circulating eosinophils in peripheral blood.

FIG. 6.—Response to sub-total gastric resection of electrolyte concentrations of thermal sweat, and circulating eosinophils and total leukocytes of the peripheral blood. The patient is a 42-year-old male operated upon for chronic duodenal ulcer.

various conditions exhibiting abnormal adrenal function.<sup>7</sup> Patients with untreated Addison's disease or adrenal insufficiency show sodium and chloride levels in thermal sweat greatly in excess of normal values. On the other hand, conditions associated with hyperactive adrenal cortices such as Cushing's syndrome demonstrate sweat sodium and chloride values below normal levels. Even lower concentrations of these electrolytes in sweat are found in adrenal cortical carcinoma.

Sweat composition patterns similar to those observed in adrenal cortical hyperactivity may be produced by administration of desoxycorticosterone. Coincidental with the sharp renal retention of sodium and chloride after injecting the steroid in normal people, the sweat concentration of these electrolytes falls. However, although the kidney resumes excretion of sodium and chloride in three or four days despite continued desoxycorticosterone administration, the sweat glands continue to secrete a fluid low in sodium and chloride as long as the steroid is given. It is for this reason that the electrolyte composition of sweat affords a more reliable index of electrolyte-regulating corticosteroid activity than does the renal excretion of sodium and chloride. We believe that the data presented above afford adequate evidence of increased activity of salt-active adrenal steroids in the postoperative period.

2. *Effects of 11-Oxysteroids.* A second type of steroid, characterized by an oxygen atom or a hydroxyl group at the carbon-11 position of the steroid molecule, has its major physiologic effects upon organic metabolism (protein, carbohydrate and fat). Catabolism of body protein and depression of lymphocytes and eosinophils are among the actions of these 11-oxysteroids.

Increased 11-oxysteroid production in Cushing's syndrome, in some cases of adrenal cortical carcinoma, and following trauma or operation, has been demonstrated by analysis of urinary excretory products.<sup>8</sup> It has been established by metabolic studies that following operation or injury to a previously healthy individual, there is an increase in catabolism of body protein with a marked rise of urinary nitrogen. Coinciding with this period of negative nitrogen balance is a six to tenfold increase in the excretion of urinary 11-oxysteroids, as measured by the glycogen deposition test.<sup>12</sup> Five days after hysterectomy the value returned to the preoperative level.<sup>13</sup> It has been observed that debilitated or carcinomatous patients respond to trauma with little or no increased excretion of nitrogen, and that the usual rise in corticosteroid output may be absent or transient.<sup>14</sup>

The administration of 11-oxysteroids to hypoadrenal patients is followed by marked depression of circulating eosinophils in the peripheral blood, and operative procedures have been shown to cause sharp reduction of these cells in animals.<sup>15</sup> Roche *et al.*<sup>16</sup> recently have reported that there is almost complete disappearance of eosinophils within one or two days after a major operation in previously healthy individuals, and that nondisappearance of these cells within two days after operation may indicate a lack of the normal adrenal cortical response to operation. A lymphocyte depression after stress

also has been described and shown to be dependent upon increased 11-oxysteroid activity.<sup>17, 18</sup> A rise in circulating neutrophils is produced by 11-oxysteroid administration.

3. *Androgenic and Estrogenic Steroids.* A third group of steroids with androgenic or estrogenic properties is believed to be elaborated by the adrenal cortex. These may be measured by determination of their urinary excretory products in the form of 17-ketosteroids (androgenic) and estrogenic substances. In healthy men a transient rise in urinary 17-ketosteroids is observed following operation, but this response is minimal in debilitated patients.<sup>4</sup>

Our data from the experiments reported above supplement that which previously has been known, in that they demonstrate the participation of increased activity of electrolyte-regulating steroids in the immediate postoperative period. They explain at least in part the capacity of the patient after operation to retain abnormally large quantities of sodium and chloride and to excrete large amounts of potassium.

Since the entire metabolic picture exhibited by the postoperative patient can be duplicated in healthy individuals by injections of anterior pituitary adrenocorticotrophic hormone (ACTH)<sup>6, 19</sup> it is now evident that a major surgical procedure constitutes an "alarming stimulus"<sup>20</sup> in man.

#### CONCLUSIONS

1. A major surgical procedure constitutes an "alarming stimulus" in man, resulting in increased elaboration of pituitary ACTH with a resultant increase of adrenal cortical activity during the first five to nine days after operation.

2. Studies of the changes in the composition of thermal sweat before operation and periodically after operation indicate that in the immediate postoperative period there occurs increased activity of those adrenal steroids which produce retention in the body of sodium, chloride and water.

3. It is concluded that increased elaboration by the adrenals of desoxycorticosterone-like steroids accounts, at least in part, for salt retention and the accompanying potassium diuresis after operation.

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DISCUSSION.—DR. JONATHAN E. RHOADS: At the University of Pennsylvania we have puzzled for a long time over the oliguria so frequently seen after major operations during the first day or two, and we were greatly interested and impressed by the presentation of Dr. Conn at a meeting of the Society of Clinical Surgery at Ann Arbor about a year ago, relating this phenomenon to adrenal cortical function.

Dr. James Hardy in our clinic has also employed the method of Thorne to correlate adrenal cortical activity with the change in fluid balance following extensive surgical operations. The eosinophil count and the fluid output followed a similar course after operation. This is in agreement with the data which has just been presented.

Dr. Hardy believes that the course of the eosinophil count may be of some prognostic value, because it was the impression that in patients with advanced malignancy,