SOME PHYSIOLOGIC ASPECTS OF SURGICAL TRAUMA*

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INJURY IN THE previously healthy subject is followed by a characteristic pattern of neuro-endocrine and metabolic activity. The purpose of this discussion is to present certain observations concerning the physiologic response to surgical trauma. These findings are not all new, and selected references to other work in the field have been given. The following topics will be considered:

I. Adrenocortical activity.
   A. Urinary steroid excretion.
   B. Total eosinophil counts.
      1. Response to major operations other than adrenalectomy.
      2. Correlation of total eosinophil counts with urinary corticoid excretion.
      3. Response to adrenalectomy.
II. Trauma and thyroid activity.
III. Relationships between fever and sweating.
IV. Trauma and creatinine excretion.
V. Fluid and electrolyte metabolism.
   A. Urinary volume and constituents.
   B. Gastro-intestinal secretion.
   C. Sweat.
   D. Body fluid compartments and internal fluid distribution.
VI. Nutrition and the alarm response.
VII. The proper staging of operations.
VIII. Hormones, enzymes, and survival.

ADRENOCORTICAL ACTIVITY

A. Urinary Steroid Excretion. The daily excretion of corticoids and 17-ketosteroids was measured in six patients.[19] The excretion of corticoids[23] increased in all instances following operative trauma, and this increase persisted for from one to six days, the average being approximately four days. At the end of the period of increased excretion there tended to be a temporary decrease to levels below those obtained preoperatively. The maximum increase in corticoid excretion usually occurred during the 24-hour period following that in which the operation was performed and representative data are presented graphically in Figure 1. The urinary excretion of 17-ketosteroids was increased only irregularly following operative trauma. Thus it would appear that the urinary excretion of corticoids more accurately reflects postoper-

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ative alterations in adrenocortical activity than does the excretion of 17-ketosteroids. The pattern of steroid excretion reported here is in substantial agreement with results previously reported by others.[6, 10, 32, 37, 39]

B. Total Eosinophil Counts.[38] 1. *Typical response to operations other than adrenalectomy.* The usual response of the total eosinophil count to operations other than adrenalectomy is shown in Figures 1 and 2. It may be seen that following a major surgical procedure there is a profound fall in the number of circulating eosinophils, and this curve bears a close inverse relationship to the urinary excretion of corticoids (Fig. 1). After the fall immediately following surgery, the eosinophil count gradually rises until on the third to the seventh day postoperatively it exceeds the preoperative level.

Anesthesia and operation are not the only stimuli which will result in a lowering of the total eosinophil count. In Figure 3 is shown also the effect of both pre- and postoperative episodes of fever. When the patient's fever spiked preoperatively, the total eosinophil count dropped markedly, though not to the extent that it did following abdominoperineal resection five days later. Six days after operation, when the fever was subsiding and the eosinophil count was again rising sharply, a sudden increase in the body temperature was accompanied by a prompt fall in the total eosinophil count. Febrile episodes have been shown to be associated with an increase in urinary corticoid excretion.[35]

In collaboration with Dr. Harold A. Zintel, we have studied the metabolic response of certain patients to subtotal ("95 per cent") adrenalectomy for essential hypertension.[22] Instead of the usual fall which is observed after other operations, the total eosinophil count actually increased immediately following almost total adrenalectomy. These findings further emphasize the fact that the total eosinophil count does give useful information regarding alterations in adrenocortical activity.

TRAUMA AND THYROID ACTIVITY

It has proved difficult to define the precise role of the thyroid gland in the alarm response, but evidence from several different approaches to this problem suggests that thyroid activity is altered in stress[20, 30, 32, 41] In collaboration with Dr. Henry C. Blount, Jr. we have studied eight control medical patients twice at an interval of ten days and 14 surgical patients before operation and again on the sixth or seventh day after operation. The thyroid uptake of radioiodine[12] and the rate of conversion of radioiodine into hormonal iodine of plasma[1, 4] were the methods used to measure thyroid activity. Doses of 200 microcuries of I^{131} were administered orally. There was a considerable spread even in the control patients. The average net change in the "conversion ratio" of the eight control patients between the first and second measurements was an increase of two percentage points; the average net change in the patients subjected to surgery was an increase of six percentage points following operation (Table I). That is, there was some evidence that the operation did increase the rate of thyroid activity. Moreover, in certain of the surgical patients this increase in activity reached toxic levels; such patients tended to have a more markedly negative nitrogen balance postoperatively. However, these apparent differences must be accepted with caution until additional observations have been made.

RELATIONSHIPS BETWEEN FEVER AND SWEATING

The increase in body temperature which frequently follows sterile trauma, such as that of simple herniorrhaphy or fracture of a long bone, has long puzzled physiologists. Efforts to prove the presence of infection in many of these patients have failed so consistently that one can scarcely doubt the existence of some mechanism other than that of pyrogenic or "foreign body" reaction often referred to in the past. There would appear to be three ways in which the body temperature can be increased: an increased heat production, a decreased heat elimination, or a combination of both. It is not unlikely that the combination of both factors represents the true state of affairs in most instances. Simulated shivering in a normal man has been shown to produce the same increase in heat production as that observed during the pyrogenic chill[2] but, in contrast to the pyrogenic reaction, a simultaneous increase in heat loss was observed in voluntary shivering, so that only a slight fever developed. It may thus be inferred that an interference with heat loss is an important factor in the production of pyrogenic fever. Such an interference with heat loss during this reaction is, however, masked by the appearance of an increased heat production due to the activity of skeletal muscles in the process of shivering. To determine whether or not a febrile response to a pyrogen could occur in an animal incapable of increased heat production by voluntary muscle movements and, if so, to determine under these conditions the nature of the alterations in heat

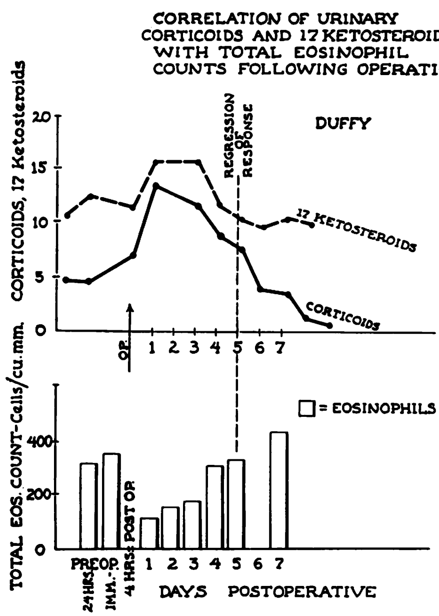


FIG. 1

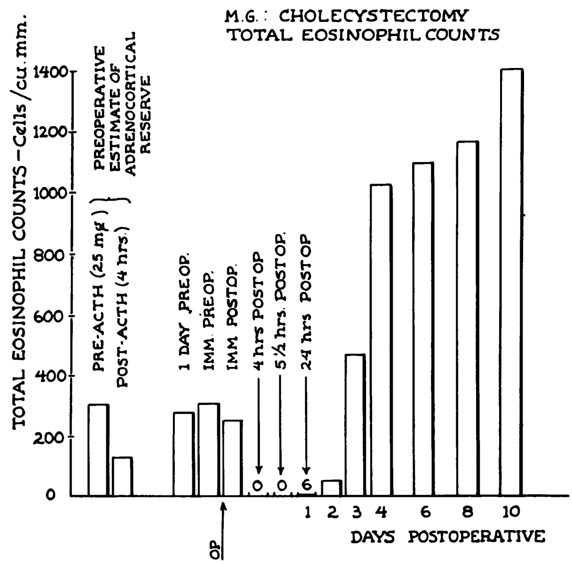


FIG. 2

FIG. 1.—The correlation of urinary corticoids and 17-ketosteroids with total eosinophil counts following operation. There is an inverse correlation between the urinary excretion of the steroids and the total eosinophil count. Note that the three curves tend to return to the preoperative base line at approximately the same time. The urinary excretion of corticoids was consistently increased following operation in the patients studied, but this was not true of 17-ketosteroid excretion. Thus the total eosinophil count would appear to reflect with considerable accuracy the increase in corticoid excretion which follows trauma.

FIG. 2.—The effect of cholecystectomy on the total eosinophil count. Immediately following operation the total eosinophil count was only slightly below the level obtained at the beginning of the operation one hour earlier. Four hours later, however, the total eosinophil count had fallen to zero. This profound fall in the total eosinophil count following operative trauma was to be expected on the basis of the preoperative estimate of adrenocortical reserve. The injection of 25 mg. of ACTH had resulted in a fall in the total eosinophil count to less than 50 per cent of the pre-injection level.

exchange, Wells and Rall[40] studied the pyrogen reaction in the curarized dog. They found that the typical pyrogen fever did occur under conditions in which increased heat production due to activity of the skeletal muscles was impossible, and they concluded that under such conditions the mechanism of the pyrogenic reaction was one of sudden and marked reduction in heat loss. The slight increase in heat production under the conditions of the experiment was correlated with the rise in body temperature and was assumed to be a consequence rather than a cause of the fever.

TABLE I.—*Trauma and Thyroid Activity.*

Average net change in the conversion ratio in control medical patients as compared with surgical patients after operation.

	Number of Patients	Average Net Change
Controls	8	+2
Experimental	14	+6

We have obtained evidence which suggests that following surgical trauma body heat is conserved through a central control of sweating.[13] Before operation it was a simple matter to obtain sweat in a rubber glove in patients who did not have fever and who were not acutely ill. In the immediate postoperative period, however, it was frequently difficult and at times impossible to obtain enough sweat in the glove for electrolyte analyses (Table II). This difficulty tended to subside as the patient improved. It has occurred to us that this limitation of sweating may be a purposeful mechanism designed to maintain and even to increase the body temperature in order to accelerate the myriad chemical reactions which together constitute the alarm response. In moderation, fever may be a useful physiologic reaction to injury.

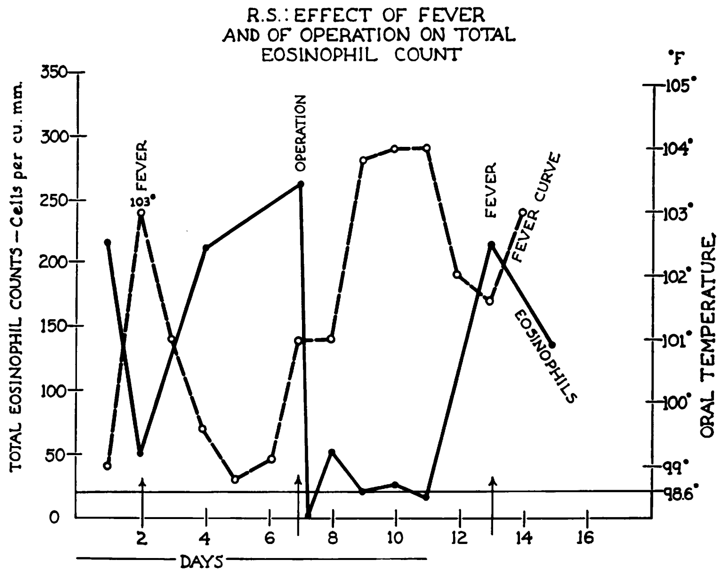
TRAUMA AND CREATININE EXCRETION

The daily urinary excretion of preformed creatinine[3] has often been held to be practically constant for a particular individual and we would agree that this is so in health. In disease states, however, it may be altered. Cuthbertson[7] reported a decreased excretion in man following fractures, but Keyser[28] reported an increased excretion in man following thermal burns. After major operations, we have found an increased urinary excretion of preformed creatinine which was usually maximal in the 24-hour period following that in which the operation was performed (Fig. 4).[16] There was an average increase of 40 per cent above the preoperative level. This increase in creatinine excretion usually paralleled the increases in the urinary excretion of corticoids, 17-ketosteroids and nitrogen (Fig. 8). It is considered that this increased creatinine excretion may reflect an increased metabolic activity in the muscle mass.

There was evidence that the urinary excretion of creatinine is influenced by adrenocortical activity. This was derived from the fact that a patient who required replacement therapy following adrenalectomy excreted very small amounts of creatinine before the therapy was begun; as the replacement therapy was administered, these values returned to normal.[22] This decreased excretion was thought to be due to a decreased production of creatinine but a decreased renal clearance was not excluded in this particular patient.

To examine the question of whether or not the postoperative increase in creatinine excretion observed by us was due to an absolute increase in the production rather than to an increased renal clearance of this metabolite, serial serum creatinine determinations were run before and after operation in a number of patients. The levels were either unaltered or increased after operation, rarely diminished. Thus it would

FIG. 3



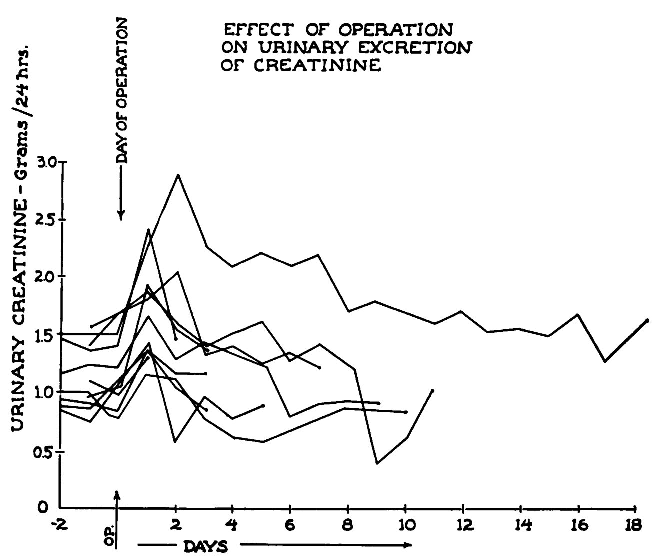


FIG. 4

FIG. 3.—The effect of fever and of operation on the total eosinophil count. When, on the second day of the study, the body temperature suddenly rose, the total eosinophil count fell, though not to zero. Following abdominoperineal resection on the seventh day, the count did fall promptly to zero. Thereafter the count remained low for four days and then began to rise. However, an upswing of the fever curve on the thirteenth day again resulted in an immediate reciprocal swing in the eosinophil curve. Febrile episodes have been shown to be associated with an increased urinary excretion of corticoids.

FIG. 4.—The effect of major operations on the urinary excretion of creatinine (preformed). Following operation there was an increase in the urinary creatinine excretion which was usually maximal during the 24-hour period following that in which the operation was performed, the average increase being approximately 40 per cent. Later there was a tendency for creatinine excretion to decline temporarily to levels below the preoperative values. These alterations in creatinine excretion may reflect variations in the metabolic activity of the muscle mass.

appear reasonable tentatively to conclude that there was an absolute increase in the production of creatinine postoperatively.

The postoperative increase in creatinine excretion may have practical implications. Since the level of creatinine excretion is considered to be an index of the magnitude of the metabolism of the tissues and especially of muscle,[2] it would appear reasonable to assume that the increased excretion of this material following surgical trauma may reflect an increased volume of metabolic activity in the muscle mass. Therefore, one wonders if the percentage increase in creatinine excretion following a particular operation may not be useful in estimating the impact of this operation on the metabolism of the patient.

TABLE II.—*Pre- and Postoperative Sweat Tests.*

Subject and Operation	Preop. Control	2nd Postop. Day	4th Postop. Day	6th Postop. Day	7th Postop. Day	8th Postop. Day	10th Postop. Day
O. W. Colon resection	Sweat obtained	No sweat after 2 hours					
S. W. Gastric resection	Sweat obtained	Too ill for test	No sweat after 2½ hours				
W. S. Gastric resection	Sweat obtained	Sweat obtained	Sweat obtained	No sweat after 2½ hours	No sweat after 3½ hours	Sweat obtained	Sweat obtained
R. Se. Nephrectomy	Sweat obtained	Sweat obtained	Sweat obtained	Sweat obtained	Sweat obtained	Sweat obtained	
R. Sa. Abdomino-perineal resection	Sweat obtained	No sweat obtained	Too ill to continue				
A. P. Gastric resection	Sweat obtained	No sweat after 2½ hours					
B. H. Colon resection	Sweat obtained	No sweat after 3 hours					
A. F. Cholecystectomy	Sweat obtained	Sweat obtained	Sweat obtained	Sweat obtained	Sweat obtained	Sweat obtained	
P. Dev. Perforated ulcer	Sweat obtained	No sweat after 2½ hours	Scant sweat obtained	Too ill to continue			
P. Duf. Gastric resection	Sweat obtained	Sweat obtained	Sweat obtained	Sweat obtained		Sweat obtained	
M. D. Adrenalectomy (95%)	Sweat obtained	Sweat obtained	Sweat obtained	Sweat obtained		Sweat obtained	
D. C. Colon resection	Sweat	Sweat	Sweat	Sweat		Sweat	
W. C. Gastric resection	Sweat obtained	Sweat obtained	Sweat obtained	Sweat obtained		Sweat obtained	
M. S. Common duct exploration	Sweat obtained	Scant sweat obtained	Sweat obtained	Sweat obtained			Sweat obtained

Note: The last four patients were studied in late spring, when less difficulty was experienced in obtaining sweat from all patients.

FLUID AND ELECTROLYTE METABOLISM

It has become increasingly evident that the regulation of water and salt metabolism is to a considerable extent mediated through the hormones of the pituitary and of the adrenal cortex. Certain effects of trauma on fluid metabolism will be mentioned.

A. Urinary Volume and Constituents. Patients subjected to major surgical procedures frequently exhibit a diminished urinary output in the immediate postoperative period and this finding is associated with an increase in adrenocortical activity, as indicated by a profound fall in the total eosinophil count[15] and by an increase in the urinary excretion of corticoids.[27] During this period of diminished volume there is also an alteration in the electrolytic composition of the urine. There is a decreased rate of excretion of sodium and chloride, and an increased rate of excretion of potassium. A reduced urinary output immediately following injury may represent a physiologic response to trauma.

B. Gastro-intestinal Secretions. The question of whether or not effective bowel decompression is being maintained postoperatively constantly presents itself following

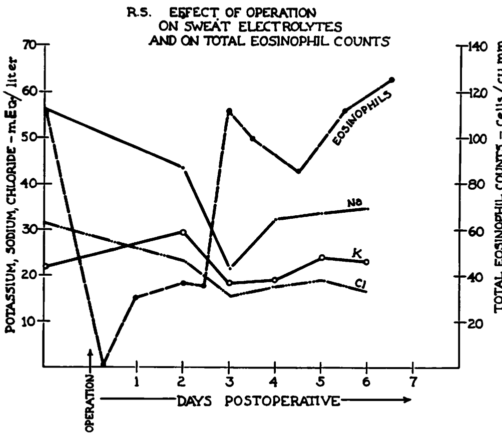


FIG. 5

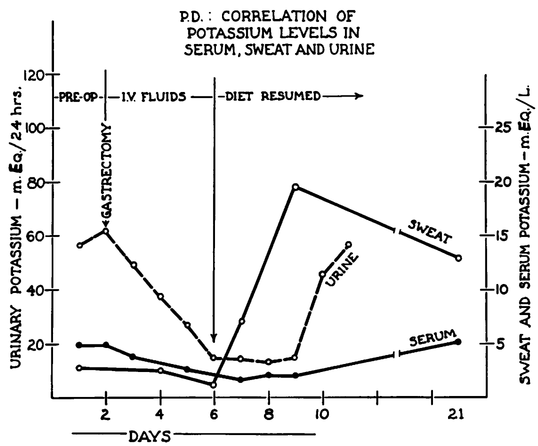


FIG. 6

FIG. 5.—Correlation of postoperative sweat electrolyte concentrations with adrenocortical activity, as indicated by the total eosinophil count. Following operation, the concentration of sweat potassium[11] increased while that of chloride[33] and sodium[11] decreased. These changes were accompanied by an increase in adrenocortical activity, as reflected in a profound fall in the total eosinophil count.

FIG. 6.—The influence of dietary potassium on the serum, sweat, and urinary content of this ion. During the period of intravenous alimentation following gastric resection the patient received only the small amounts of potassium present in Amigen. The low potassium intake resulted in a progressive decline in the urinary excretion of this ion and in a reduction in the serum potassium level. When the full diet was resumed, the potassium level in sweat rose immediately, but the urinary excretion remained at a fixed level of approximately 12 mEq. per 24 hours for three days before an increase was noted. It is probable that during this period a cellular deficit was being corrected. The serum potassium concentration had not reached the preoperative level when the patient was discharged from the hospital, but a specimen taken 19 days following operation revealed a normal value.

an intestinal anastomosis, and the surgeon is often dismayed when the tube in the small bowel does not drain what he considers an adequate volume of fluid in the early postoperative period. However, this diminished secretion of succus entericus after operation has been shown to be correlated with an increase in adrenocortical activity.[14] Once the patency of the tube has been established, if the abdomen remains soft and flat and the patient has no pain, the bowel is probably decompressed.

C. Sweat. 1. *Effect of trauma on volume and ionic composition.* The diminished volume of sweat which can be obtained in a rubber glove postoperatively has been discussed. The postoperative changes in the ionic composition of sweat are similar to those which occur in the urine.[27] A decreased rate of excretion of sodium and chloride is accompanied by an increase in the rate of excretion of potassium (Fig. 5). These changes are accompanied by a decrease in the total eosinophil count and an increase in the urinary excretion of corticoids. Conn[5] has shown that similar changes in the ionic composition of sweat may be induced by the administration of desoxycorticosterone.

2. *Effect of dietary potassium[11] on concentration of this ion.* In addition to endocrine effects, the dietary intake of potassium also influences the sweat concentration of this ion. This may be observed in Figure

6. During the period of intravenous therapy following gastric resection, the patient was deliberately given only the relatively small amounts of potassium contained in Amigen. Our purpose was to determine the ability of his kidneys to conserve this ion. There was a progressive decline in the daily urinary potassium excretion until a fixed amount of only about 15 m.Eq. was being excreted each 24 hours. During this period the potassium concentrations of the serum and sweat also declined. When oral feedings were resumed, the increased potassium intake was promptly reflected in the sweat. However, approximately three days elapsed before the increased potassium intake was reflected in the urine. Presumably a cellular deficit was being replaced during this interval.

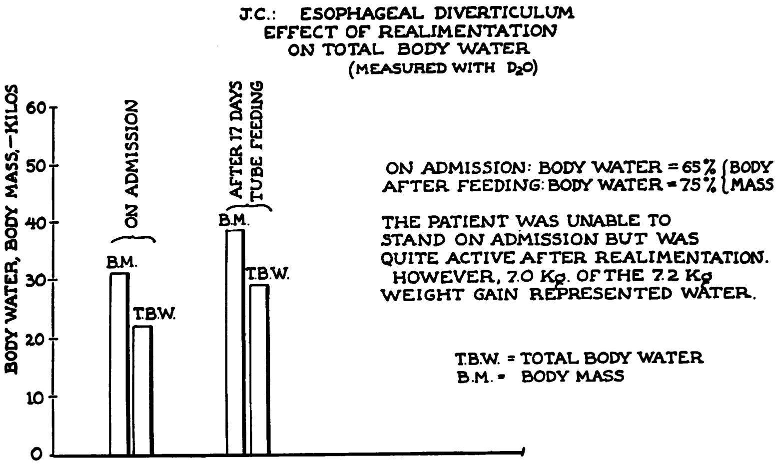
D. Body Fluid Compartments and Internal Fluid Distribution. It is beyond the limits of this discussion to outline in any detail the changes which may occur between the intracellular and the extracellular fluid compartments following trauma. Following injury the extracellular fluid volume is increased at the expense of the intracellular compartment, according to the methods currently available for measuring the extracellular space. These alterations in the size of the body fluid compartments are very likely produced through variations in the permeability of the cell membrane to sodium, chloride and potassium, perhaps effected through adrenocortical hormones. We do wish to make one particular point in connection with body fluid compartments, however, and this is that the body water content of an individual must be measured if accurate data are desired. It has been shown that there exists an inverse correlation between total body water and body fat, on a percentage basis.[18, 21, 34, 36] That is, if two healthy individuals of the same weight and height but of different degrees of obesity are compared, the lean individual will be found to contain a greater absolute volume of water and his body water will represent a greater percentage of body weight. For example, a very obese subject may contain only 43 per cent water.[21] Therefore, the commonly used value of 70 per cent for body water is acceptable only in the abnormally lean subject.

The rapid weight changes associated with certain disease states may represent changes in body water content. In Figure 7 are presented the relationships which existed between body weight and total body water before and after 17 days of tube feeding of a starved 79-year-old female patient admitted with a cervical esophageal diverticulum. On admission the patient was unable to stand unaided, but after realimentation she was quite active about the ward. Despite this clinical improvement, the measurements with D_2O (heavy water)[18, 24, 31] revealed that 7.0 of the 7.2 Kg. which she gained during the period of tube feeding represented water, though she was not clinically edematous. On admission the body water represented 65 per cent of body weight, and after tube feeding it represented 75 per cent of body weight. These findings emphasize the fact that relatively large variations in body water content may escape clinical detection.

RELATIONSHIPS BETWEEN THE NUTRITIVE STATE AND THE RESPONSE TO INJURY

It has long been appreciated that the malnourished patient is a poor operative risk, but the reasons for this have not been entirely clear. The starved patient has a diminished blood volume and protein reserve; his hepatic function is often abnormal; and the cardiovascular reflexes to changes in posture are defective. However, it is less generally appreciated that starvation is also associated with a decreased thyroid activity as indicated by a decline in the basal metabolic rate,[26] and with a decreased adrenocortical activity as indicated by a

FIG. 7



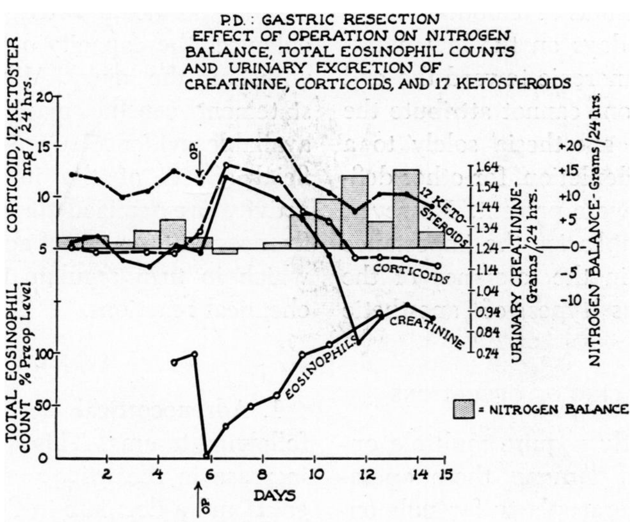


FIG. 8

FIG. 7.—The effect of tube feeding on total body water. On admission the patient was unable to stand unaided, but after 17 days of tube feeding she was active about the ward. Despite a gain of 7 liters in total body water during realimentation, she was not clinically edematous. Thus relatively large variations in body water may escape clinical detection. One should hesitate to attribute rapid weight gains to actual fabrication of tissue in the absence of total body water measurements.

FIG. 8.—P. D.: Gastric resection, effect of operation on nitrogen balance, total eosinophil counts, and urinary excretion of creatinine, corticoids, and 17-ketosteroids. The most interesting single feature presented by this graph is that, following the postoperative increase in the urinary excretion of steroids, creatinine, and nitrogen, there was a return to the baseline and then a definite decrease in the excretion of these substances to levels below those observed preoperatively. This occurred on about the sixth postoperative day, a time when the total eosinophil count had returned to and exceeded the preoperative levels. These time relationships were somewhat different for different patients. It is submitted that a closer scrutiny of such relationships may result in a more sound policy regarding the spacing of staged operations.

subnormal urinary excretion of steroids.[19, 29] This is in line with the clinical experience that patients with subnormal adrenal or thyroid activity tolerate operation poorly. Moreover, the pattern of nitrogen excretion following injury in the starved patient is different from that observed in the well-nourished subject.[7, 9, 25]

Depleted individuals frequently exhibit a diminished tolerance for opiates and anesthesia, and recent studies in animals have quickened our interest in such relationships. During the course of a study of the effect of dietary potassium depletion on wound healing in dogs, it was observed that the experimental animals exhibited a markedly diminished tolerance for both ether and intravenous Nembutal anesthesia.[17] Since the dogs on the low potassium diet became anorexic toward the end of the experiment, one cannot attribute the poor tolerance for anesthesia solely to a state of potassium depletion, for other deficiences very likely were present. However, these results do emphasize the importance of dietary factors in the tolerance of the patient for various types of anesthetic agents.

THE PROPER STAGING OF OPERATIONS

Patients frequently require multiple operative procedures. Among these operations are staged thoracoplasty for pulmonary tuberculosis, skin grafting in burns, and prolonged reconstructive orthopedic procedures in military hospitals. For the most part, the time interval between stages is selected entirely on the basis of clinical impression, and this method has proved reasonably satisfactory in the past. However, it should be possible to identify certain physiologic processes which could be quantitated and thus permit the construction of a more sound physiologic basis for staging multiple operations. In Figure 8 it may be seen that approximately five days after operation the curves representing the urinary excretion of creatinine, corticoids, and 17-ketosteroids returned to the preoperative baseline and then declined to levels somewhat below those values obtained preoperatively. The interval of time between the day of operation and the day of return of the excessive metabolic activities to and below preoperative levels was greater in those patients who had the more severe operations. Further study of such relationships should be useful in the formulation of an objective basis to supplement the "clinical impression" in the proper staging of multiple operative procedures.

HORMONES, ENZYMES, AND SURVIVAL

The question arises as to how the increased hormonal activity after operation enhances the capacity of the individual to withstand the injury. While no conclusive statement can be made at present, the available evidence suggests that the beneficial effects of the increased endocrine activity are realized through hormonal influences on the rates of activity of enzymes, which in turn regulate many basic cytochemical reactions.

SUMMARY

1. Adrenocortical activity is increased following trauma. This is manifested by an increase in the urinary excretion of corticoids and a decrease in the total eosinophil count.

2. Thyroid activity may be increased following injury.

3. Postoperative fever may be due in part to a decreased heat elimination. It is possible that fever is a useful segment of the alarm response.

4. Creatinine excretion is increased following major operations. It is considered that this may reflect an increased metabolic activity in the muscle mass. It is suggested that the percentage increase in the urinary creatinine excretion following a particular operation may be useful in estimating the

relative impact of this operation on the metabolism of the patient.

5. The volume and the ionic composition of many body fluids are altered following major operations. Relatively large changes in body water content may escape clinical detection. Body fat and total body water bear an inverse relationship to each other, and the commonly used value of 70 per cent for body water is acceptable only in the abnormally lean subject.

6. Various segments of the alarm reaction are adversely affected by inadequate nutrition.

7. The beneficial effects of the increased endocrine secretion following trauma may be mediated through hormonal influences on the activity of enzyme systems, which in turn regulate many basic cytochemical reactions.

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DISCUSSION.—DR. I. S. RAVDIN, Philadelphia: This represents a portion of the work which Dr. Hardy and his associates did with us over a period of three or four years. I wonder how many of you realize how difficult it is to do these steroid excretion studies, the enormous amount of work that it takes in order to provide a better understanding of the physiologic processes that are involved, especially as they regard reactions involved in trauma?

It is only by a clearer understanding of these processes, as has recently been given by Dr. Hardy in his small monograph on "The Endocrine Response to Trauma," and by Dr. Francis Moore on "The Metabolic Aspects of Surgery," that we are going to get the better understanding that we have so long sought for, involving many processes in disease.

I want to say here that this represents the work of Dr. Hardy and his associates, and is in no sense the work in which I have made any major contribution.