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ENDOCRINE INTERRELATIONS IN MAN'S METABOLIC RESPONSE TO TRAUMA

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OBJECTIVES

To determine whether other endocrine glands are involved by depression or activation of function in man's metabolic response to trauma; to evaluate the activity of other endocrine glands in relation to the adrenal cortex as to how the metabolic response of the latter may be mpdified. To determine alterations in normal convalescence and in the period after trauma that are not characterized as part of the endocrine response to trauma. To seek out and to apply improved methods of managing derangements in man during and after trauma.

SUMMARY OF PROGRESS

(1) Endocrine responses during operative procedures. Ann. Surg., 1959, 150: 196.

Thyroid activity was studied by determination of the I^{131} conversion ratio

$$C.R_1 = \frac{\text{net counts } PBI^{131} \text{ (2 ml. serum)}}{\text{net counts (2 ml. serum)}} \times 100$$

Each subject received orally a tracer amount of I^{131} 48 hours before operation. No significant urinary excretion of I^{131} was observed after 48 hours had elapsed. Blood samples were drawn at significant events during the operative trauma: prior to premedication, prior to induction of anesthesia, prior to operation, 40 to 60 min. intervals during operation, end of operation, 3 to 4 hours after operation and 24 hours after operation. Results were controlled by conversion ratios established for a comparable group of non-operated patients.

Adrenocortical activity was determined by plasma hydrocortisone levels as measured by the method of Silber and Porter.

All patients displayed evidence of operative adrenocortical stimulation as reflected by increased plasma hydrocortisone levels; all but two patients had preoperative levels within the range of normal; these were above the normal

range. The degree as well as the pattern of increase varied from patient to patient; but, in general, a rather gradual rise during the operation was noted with the peak usually occurring at the end of operation or three to four hours after the completion of it.

Four persons of the 14 studied showed a significant increase in the conversion ratio during the operation ("thyroid reactors"). Generally, the members of this group were in good preoperative condition (three of four) while the "nonreactors" were classed as poor preoperative condition (seven of ten). In most of the patients a reciprocal relationship was evident between the conversion ratio and the steroid level.

(2) A study of alterations in gastrointestinal absorptive mechanisms after operation and trauma. Surg. Gyn. and Obst., 1959, 109: 762.

Thirty-nine patients undergoing major, extra peritoneal operation were studied. The patients were divided into two groups: 20 patients received I^{131} labeled triolein and 19 patients, labeled oleic acid. All degrees of trauma were included ranging from hemorrhoidectomy to pneumonectomy. Patients ranged in age from 16 to 89 years and preoperatively were in varying clinical states of well-being. No patient had known gastrointestinal or endocrine disease. Each patient acted as his own control since he was studied before and after operation in precisely the same manner.

Twelve hours prior to starting the study each patient received 4 ml. of Lugol's solution orally to flood the body with iodine to prevent thryoid trapping of the I^{131} to be administered later. Twenty-four hours after operation each patient received a capsule containing a known amount of I^{131} triolein or oleic acid. The dose varied from 6-30 microcuries. Heparinized blood samples were drawn at 2, 4 and 6 hours after administration of the capsule and radioactivity of whole blood (1.0 ml.) determined.

The analysis involved

n = number of blood samples
X = differences (preoperative-postoperative)
I^{131} uptake of blood samples
M = mean of differences (X)
V_1 = variance of individual values
V_2 = variance of mean of differences (M)
SE = standard error of mean
t = significant deviation from true mean of difference

$$V_1 = \sum \frac{(X - M)^2}{n - 1}$$

$$V_2 = \sum \frac{(X - M)^2}{n\,(N-1)}$$

$$SE = \sqrt{V_2}$$

$$t = \frac{M}{SE}$$

A statistically significant depression was found in the uptake of triolein in the postoperative period while oleic acid hptake was unchanged.

	2 hr.	4 hr.	6 hr.
Triolein	1.94	4.11	3.88
Oleic acid	1.50	0.77	1.47

Significance established 5% level at 2.09 and 1% level at 2.86 (triolein).

Significance established 5% level at 2.10 and 1% level at 2.88 (oleic acid).

(3) A continuation of metabolic data acquired as indicated in previous progress reports.

To date complete metabolic studies including sodium, potassium, water, calcium, phosphorus, sulphur and calorie balances have been done on six patients in the metabolic ward. These patients have varied as to the age and physical condition when they underwent the traumatic experience. They have varied also as to the type of nutrition they received prior to and immediately after the operative procedure. Both minor and major trauma has been preceded and followed by periods of starvation, periods in which only suitable water and electrolytes were given by either mouth or parenteral routes, or complete parenteral alimentation preceded and followed the operative procedure. In addition to the studies outlined on these patients, respiratory quotient and nonprotein respiratory quotients were determined at suitable intervals. Fractionation of the urinary 17-ketosteroids was done at suitable periods as well as following the plasma levels of the 17-hydroxycorticoster

Though this study is not complete it has now been in progress for over four years and the extent of the analyses makes it a necessary requirement that the laboratory proceed slowly in accomplishing and collecting the data.

Impressions as to the results so far indicate that in a person receiving no supplementary nutrition after operation or before and after operation, caloric expenditures are exactly what they would be expected in a starved person. The activation of the adrenal cortex influences very little if at all the metabolic changes that would be expected from large dose schedules of exogenous adrenocortical steroids. If parenteral alimentation isocaloric in value and composed of the same distribution as the general diet taken orally is provided before and after operation, little or no negative nitrogen balance is encountered and caloric expenditures as evidenced by the respiratory quotient show that the energy is coming from the generally distributed diet. If on the contrary the patient is starved the energey expenditure comes principally after the first 24 hours from nitrogen stores and fat stores within the individual's body.

Fractionation of the 17-ketosteroids shows that there is suppression of the androgenic steroid pattern after operative procedure and is principally the end metabolic product of the glucocorticoid type of adrenocortical steroid in the urine. This fits in very well with our knowledge of the starvation procedure.

This activity has been slowed up in its completion because of a hiatus in financial support. The five year grant from the Josiah Macy Foundation terminates as of 1 January 1960 and an anticipated renewal grant will not be acted upon until early in the spring of 1960. The interim supplementary assistance from CNR of $5,000.00 has been very valuable aid.

(4) Water and electrolyte exchanges during operation and convalescence. Surgery 1959, 46:123.

Calculations. Clearance techniques were used to study the various parameters in this study:

$$C_{osm} = \frac{U_{osm}}{S_{osm}} \times V$$

$$C_{H_2O} = V - C_{osm}$$

$$C_{Na} = \frac{U_{Na}}{S_{Na}} \times V$$

GFR = endogenous true creatinine clearance. % glomerular filtered sodium appearing in the urine was obtained by $\frac{C_{Na}}{GFR}$.

Knowing "pure" water requirements from previous publication (Surgery 1957, 41: 353), then to provide water as lactate Ringer's solution multiply water required per 24 hours by 1.4.

a) Plasma hydrocortisone levels were determined during operation by the method of Silber and Busch.

b) Plasma pressor amines were determined by the method of Weil-Malherbe and Bone as modified by Aronow and Howard.

c) Preoperative and postoperative control periods as well as studies on the operative day were characterized by the following observations: urine flow (ml/min), serum and urine osmolarities (freezing point depression), serum N_a, urine N_a, urine K (flame photometry); serum and urine creatinine. Body weight was measured by a scale accurate to ± 10 gms.

d) Results. It appears from this study that the endogenous production of aldosterone by patients subjected to operative trauma as measured by bioassay or the K/N_a ratio is at least in part induced by the medical management of the patient. For example, it is quite apparent that the principal increase in aldosterone as a response to operative procedure appears to be associated with the restriction of sodium intake. If patients receive electrolyte solution during the course of an operative procedure and the immediate postoperative period in adequate volumes, the release of aldosterone from the adrenal cortex will be minimal.

The observation that the plasma cpd F levels are consistently elevated in patients operated upon strongly suggests that aldosterone release is not under pituitary ACTH control in responses to operative trauma. The absence of significant increase in the tubular reabsorption of sodium in patients receiving lactate Ringer's solution in the presence of elevated levels of plasma cpd F indicated that this hormone is not active in producing sodium retention. There was evidence that it actually may promote an increase in urinary excretion of this ion.

Since cpd F does not effect sodium retention and the release of aldosterone is induced by restriction of sodium intake, it seems that,

if electrolyte containing solutions are supplied at a proper rate and amount to a patient during the course of operation and convalescence and excessive primary water retention does not occur, there is no hormonal increase in renal retention of sodium as shown by the percentage of glomerular filtered sodium that appears in the urine. Since sodium retention has been demonstrated in the presence of low aldosterone output, it is reasonable to assume that the sodium retention is a reflection of altered vascular permeability in damaged tissues at the operative site. This is comparable withthe mechanisms that have been known to be acting in burn trauma.

An additional advantage in providing electrolyte solution to the traumatized patient would seem to be indicated by the better maintained GFR in the convalescent period. It is true that hyponatremia is associated with decreased renal blood flow, glomerular filtration, and tubular function. For these reasons, though the serum sodium levels did not change significantly in the patients studied, at least the increased sodium load maintained glomerular filtration.

(5) Urinary 17-ketosteroids in surgical stress. J.C.E.M. 1959, 19: 849.

Four surgical patients studied showed a decrease in the excretion of C-19 O_2 steroids associated with a variable increase in the excretion of 17 KS carrying an oxygen function in C-11. The latter observation is not surprising, since these compounds are known to derive, at least in part, from C-21 compounds. The increase following operation is therefore comparable to the findings of other investigators concerning the response of corticoids to trauma. The diminished excretion of androsterone and etiocholanolone following operation is of great interest, particularly when one compares these data with those obtained following administration of ACTH, when a two-to threefold increase of these steroids is observed. It has been shown before that the excretion of androsterone and etiocholanolone for a specific individual is remarkably constant (Arch. Biochem. 53:258, 1954 - J. Biol. Chem. 225:39, 1957). This, and the fact that our determinations were made on large specimens of pooled urine make random variation unlikely. It is also apparent from this study that the changes cannot be explained by ACTH stimulation alone. Presumably, stress influences adrenal steroid metabolism by other means than ACTH stimulation. One can speculate that in order to preserve the homeostatic milieu, the synthesis of C-19 O_2 precursors is decreased in the presence of accelerated synthesis of cortisone-like material. A second but less appealing possibility would be a differential change in the pathways of catabolism and excretion of these compounds.

(6) In progress is a study in dogs of the effects of 5% dextrose in water compared with lactate Ringer's solution in maintaining the renal tubular compensatory activities in respiratory, metabolic and combined respiratory-metabolic acidosis, with and without a standard type of injury. Preliminary results strongly suggest that the tubular mechanisms operating against severe acidosis is much better preserved when fluid requirements are met with the balanced electrolyte solution.

PLANS FOR THE FUTURE

(1) It is planned to continue the intensive study of metabolic changes.

(2) Tubular mechanisms of acid-base compensatory mechanisms will be studied in man under conditions closely approximating the outlined procedure in dogs.