

ENDOCRINE INTERRELATIONS IN MAN'S METABOLIC RESPONSE TO TRAUMA

Mark A. Hayes, M.D., Ph.D.

Annual Summary Report
NR 109057
Contract # Nonr-609 (10)

1956

70-A-5204

OBJECTIVES

NAV1.941208.078

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 endocrines in relation to the adrenocortex as to how the metabolic response of the latter may be modified.

SUMMARY OF PROGRESS

(1) Thyroid Activity During Operation (See Appendix A) (Surgery, Gynecology and Obstetrics 1956, 102: 129-133) An increase in thyroid conversion ratios following the onset of surgical trauma, in this study, corroborates previous observations suggesting increased thyroid activity as a consequence of operation. The increase in thyroid activity apparently can be interpreted as part of the normal response to operative trauma. When such abnormal, long-standing disease states as chronic hemorrhage, debilitating illness, poor nutrition and weight loss are present, the thyroid response is decreased or absent. The effects of acute stress in altering the metabolic-endocrine responses to subsequent episodes of trauma are also important. Initial effects brought about by a traumatic episode do not disappear quickly as noted by Moore and Ball and until complete return to normal has been made, there will not be thyroid activation when further stress occurs. This concept is emphasized by the patients reported here who had surgical procedures shortly before undergoing a second operation (which was studied here) and did not show activation of the thyroid gland at the second operation. One of the patients was a good example of this phenomenon responding with thyroid activation after the first operation but displayed no thyroid response subsequent to the second surgical procedure.

The level of the thyroid activity before operation appeared to have some influence on the stress response. Those patients who preoperatively had a glandular uptake of radioiodine of 40% or more after 24 hours (high euthyroid) had a much greater thyroid activation in general than those whose uptakes were less than 40%. Age apparently had little effect on thyroid activation as did also the degree of trauma. Young and old, minor and major degrees of surgical trauma are all included among those patients in this study who had thyroid activation as well as those who did not.

After an increase in the conversion ratio at some time early in the operation a fall to preoperative or lower than preoperative levels followed in most patients. This suggests a decrease in production of thyroid hormone or increased utilization of hormone at the cellular level. Antagonism of adrenocortical hormone for thyroid glandular activity has been demonstrated in previous publications and may also play a part here, and many of these patients who showed a subsequent decrease in the conversion ratio may have had adrenocortical responses of some marked degree.

One group of patients who never returned to preoperative conversion ratio levels for the period of observation after trauma may represent one of the patterns of response which has been described earlier in this laboratory, that is thyroid activity without adrenocortical activation.

The stability of the hematocrit and total protein determinations suggests that neither blood dilution or alterations in protein composition present for iodine binding alter the results found in this study. The elevated conversion ratio observed would certainly have been more elevated had dilution from intravenous fluids during operation indeed played a part. By the same token, possibly those patients who showed no increase in conversion ratio would have shown some increase.

The conclusions obtained from this study are as follows: An increase in circulating thyroid hormone as measured by the conversion ratio (PBI 131) has been demonstrated to be present in a group of patients during operative trauma. Patients who had chronic illness or recent acute stress prior to the study did not show increased conversion ratios during operation.

The present study as well as previous work suggest that thyroid activation may play a very important role in the entire endocrine metabolic response to operative trauma. In the absence of thyroid response, the entire chain of post-stress events in the organism may be quite different from the standardized description.

(2) The Effect of Operative Trauma on the Utilization of Thyroid Hormone.
(Surgery, Gynecology and Obstetrics - in press)

Eight patients varying from 18 to 78 years of age were studied before and after major operations performed under general endotracheal anesthesia. Each patient had been given a small amount (20-25 microcuries) of chromatographically pure radioactive thyroxine which is administered intravenously several days prior to operation. Samples of blood were obtained at 24 hour intervals following administration and the conversion ratio (PBI 131) was determined for each sample by the methods previously described. To block endogenous thyroid hormone production and to prevent significant recirculation of the Iodine 131, each patient was given Lugol's solution daily for 5 to 7 days. This was continued during the entire course of the study employing intravenous iodine solution when the patient was unable to take oral fluids.

The results obtained here were much the same as those noted previously in studies of thyroid gland activation and the level of circulating thyroid hormones during operation. Four of the patients who had not experienced recent acute stress or long-standing chronic illness displayed an increased utilization of the labelled thyroxine after operation. This is indicated by the significantly steeper line showing the diurnal change in the log of the conversion ratio. On the other hand, the remaining four patients had postoperative thyroxine utilization curves not significantly different from their preoperative curves. All of these patients had severe acute stress or had had advanced chronic illness prior to the study here.

The present study strongly suggests that an alteration in the peripheral cellular utilization of thyroxine follows operation. Therefore, it would appear

that not only is the central thyroid gland activation present after operation, but also change in the ultimate end organ utilization of the hormone. It is not clear at this time which of the series of reaction is primary - increased output of hormone by the gland or increased demand by the cell. The chain of events after operation may depend upon a delicate balance between humoral and neural controls of homeostasis. Operative stress causes a generalized increased cellular demand for thyroid hormone by pathways not yet delineated. This increased demand affects the area of the hypothalamus devoted to increasing pituitary thyroid stimulating hormone production. The thyroid gland then responds with an increased output of hormone, satisfying the new cellular demands. Important for the inter-related events to take place appears to be a "normal" organism. Chronic illness such as evidenced in one group of patients upsets the balance such that anticipated events already described do not follow. Recent acute stress has the same effect. The complete basic response pattern after operation has now been demonstrated in all its phases - increased thyroid glandular activity, increased circulating thyroid hormone, and now increased peripheral utilization of the hormone. In summary, then, increased tissue utilization of thyroxine as measured with isotopically labelled hormone has been demonstrated to follow operation in patients who have not had recent acute stress or whom are not chronically ill. Patients who fall into either of the latter categories do not display the same increases.

(3) The Determination of Calcium and Magnesium in Serum, Urine, Feces and Diet. (manuscript in preparation)

In the course of a study determining whether the parathyroid gland participated in man's metabolic response to trauma, or the factors involved in calcium and magnesium losses in the postoperative period, a method was developed for the determination of calcium and magnesium in biological fluids. The reaction between calcium and ethylenediaminetetra-acetic acid (EDTA) in the presence of murexide has been examined in a semi-automatic, microphototitrometric procedure for the estimation of as little as 0.0005 meq. of calcium in a sample has been developed, using a graphic method for the calculation of results. The reaction between calcium, magnesium and EDTA, in the presence of EBT, has been studied. The estimation of calcium plus magnesium has been developed using a new graphic method for the calculation of results. The new methods have been applied to the estimation of calcium and magnesium in serum, urine and feces and diet. (A copy of this manuscript has already been submitted to the Office of Naval Research.)

(4) A Study of Parathyroid Gland Activity, Calcium and Magnesium Metabolism in the Postoperative Period. (Manuscript in preparation) A group of patients has been studied by the calcium infusion technique (Howard et al., Journal of Clinical Endocrinology and Metabolism 13:1, 1953; Kyle et al., American Journal of Medicine 14:754, 1953; and Lewin et al., Journal of Clinical Investigation 32:584, 1953) to evaluate preoperatively and postoperatively any alteration in parathyroid activity that might be related to operative trauma. No significant alteration in serum phosphorus levels during the infusion of the calcium salts or in the urinary excretion of phosphorus was determined that could be related to operative trauma. Thus it is concluded that there is no essential alteration in parathyroid activity as effected by trauma itself. On the other hand, careful metabolic studies in patients who from other studies would be predicted to be thyroid-adrenocortical hyper-reacters, and thyroid-adrenocortical nonreacters, showed that on restricted calcium intake prior to

operation there was still a considerable loss in the postoperative period of calcium and magnesium. These ions because of their importance in determining the integrity of all cellular processes, including neuromuscular irritability, must be considered as being in negative balance during the immediate postoperative period. As a consequence of this study, it is advisable to include these ions in intravenous fluids that are given during the postoperative period, particularly in extensive trauma and in patients in whom prolonged parenteral alimentation is predictable.

(5) Endocrine Mechanisms Involved in Water and Sodium Metabolism During Operation and Convalescence (in press - Surgery)

An exact definition of the mechanisms involved in water and electrolyte metabolism as modified during and after operative procedures and trauma has never been made. The recognition that the early convalescent period is complicated by an intolerance for sodium and water has determined qualitatively the amount and character of fluids administered parenterally to patients. Observations on coincident sodium retention and increases in either plasma or urinary excretory levels of 17 hydroxy-adrenocortical steroids during and after operation has led to the conclusion, perhaps without justification, that increases in these adrenocortical steroids produce a disturbance in sodium homeostasis. It is necessary to recognize that concomitant alterations in the normal constituents of the body do not imply of necessity that they are related causally.

(a) A Study of Anti-diuresis. Though biological identification of antidiuretic hormone is lacking in this study, as well as others, the experimental results make it clearly mandatory to accept an anti-diuretic mechanism as being active after trauma. Since so many features of the experimental results find counterparts in physiological experimentation with natural anti-diuretic hormone, it seems logical to accept a neurogenic release of ADH from the posterior pituitary as the mechanism involved in post-traumatic water retention. Since the water retention occurs in the presence of the progressive and often alarming decrease in serum osmolarity (a mechanism normally inhibiting ADH release) it would be justifiable to assume that it is "centrally driven", that is, forced discharge comparable to the mechanism that elevates the levels of the adrenocortical steroids in the serum, both being instances of disturbed physiologic equilibrium. Further evidence for ADH being forcibly released is the failure of alcohol to inhibit its release during operation, when the alcohol is given intravenously as supplementary to anesthesia, an observation made on two patients during this study.

(b) A Study of Insensible Water Loss. It is possible to administer fluid as 5% glucose in distilled water to compensate for insensible loss in post-operative patients on a metabolic basis, confirmed both by calculations done and information previously published and by accurate measurements of the actual loss in surgical patients. This amount conveniently is rounded off to 750 ml. per sq. meter per 24 hours. If this amount is added to the values recommended for obligatory urinary function, the total requirement, excluding abnormal losses by drainages, total 1,000 ml. per square meter per 24 hours for the operative day, adding 250 ml. per sq. meter each of the two successive days. A simple rule of thumb is thus obtainable: from a Dubois-Benedict chart, the body surface is obtained - for example, at 1.73 sq. meters the fluids required for the operative day are 1730 ml. (750 ml. insensible loss plus 250 ml. for renal function totalling 1,000 cc. per sq. meter, thus 1730 ml. per 1.73 sq. meters; 2080 ml. the first postoperative day; 2080 ml. the second postoperative day. The calculated amount, theoretically, should be administered over

the entire 24 hour period, thus supplying the water as it is metabolized. For the operative day, the theoretically "normal" man (1.73 sq. meters) would receive 72 ml. per hour, the rate at which he is losing the water; if given faster, temporary water retention will occur with temporary falls in serum sodium and serum osmolarity.

(c) A Study of Adrenocortical Activity in Sodium Metabolism.

Summarizing this portion of the study, it seems that, in effect, there is little evidence to show the pituitary controlled adrenocortical steroids play a major role in the well recognized postoperative intolerance to sodium. It primarily is a result of increased aldosterone secretion from the adrenocortex, which occurs independent of pituitary control and is related to prior or operative period restricted sodium intake.

(d) Summary and Conclusions of this Study. Trauma influences hypothalamic centers through the media of various neural effectors and possible humoral mediators. By disturbing the usual homeostatic mechanisms operating in the hypothalamus, its effect on the pituitary gland is altered; by neural connections, the posterior pituitary (the neurohypophyseal system) discharged anti-diuretic hormone and, by probable humoral influences, the anterior pituitary discharges at least thyrotrophic and adrenocorticotrophic hormones, each acting on its specific target gland.

Thyrotrophic and adrenocorticotrophic effects on the thyroid and adrenocortex are antagonistic and a new level of physiologic equilibration is effected. Among the other metabolic effects of the increased release of adrenocortical steroids which are controlled by the anterior pituitary is the possible increase in renal excretion of sodium, tending to a lowered serum sodium concentration.

On the other hand, the increased anti-diuretic activity when water is supplied too rapidly or in amounts beyond metabolic requirements, results in primary water retention and serum dilution leading to a lowered serum concentration.

The lowered serum sodium level, with an inadequate sodium intake, acts independently of any known controlling mechanism to increase adrenocortical release of aldosterone. This steroid effects maximal renal conservation of sodium.

Practical implications from and applications of this theory would caution against the administration of amounts of water exceeding metabolic requirements or exceeding rates of metabolic utilization. If the state of sodium metabolism is not known with certainty, prior to trauma, it probably would be unwise to give extra sodium during trauma and convalescence. If sodium depletion or restriction has not antedated the traumatic episode normal daily requirements for sodium can be given throughout operation and convalescence without a fear of excessive retention and edema.

PLANS FOR THE FUTURE

Since July 1 (the beginning of this fiscal year) the laboratory personnel have been busily occupied with developing methods for the study which will begin in January of 1957. Employing the basic methods of indirect calorimetry and the metabolic interrelationships as described by Albright and his group and Newburgh and his group, we plan on investigating total metabolism in surgical patients as their metabolic activities may be altered by the traumatic experience of an operative procedure.

These studies will include the following balances: sodium, potassium, water, nitrogen, phosphorus, calcium and sulfur. Very careful weight measurements will be made on this constant dietary program preoperatively and postoperatively and in view of this accurate reflections of metabolic changes within the body will be done.

The endocrinologic relationships as associated with these metabolic changes will be evaluated by sequential studies of anti-diuretic hormone release, thyrotrophic hormone release, and adrenocortical hormone levels in the blood during the course of the operation and during convalescence. By accurately evaluating these hormonal interrelationships, it may be possible to detect different metabolic responses to trauma which have been characterized in a lesser way in the past five years' activities of this laboratory. It is anticipated that by properly selecting patients of the known clinical types that we have begun to recognize, it will be possible to document these characteristic changes at this time. Previously, in the technical reports to the Office of Naval Research, conflicting reports have been made by us concerning gonadotrope activity as effected by operative trauma. It is hoped that with known nutritional states and a carefully controlled metabolic program as outlined above, it will be possible to clarify whether or not pituitary gonadotrope is released in increased or decreased amounts in the immediate and later postoperative period and how it is correlated with the complete convalescent period back to the original preoperative weight.

It is anticipated that this program will occupy the better part of the forthcoming calendar year and the results will be available for incorporation in the next technical report.

PUBLICATIONS

The publications during this current reporting period are as indicated under SUMMARY OF PROGRESS.