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 modified. To determine alterations in normal convalescence and in the period after trauma that are not characterized as part of the endocrine response to trauma.

SUMMARY OF PROGRESS

(1) The Effect of Operative Trauma on the Utilization of Thyroid Hormone. (Surg, Gyn. and Obst: 1957: 104, 295-298) (Appendix A)

Eight patients varying from 18 to 78 years of age were studied before and after operations performed under general endotracheal anesthesia. Each patient had been given a small amount (20-25 microcuries) of chromatographically pure radioactive thyroxine which was administered intravenously several days prior to operation. Samples of blood were obtained at 24 hour intervals following administration and the conversion rate (PBI^{131}) was determined for each sample by a method previously described. To block endogenous thyroid hormone production and to prevent significant recirculation of the I^{131}, each patient was given Lugol's solution daily for five to seven 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 hormone 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 the pre-operative curves. All of these latter patients had severe acute stress or had had advanced chronic illness prior to study.

This study strongly suggests that an alteration in the peripheral cellular utilization of thyroxine follows operation. It would appear, therefore, that not only is the central 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 reactions 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 increase of 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 interrelated 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 trauma in patients who have not had recent acute stress or who are not chronically ill. Patients who fall into either of the latter categories do not display the same increases.

(2) Endocrine Mechanisms Involved in Water and Sodium Metabolism During Operation and Convalescence. (Surgery: 1957: 41, 353-386) (Appendix B)

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-hydroxyadrenocortical 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 the necessity that they are related causally.

(a) A Study of Antidiuresis:

Although biological identification of antidiuretic hormone is lacking in this study, as well as others, the experimental results make it clearly mandatory to accept an antidiuretic mechanism as being active after trauma. Since so many features of the experimental results find counterparts in physiological experimentation with natural antidiuretic hormone, it seems logical to accept a neurogenic release of ADH from the posterior pituitary as a 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 physiological 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 postoperative 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 by the obligatory urinary function, the total requirements excluding abnormal losses by drainages, total 1,000 ml. per sq. 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 fluid required for the operative days is 1730 ml. (750 ml. insensible loss + 250 ml. for renal function totalling 1,000 ml. 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 on Sodium Metabolism.

Summarizing this portion of the study, it seems, in effect, there is little evidence to show that 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 or changes affecting the volume receptors.

(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 neuro-hypophyseal system) discharges antidiuretic 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 the renal excretion of sodium, tending to a lowered serum sodium concentration.

On the other hand, the increased antidiuretic 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 sodium concentration.

The lowered serum sodium level, with an inadequate sodium intake, acts independently through volume receptors to increase the adrenocortical release of aldosterone. This steroid effects maximal renal conservation of sodium.

Practical implications from and application 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 INCLUDING STUDIES IN PROGRESS

(1) Estimation of Third Space Effects Resultant from Trauma and Operative Procedures.

From the information available from the previous summary report concerning sodium metabolism in the immediate post-traumatic period, it would be possible by accurate sodium balances and continuous early administration of sodium as a physiologic salt solution (lactate Ringer's solution) to measure the volume of the third space. It is accepted that any trauma or operative procedure results in tissue damage remaining within the individual which allows the same transudation of protein, electrolytes and water that occurs after a burn. If lactate Ringer's solution is started as the primary fluid during the course of the operative procedure and is continued in order to provide an excess of electrolytes on the operative day and through the postoperative period until the patient is receiving nutrition by mouth, accurate sodium balances should reflect the amount of sodium retained in the tissue spaces as a result of the trauma. These accurate balances would then give an estimate of the size of the third space resultant from varying operative procedures and certain forms of trauma.

(2) Renal Clearances of Water and Sodium after Various Concentrations of Serum Albumin Injection.

This study would evaluate the various forms of serum albumin that are available for the treatment of burns, shock and blood replacement. The method involves the effects of the injection in a constant manner of a given quantity of serum albumin either as a concentrated or isotonic form on a patient who is undergoing a sustained water diuresis at the time of injection. Serum samples will be taken at hourly intervals and urine collections made over hourly intervals and both analyzed for sodium and osmolarity. Knowing urine volume, serum concentrations and serum osmolarity and urine sodium concentration and urine osmolarity, it is possible to then calculate water, sodium and osmolar clearances under the effects of these various injection forms of serum albumin. This would prove to be of value in the management of blood replacement by iso-osmotic or hyperoncotic serum albumin after trauma, in burns and various other clinical instances in which there is need for serum albumin.

(3) A Comparison of the Activity of the Adrenal Cortex, the Thyroid and the Adrenal Medulla during Operative Trauma and the Immediate Convalescent Period.

Employing techniques previously described measuring the serum level of 17-hydroxycorticoids and the PBI^{131} (conversion ratio) as indication of adrenal cortical and thyroid activity, supplementary work will be done measuring the plasma levels of epinephrine and norepinephrine. Sequential serum analyses will be done to determine the sequence of events as far as these three glands are concerned in the immediate metabolic and endocrinologic response to trauma.

(4) A Study into Alterations in Gastrointestinal Absorption after Operation and Trauma.

By employing radioactively labelled fats and protein (in the form of albumin) a study is underway determining any alterations in gastrointestinal absorption of protein and fat after the postoperative period is completed and the patient is taking nutrition orally. Previous work in this laboratory has indicated that there may be a faulty absorption of the essential food materials for a period of four to six weeks after trauma. The exact technique involves the ingestion of a known amount of I^{131} labelled fat and I^{131} labelled fatty acid and I^{131} labelled protein (in the form of albumin) and measuring the serum levels of radioactive iodine sequentially after the gastrointestinal absorption pattern is established.

(5) A Continuation of Metabolic Data Being Acquired as Indicated in Previous Progress Report.

Completed studies to date are in the process of being analyzed for

energy expenditure as well as nitrogen alterations that occur independent of known endocrinologic responses to trauma. Using sulphur, potassium and phosphorus (corrected by calcium balances), it is apparent that in the immediate postoperative period the nitrogen excreted cannot be accounted for entirely on the basis of muscle protein providing the negative nitrogen balance. Further studies on this are being done to determine if uric acid is the important part that occurs as a result of increased adrenocortical activity in the immediate postoperative period, acting on the lymphoid and nucleo-protein tissue of the human body.

This study also is a continuation showing that for a period as long as 45 to 60 days after a traumatic experience, at which time positive nitrogen balance is in effect, that the respiratory quotient still indicates the predominant source of calories to be from fat. Using the Pace-Behnke-Rathbun formulations as now modified by Cowgill, it is possible to use indirect calorimetry to determine the amount of fat that is being lost daily to supply calories if nitrogen balance is similarly known at the same time. These studies are being continued and further analyses are necessary.

PUBLICATIONS

Publications during the current report period are indicated under the summary of progress.