SERUM CHANGES FOLLOWING THYROPARATHYROID-ECTOMY.

STUDIES ON FERMENT ACTION. XXXI.

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As a result of the work of MacCallum and his coworkers (1), our knowledge concerning disturbances of the inorganic constituents of the blood serum particularly, following the removal of the parathyroids has been greatly advanced, and the antagonistic effect of the calcium ions established.

Certain observations have accumulated, largely of a clinical nature, which seem to indicate that in the tetany of infancy dietary factors are of considerable importance both from an etiological and therapeutic point of view. The spasmophilic infant rapidly recovers on a proper diet, and the evidence seems to indicate that phosphorus and certain of the unsaturated oils are of aid in expediting a favorable outcome.

In adults, too, we have to consider the peculiar form of tetany associated with gastric and occasionally intestinal disturbances, under conditions, therefore, which may be considered to offer opportunities for the absorption of the higher split products of proteins, the gastric digestion, of course, only splitting through to the peptones.

Experimentally the observation has been frequently recorded that the feeding of meats is particularly prone to lead to the onset of tetany in parathyroidectomized dogs.

Considerations such as these probably led Kling (2) to study the electric excitability of animals during anaphylaxis, in an effort to correlate the increased irritability of tetany with an anaphylactic state depending on a protein intoxication.
Our knowledge concerning the pathological effects of a faulty absorption of the higher split products of proteins from the gastrointestinal tract is as yet fragmentary, despite the obvious clinical evidence pointing in this direction. It has been observed, however, that in gastric tetany a gastro-enterostomy usually relieves the condition, the operative interference probably enabling a more rapid emptying of the stomach to the intestine with an augmented splitting of the protein contents to lower stages. Kaufmann's work is of particular interest in this connection (3).

In the few cases of true intestinal tetany that have been reported, there is considerable evidence that an achylia gastrica frequently complicates the picture, which again would offer every opportunity for a rapid absorption of the higher split products from the intestine, which under normal conditions is only afforded an opportunity to absorb the lower split products (Fleiner (4), Quosig (5)). The relation of tetany in infants is of particular interest in this connection; for substances which tend to increase the antiferment titer—unsaturated fats, phosphorus—have on empiric grounds been employed in the therapy of spasmophilia for many years, indicating that a suppression of a possibly faulty splitting of proteins may form the basis for this theory. Our interest in experimental tetany has centered chiefly, therefore, in a study of the changes of the serum and the relative amounts of split products therein contained.

The experiments were made on dogs. Thyroparathyroidectomy was performed in fifteen animals, and the serum changes were studied. The following two experiments are typical of the relations noted.

**Dog 1.**—Weight 5 kilos. Complete thyroparathyroidectomy on June 1, 1915. Tetany was observed on the 3rd day following the operation; on the 4th day the dog showed no symptoms; but on the next day (June 5, 1915) there was marked tetany. The animal was found dead the following morning. In Text-fig. 1 the serum changes are illustrated in detail.

**Dog 2.**—Weight 8 kilos. Complete thyroparathyroidectomy on June 8, 1915. Tetany was noted in the afternoon of June 10, 1915, again in the following afternoon, and the next morning (June 12, 1915), when the animal was killed. The serum changes are shown in Text-fig. 2.

In the first dog there will be noted a gradual increase in the antiferment titer until the time of death, with an irregular protease curve.
TEXT-FIG. 1. Serum changes following thyroparathyroidectomy in Dog 1.
TEXT-Fig. 2. Serum changes following thyroparathyroidectomy in Dog 2.
The maximum protease activity was noted in the animal during the time when the tetany was most apparent. The non-coagulable nitrogen of the serum increased to more than twice the original amount. The lipase remained constantly low. The proteoses increased markedly. The amino nitrogen of the serum in this animal showed no change except an initial decrease.

In Experiment 2 (Dog 2) the conditions are different. The antiferment titer showed marked fluctuation, the first decline appearing shortly after the operation. The protease remained low until the last day, but the non-coagulable nitrogen increased as in the previous animal; the proteoses also accumulated during the period of tetany. The increase in amino-acids is similar to that observed in practically all the other animals during tetany. This is the only animal of the entire series in which a rise in the lipase titer was observed.

DISCUSSION.

It is apparent that the ferment changes in these animals are not in themselves related to the onset of tetany, because the protease and lipase titers, as well as the antiferment index, have no constant relation at any time. It is equally apparent that a considerable accumulation of non-coagulable nitrogen occurs in the serum long before the onset of the actual tetany.

Thus an average of all the dogs examined gives the following figures for the non-coagulable nitrogen per cc. of serum:

<table>
<thead>
<tr>
<th>Before operation</th>
<th>24 hrs.</th>
<th>48 hrs.</th>
<th>72 hrs.</th>
<th>96 hrs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.21 mg.</td>
<td>0.31 mg.</td>
<td>0.39 mg.</td>
<td>0.50 mg.</td>
<td>0.44 mg.</td>
</tr>
</tbody>
</table>

The average proteose content per 5 cc. of serum was as follows:

<table>
<thead>
<tr>
<th>Before operation</th>
<th>24 hrs.</th>
<th>48 hrs.</th>
<th>72 hrs.</th>
<th>96 hrs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.41 mg.</td>
<td>0.50 mg.</td>
<td>0.58 mg.</td>
<td>0.74 mg.</td>
<td>0.84 mg.</td>
</tr>
</tbody>
</table>

In four animals of the series the onset and recovery from tetany followed at equal time intervals, and the amino-acid content of the serum per cc. has been averaged under comparable conditions.
Some observers, among them Morel (6), consider the pathological effect of the parathyroidectomy due to an auto-intoxication, regarding the tetany as a secondary character. An increased nitrogenous metabolism following the removal of the parathyroids is well recognized, but it is difficult to obviate the effect of the tremendous muscular stimulation in the interpretation of the result. It is interesting to note that Falta and Kahn (7) noted an increase in the peptide nitrogen of the urine in their animals, a result possibly of the large increase in the serum which we have observed.

Whether or not the alteration in the nitrogenous constituents indicated by the serum and urine changes is wholly the result of the increased muscular activity due to the increased irritability of the nervous system, or whether the change in these constituents from a quantitative and possibly a qualitative point of view is the cause of the increase of irritability of the nervous system, is, of course, not determined in these experiments.

During the course of the work it was observed that despite the marked fluctuation of the serum protease the titer of the serum lipase remained constantly at a very low level. Stuber and Heim (8) have previously expressed the opinion that the titer of the serum lipase (esterase) was at least partially under the control of the glands of internal secretion. In a series of dogs we have injected dried typhoid bacteria (10 to 20 mg.), which normally cause a prompt and not inconsiderable mobilization of serum lipase, into the circulation of thyroparathyroidectomized dogs and into dogs after complete parathyroid and partial thyroid removal. In the majority of instances the mobilization of lipase has been less constant and of less magnitude than in normal dogs, but the experiments are not sufficiently clear cut to warrant the conclusion of a definite relation between the glandular function and the lipase titer.
CONCLUSIONS.

1. In thyroparathyroidectomized dogs the onset of tetany bears no constant relation to the ferment-antiferment balance of the serum.
2. The serum lipase titer remains at a low level throughout.
3. A progressive increase in non-coagulable nitrogen and proteoses is observed in the serum following the removal of the glands.
4. The amino nitrogen of the serum is usually increased at the time when tetany is most marked.

BIBLIOGRAPHY.