

PARATHYROIDS AND CALCIUM METABOLISM.

By EDUARD UHLENHUTH.

(From the Laboratories of The Rockefeller Institute for Medical Research.)

(Received for publication, November 27, 1918.)

MacCallum and Voegtlin,¹ as well as other authors, have found that in tetany resulting from the extirpation of the parathyroids the Ca content of the blood and the organs (brain) is greatly reduced and that the introduction into the organism of Ca salts, subcutaneously, intravenously, or *per os*, suppresses the tetanic convulsions of the animals operated on. These findings have been confirmed recently by Howland and Marriott² in tetany of children. Spontaneous tetany in human beings has apparently the same cause as parathyreoprival tetany, both being due to the non-functioning of the parathyroids. Furthermore, it is known¹ that after parathyroidectomy, tetanic convulsions may be suppressed by bleeding the animals and substituting the amount of blood drawn by an equal amount of salt solution. From the latter fact MacCallum and Voegtlin conclude that in the absence of the parathyroids some toxic substance accumulates in the blood, which normally is antagonized by the parathyroids. They assume further that the toxicity of this substance is due to its ability to combine, in some unknown way, with calcium which it extracts from the organs, causing its excretion and thereby diminishing the Ca content of the blood and organs. MacCallum thinks that the muscular convulsions in tetany are the result of the diminution of the Ca concentration, the function of the parathyroids being to regulate the Ca concentration by antagonizing the toxic substance and thus preventing it from extracting the Ca salts from the body.

As regards the existence of a toxic substance involved in the causation of tetany, the writer has shown that such a substance actually

¹ MacCallum, W. G., and Voegtlin, C., *J. Exp. Med.*, 1909, xi, 118.

² Howland, J., and Marriott, W. McK., *Bull. Johns Hopkins Hosp.*, 1918, xxix, 235.

exists and is contained in the thymus gland.³ In the present article certain experiments will be reported demonstrating that calcium is able to suppress the tetanic convulsions, at least to some extent; the writer, however, was unable to convince himself that this effect upon tetany is characteristic for the calcium and furthermore the experiments in question, though they do not exclude a possible relation between the toxic substance and the calcium, prove conclusively that, as far as the animals used in these experiments are concerned, the tetany toxin, even in the presence of the calcium and in the absence of convulsions, brings about severe lesions of the muscular system resulting probably from lesions of the central nervous system caused by the tetany toxin and not prevented by the calcium.

EXPERIMENTAL.

In order to test the action of Ca lactate upon tetanic animals, a number of larvæ of the salamander *Ambystoma opacum* were fed on thymus and kept at the same time in a solution of Ca lactate in ordinary tap water; another set of larvæ of the same age and from the same female were kept in a solution of Mg lactate of the same concentration as the Ca lactate solution. A series of larvæ from a different female, fed on thymus, but kept in ordinary tap water, served as controls; since differences between larvæ from different females as regards the severity of tetany when fed on thymus are so small as to be negligible, the error introduced by comparing larvæ of different females is very small. For each of the three thymus series one series was kept as control, in which all conditions were the same as in the thymus-fed series, except that small pieces of earthworms instead of thymus served as food. None of the worm-fed control series developed tetany.

I. Thymus-Fed, Untreated Controls (Fig. 1, Curve I).—Six larvae of *Ambystoma opacum* were fed on thymus exclusively. As usual the tetanic attacks began after the larvæ had reached a certain developmental stage³ and soon reached a maximum. Each single individual came down with tetanic convulsions. When metamorphosis was

³ Uhlenhuth, E., *J. Gen. Physiol.*, 1918, i, 23, 33.

approached, tetanic convulsions ceased, and after metamorphosis all larvæ were free from it.

Besides the tetanic convulsions the other symptoms of tetany were also present in all animals; the legs and feet became permanently twisted and contracted and the entire body assumed the shape char-

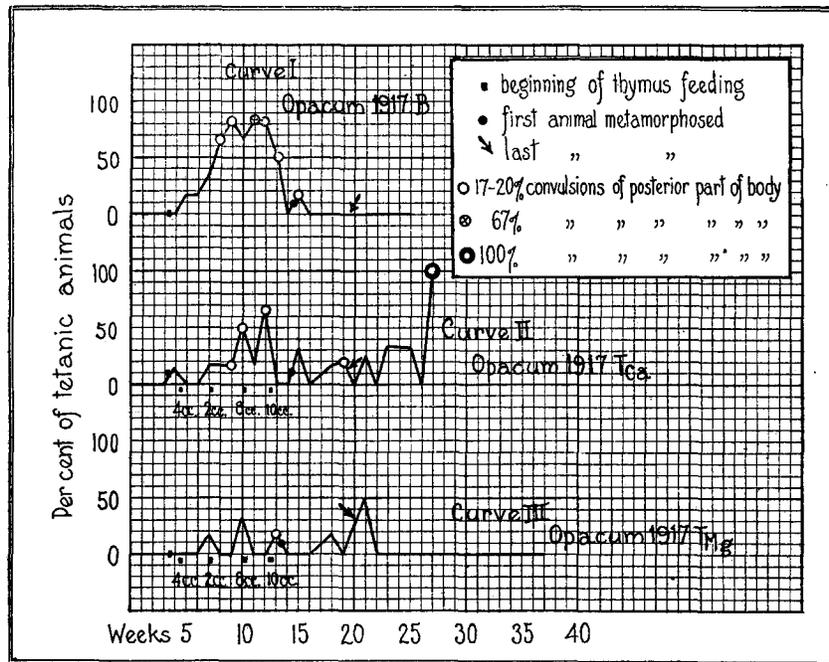


FIG. 1. Tetanic convulsions in a thymus-fed series of *A. opacum* (Curve I); in a thymus-fed series, kept in Ca lactate (Curve II); and in a thymus-fed series, kept in Mg lactate (Curve III). The ordinates indicate the percentage of animals showing tetanic convulsions at the time indicated on the abscissæ. Convulsions of the entire body and convulsions of the posterior portion of the body alone are considered.

acteristic of tetanic animals. The limbs and most of the muscles necessary for the movements of the animals became permanently paralyzed.

II. *Thymus-Fed Series, Kept in Ca Lactate (Fig. 1, Curve II).*—Seven larvæ of *Ambystoma opacum* were used, one of which died soon after the experiment had been started. Several days after the thy-

mus feeding had been started, one of the larvæ had a tetanic attack. 8 days after the beginning of thymus feeding the larvæ were transferred to a 1/1250 M solution of Ca lactate in tap water; this suppressed tetanic convulsions up to the 7th week, while in the untreated controls tetany had started at the end of the 5th week. Though the concentration of the solution was lowered to only 1/2500 M Ca lactate, the tetany curve did not rise as it did in the controls, but remained low until at the end of the 10th week. The concentration of the solution was increased to 1/625 M, upon which the curve fell, but soon it rose again and, after a further increase of the concentration to 1/500 M, it fell to zero; this latter fall, however, is probably due in part to the approach of metamorphosis, though the rise of the curve soon after the commencement of metamorphosis was due to tetanic convulsions of two larvæ.

As compared with the control thymus series the tetanic convulsions in the Ca lactate series were doubtless somewhat decreased; in particular it is very evident that an increase of the concentration resulted in a fall of the curve. It is worth noting that in the Ca series as in the untreated thymus series each single individual suffered from tetanic convulsions though for a shorter period of its larval life than the larvæ of the thymus-fed, control series.

The most important observation, however, is that though the muscular convulsions were decreased by the action of the Ca salt, the other symptoms of tetany, in particular the permanent paralysis of almost the entire muscular system, developed at the same time and with the same severity as in the untreated thymus-fed control series.

Finally, it should be mentioned that in the Ca series the metamorphosed animals behaved entirely differently from untreated thymus-fed animals. When the larvæ metamorphosed, they were taken out of the solution and placed on moist filter paper. As in all other thymus-fed animals, their muscles were paralyzed and the shape of the body and of the legs was greatly deformed, abnormalities which they had acquired during the tetanic period; like the untreated thymus-fed animals, they did not suffer from tetanic convulsions. Several weeks, however, after metamorphosis tetanic convulsions started again in the Ca animals, in contradiction to what we have observed

in all the untreated thymus-fed animals. This surprising difference has not found so far any explanation and will not be considered in the present article, detailed discussion being reserved until further experiments upon this phenomenon are available.

*III. Thymus-Fed Series, Kept in Mg Lactate (Fig. 1, Curve III).—*Seven larvæ of *Ambystoma opacum* were used; one of them died soon after the experiment had been started. 8 days after the beginning of the thymus feeding and before tetanic convulsions had made their appearance, the larvæ were transferred to a 1/1250 M solution of Mg lactate in tap water. By this concentration tetanic convulsions were suppressed until the end of the 7th week; at this time one larva had convulsions. But even though the concentration had been lowered to only 1/2500 M, no further convulsions occurred until the 10th week; the concentration was increased to 1/625 M, upon which the curve fell immediately to zero. The concentration was further increased to 1/500 M; only one larva developed tetanic convulsions of the posterior portion of the body, and no further attacks were observed among the larvæ, the rise of the curve at the end of the 18th week being due to tetany of a metamorphosed animal.

In this series the Mg lactate had a distinct and very definite influence upon the frequency and severity of the muscular convulsions; not only is the curve running far lower than in the untreated thymus-fed series, but it is also lower than in the Ca series. Furthermore, three of six larvæ had no muscular convulsions during the larval period. Evidently the effect of the Mg lactate in suppressing the muscular convulsions during tetany is far greater than that of the Ca lactate, when used in the concentrations employed in these experiments.

This influence of the Mg lactate upon the convulsions of the muscles, however, does not mean that Mg is able to suppress tetany, for the other symptoms of tetany, *i.e.* paralysis of the muscles and deformation of the extremities and of the body, develop and to the same degree as in non-treated thymus-fed larvæ.

Concerning the metamorphosed animals the same phenomenon is observed as in the Ca series. A number of weeks after the animals had metamorphosed and were set on moist filter paper without being exposed longer to Mg lactate, they began to suffer again from tetanic

convulsions. And two of the animals which did not have convulsions during their larval period had convulsions after metamorphosis. But the third specimen, which had no convulsions during its larval life, never had tetanic convulsions; it was still alive 43 weeks after metamorphosis.

DISCUSSION AND CONCLUSIONS.

The experiments reported in this article are in full agreement with the facts known about the action of Ca and Mg salts in tetanic animals. In the concentrations used here both Ca lactate and Mg lactate suppressed the muscular convulsions in the tetanic salamander larvæ. The Mg lactate, however, appears to be more effective than the Ca lactate. At any rate the suppression of the tetanic convulsions does not seem to be a specific action of the calcium.

The most important result seems to be the fact that the salts used, though they prevented the muscular convulsions, did not prevent the other symptoms of tetany which in the salamander larvæ are very definite and constant. The permanent spasmodic contractions and the paralysis of the muscles developed in spite of the presence of the Ca and Mg. Furthermore, the muscular contractions and the paralysis developed even in such thymus-fed animals in which the convulsions had been suppressed completely; this was the case in one of the animals of the Mg series.

From the experiments of Biedl⁴ and others it is likely that the tetanic convulsions are due to lesions of the central nervous system, since convulsions of a leg can be prevented by isolating it from the central nervous system by cutting the nerves which connect the muscles with the central nervous system. Evidently these lesions of the central nervous system are the chief factor in tetany, while the convulsions of the muscles are only an effect. In the larvæ of salamanders these lesions find a definite expression in the permanent paralysis of almost the entire muscular system.

In the writer's opinion, MacCallum's hypothesis that the tetany toxin has a special affinity for Ca, thereby diminishing the Ca content of the organism, cannot be disproved at present. But the

⁴ Biedl, A., *Innere Sekretion*, Berlin and Vienna, 1913, i, 126.

present experiments seem to prove, first, that the tetany-producing substance causes permanent lesions of the nervous system, which lead to permanent spasmodic contractions and paralysis of the muscle even in the absence of tetanic convulsions, and second, that these cannot be prevented by either Ca or Mg. For the most part they result in an early death of the animals no matter whether or not Ca or Mg has been applied.

In connection with this fact we wish to mention Biedl's claim⁴ that no one has yet succeeded in prolonging the life of parathyroid-ectomized animals by the application of Ca. From MacCallum's paper, on account of the lack of controls, it cannot be seen whether his parathyroidectomized dogs lived longer with Ca treatment than without.

That in spontaneous tetany Ca treatment may effect a cure, as is evident from the report by Howland and Marriott, does not prove that in this case Ca has inhibited tetany as a disease. In spontaneous tetany the period of the action of the tetany-producing substance may be a very short one and the mere prevention of the tetanic convulsions may keep the patient alive until normal function of the glands involved has been restored. The pathological changes which the central nervous system undergoes in this short period may not be severe enough to endanger the life of the patient after the cessation of the action of the tetany toxin.

In the light of the facts presented our experiments lead to the following conclusions:

1. The thymus gland excretes a tetany-producing substance which in the normal animal is antagonized in an unknown way by the parathyroids.
2. In animals devoid of parathyroids (salamander larvæ, parathyroidectomized mammals) this substance may, according to MacCallum, reduce the Ca content of the organism; but by far the most dangerous and important quality of this substance is its highly injurious effect upon the central nervous system, which causes permanent spasmodic contractions of the muscles and paralysis of almost the entire muscular system.
3. It is possible to prevent the muscular contractions by introducing Ca salts into the body, though this can be done more effectively by means of Mg salts.

4. No substance, however, has been found so far to antagonize the tetany toxin and to prevent the development of the lesions of the central nervous system caused by the tetany toxin.

5. This explains why in spite of the application of Ca or Mg and in spite of the suppression by these substances of the tetanic convulsions the other symptoms of tetany develop and frequently lead to the death of the animal.

6. Accordingly the most important function of the parathyroids is to prevent the tetany toxin, by antagonizing it, from coming into contact with the central nervous system.

The writer wishes to express his thanks to Dr. G. M. Meyer, of The Rockefeller Institute, for preparing the solutions used in these experiments.