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Increased gastrointestinal permeability as a possible factor in parathyroid tetany.

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It is generally conceded that young mammals develop parathyroid tetany sooner and in severer form than adults of the same species. Starvation of any animal prior to and following a complete thyroparathyroidectomy delays the onset of tetany, diminishes its severity, and prolongs life.

There is some evidence that the gastrointestinal tract of the young is more permeable than that of adult animals. The disastrous effect of a meat diet following a parathyroidectomy has been known for a long time and has directed attention to the possibility that toxic products of gastrointestinal origin were responsible for the marked depression or convulsive death of parathyroidectomized animals. The work of Dragstedt and Luckhardt support that possibility (see following article for references). Various observers have described pathological changes in the mucosa of the stomach and upper portion of the small intestine of dogs following fatal tetany.

Such considerations suggested the hypothesis that parathyroid tetany might in part be due to an increased permeability of the gastrointestinal tract allowing toxic products of protein origin to pass into the blood stream in larger amounts and at a more rapid rate than under normal conditions. Such an increased permeability would account for the marked depression and convulsive death. The increased permeability is capable of accounting also for the increased elimination of calcium by the gut and the hypocalcemia which apparently exists. Oral administration of calcium salts might under such conditions render the gut less permeable, preventing the absorption of toxic compounds; restore the calcium balance upset by the increased excretion of calcium by the gut; and meet the heavy demands on the body calcium of a high meat (calcium poor) diet.

If complete parathyroidectomy results in an increased permeability of the gut, the recovery reported in previous publications might indicate either an increased tolerance to the toxins or a

return to a nearly normal functional activity of a deranged gastrointestinal tract. It might be expected, however, that such animals that had escaped an otherwise certain death, because of treatment, might be more easily thrown into tetany by any measure designed to injure their gastrointestinal tract and make the latter more permeable.

We accordingly made use of a number of dogs whose life had been observed by either the intravenous injection of Ringer's solution or the oral administration of various forms of calcium salts.[3] These animals were on the usual stock diet or on a daily ration of 1/3 to 1/2 lb. meat and 1/2 lb. bread. As soon as the animals showed no signs of developing tetany spontaneously they were given several cascara pills, 30 to 60 or more grams of sulfur ointment for one or two days, or on other occasions, 3 to 5 minims of croton oil. It was expected that such treatment would set up a more or less intense gastritis and enteritis and by so doing effect a change in the permeability of the gut.

RESULTS.

1. Following the oral administration of a drastic cathartic (croton oil) or the ingestion of moderate quantities of a laxative (cascara or sulfur ointment) dogs that have recovered from the acute effects of a complete parathyroidectomy can be thrown into more or less severe tetany. Marine[4] was "inclined to think that the administration of large amounts of sulfur favors the development of tetany" by "bringing about a state of nutrition favoring the development of tetany" or because possibly some "alkaline earths are withdrawn from the field of absorption by this element."

2. If a slight tendency to tetany exists only small amounts of an irritant are necessary to bring out the symptoms.

3. Such tetany usually develops within the first 24 to 48 hours after administration. Within 24 hours the animals are visibly depressed, show an anorexia, enophthalmos, corneal and conjunctival injection, and some spasticity. More or less severe tetany (clonic or tetanic seizures) may develop in 24 hours but usually occurs in 48 hours.

4. Dogs but recently parathyroidectomized (3 mos.) show

[3] Compere, E. L., and Luckhardt, A. B., PROC. SOC. EXP. BIOL. AND MED., 1924, xxi, 526.

[4] Marine, D., *J. Exp. Med.*, 1914, xix, 89.

the symptoms earlier and in severer form than such animals which have survived the removal of their parathyroids from 1 to 2 years. Tetany has not been induced in normal animals by such treatment.

5. The fact, that in several animals tetany, after the administration of croton oil, develops in the absence of catharsis but following repeated emesis of copious amounts of blood stained gastric mucus seems to indicate that the stomach had suffered the greatest injury and that the subsequent tetany may have been due to the absorption of toxic compounds from the stomach (gastric tetany).

6. This fact would indicate that the stomach may under certain conditions possess greater absorptive power than has been accredited to it. In support of this view we cite the further evidence (collected in previous work) that the symptoms of parathyroid tetany become less severe quite *promptly* after emesis of a meal taken 48 *hours previously;* and that necropsy findings of animals dead from tetany often reveal large amounts of food in the stomach with but little material of any kind in the small or large intestine.

7. The development of some of the symptoms of tetany in parathyroidectomized dogs following the administration of monobasic calcium phosphate may be ascribed to its marked irritating action on the gastrointestinal tract.

8. Animals in which tetany has been induced intentionally by a drastic cathartic can be restored to a normal condition by the administration of calcium salts other than the soluble phosphate (*i. e.,* by the acetate, nitrate, carbonate, lactate).

At present we are inclined to interpret the above facts as follows:

1. More or less violent gastrointestinal irritants change the permeability of the gut of parathyroidectomized dogs and permit (a) the more rapid and complete absorption of toxic compounds from the stomach and intestines; and (b) of the more rapid excretion of calcium compounds.

2. The administration of calcium compounds may conserve the life of recently parathyroidectomized animals or those thrown into tetany by gut irritants by restoring the normal impermeability of the gut and supplying the blood and tissues with calcium lost by the increased excretion by the bowel due to an increased permeability.

CONCLUSION.

In a previous publication we have called attention to the possibility that our completely parathyroidectomized animals may on occasion show convulsive seizures indistinguishable from grand mal attacks of idiopathic epilepsy seen in man. The same factors which predispose to such attacks in man favor the convulsive attacks in such dogs. Indiscretions of diet particularly in infants are likely to induce convulsive seizures with definite clinical indications of a gastritis and enteritis. Whereas it is desirable to prevent constipation in epileptics and promote intestinal evacuation following any dietary indiscretion, it is obvious, on the basis of the results just described, that too drastic catharsis may be more harmful than beneficial in that any violent cathartic may for reasons advanced rather induce convulsive seizures than prevent them.

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On the efficacy of various calcium salts in parathyroid tetany.

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Several satisfactory methods are now available to preserve the life of dogs following an otherwise rapidly fatal thyroparathyroidectomy. Forced diuresis by the intravenous injection of large quantities of Ringer's solution quite rapidly controls the symptoms of parathyroid tetany, or if maintained in the absence of any symptoms even prevents it appearance.[1] The oral administration of calcium lactate[2] is less laborious and even more effective. If, however, the animal at any time develops *severe* tetany in spite of treatment the intravenous injection of Ringer's solution is indicated as the first measure of choice to obviate the extreme tetany with exitus possibly attendant on the passage of

[1] Luckhardt and Rosenbloom, PROC. SOC. EXP. BIOL. AND MED., 1921, xix, 129; Luckhardt and Rosenbloom, *Science*, 1922, lvi, 48; Luckhardt and Blumenstock, *Science*, 1922, lvi, 257.

[2] Luckhardt and Goldberg, *J. Am. Med. Assn.*, 1923, lxxx, 79; Luckhardt and Blumenstock, *Am. J. Physiol.*, 1923, lxiii, Feb. (Proceedings).