THE CALCIUM METABOLISM IN INFANTILE TETANY, WITH REPORT OF A CASE *

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Before discussing the rôle of calcium in the etiology of tetany it is important to summarize the present status of our knowledge of calcium in the healthy organism.

To illustrate how minute is the amount of calcium involved in metabolic processes, one needs but consider that the soft tissues contain 0.01 per cent. of the calcium in the body, the remainder forming 7.7 per cent. of the skeleton; thus, a child weighing 10,000 gm. would only have 1 to 2 gm. in the soft parts.

The calcium content of the brain, according to Quest¹ is relatively high in early infancy, but diminishes as the child grows older, most rapidly in the first few months, then more slowly. In the fetus he found 0.168 per cent. calcium, in a new-born child 0.107 per cent., in a 4 months child 0.072 per cent., at 16 months 0.074 per cent., and at 2½ years there was 0.067 per cent. The nitrogen content was fairly constant, being 10 to 12 per cent. of the dried powder. In the brains of three infants dying with tetany 10, 11, and 12 months old, however, Quest found the calcium content distinctly diminished (0.041 per cent., 0.047 per cent., 0.0535 per cent.). Aschenheim² found the percentage diminished in two patients aged 7 and 10 months, and approximately normal in a third case (0.0373 per cent., 0.0234 per cent., 0.0557 per cent.). Leopold and von Reuss,³ however, did not find any change from the normal in two infants 4 and 5 months old, respectively (0.062 and 0.038 per cent.). Michel Cohn⁴ also found the calcium content of the brain in one case of tetany normal. In animals suffering from tetany parathyreopriva it has been demonstrated by MacCallum,⁵ Pexa,⁶ and Aschenheim² that the calcium of the brain is diminished. Cooke,⁷ on the other hand, found a slight increased calcium content in the brains of dogs dying of tetany. However contradictory the results may appear.

*From the Chemical Laboratory of Cornell University Medical College.

1. Quest: *Jahrb. f. Kinderh.*, lxi, 114.

2. Aschenheim: *Monatschr. f. Kinderh.*, vii, 374.

3. Leopold and von Reuss: *Wien. klin. Wchnschr.*, 1908, No. 35.

4. Cohn, Michel: *Deutsch. med. Wchnschr.*, 1907, No. 48.

5. MacCallum and Voegtlin: *Jour. Exper. Med.*, 1909, p. 119.

6. Pexa: *Arch. f. Kinderh.*, 1910, No. 54.

7. Cooke: *Jour. Exper. Med.*, 1910, No. 12, p. 45.

they may be better interpreted in the researches of Loeb who showed that it is not the presence of one salt alone in the solution, but its interaction with other salts which influences nerve irritability. Either a diminution of the Na or an increase of the Ca diminishes the irritability. This is well illustrated by Aschenheim in his third tetany brain, in which, although the calcium content is high, the sodium also being high causes

$$\frac{\text{Ca}}{\text{Na}}$$

the quotient of the fraction — to equal 46, whereas in normal brains

$$\frac{\text{Ca}}{\text{Na}}$$

it is only 19 to 26.

The application of calcium to the cerebral cortex has been shown by Sabbatani⁸ to diminish its electrical excitability. Quest⁹ was able by means of calcium-poor food to diminish the electrical excitability of the peripheral nerves in dogs, presumably by diminishing the calcium content of the nervous system. Stoeltzner¹⁰ in an attempt to repeat this work, obtained contradictory results; and Pexa,⁶ who fed puppies on a calcium-free diet, was unable to show any hyperexcitability of the peripheral nerves, although at autopsy the brains contained but one-fourth the normal amount of calcium. Rosenstern¹¹ attempted to attack this problem from the clinical side, and in cases of spasmophilic diathesis gave large doses of calcium chlorid (3 gm.) by means of which he was enabled to diminish the electrical excitability, the kathodal opening contraction rising within an hour to its maximum, the effect disappearing within twenty-four hours. Of twenty cases tested fifteen responded to the calcium and five were unaffected. To prove that it was the calcium and not the chlorid that was active, he used various other chlorid salts, but with them was unable to obtain results. Large doses of NaCl, on the other hand, increased the irritability. These influences on the electrical reactions have been investigated in the nerve-muscle preparation of the frog by Reiss¹² who showed that variations, i. e., a diminution in the calcium concentration of the solutions applied, could explain most of the electrical reactions of tetany with the exception of anodal closure.

An examination of the calcium content of the blood has also been carried out in order further to clear up the relationship of this substance to tetany. In parathyroidectomized dogs MacCallum and Voegtlin⁵ found the amount diminished. Neurath,¹³ using Wright's method, found that the calcium content of healthy children's blood was highest in early age and diminished as the child grew older, breast-fed children showing

8. Sabbatani: Quoted by Quest (see Note 9).

9. Quest: *Wien. klin. Wchnschr.*, 1906, No. 27.

10. Stoeltzner: *Neurol. Zentralbl.*, 1908, No. 2 (quoted by Escherich).

11. Rosenstern: *Jahrb. f. Kinderh.*, ii, No. 2, p. 72.

12. Reiss: *Ztschr. f. Kinderh.*, iii, No. 1.

13. Neurath: *Ztschr. f. Kinderh.*, 1910, i.

a higher percentage than the artificially fed. Adding calcium to the food does not seem to increase the calcium in the blood. Parathyroidectomized animals also showed diminution of the blood-calcium. However, he emphasizes the fact that by Wright's method only ionic, i. e., precipitable calcium is estimated.

From the clinical standpoint this problem has been attacked by watching the therapeutic effect of doses of calcium in tetany. In post-operative tetany both in animals and man, large doses of calcium have been successfully used to relieve the symptoms. In the tetany of adults Curschmann and many others have had good results. In the infantile form Gerstenberger¹⁴ got no results by the oral administration of calcium lactate, but his doses were only 2 gr. three times a day. Rosenstern¹¹ used it effectively by giving large doses. Intravenously calcium has yielded even better results.

At first sight it would seem that the most rational method of solving the whole problem would be by means of metabolism experiments; that is to say, ascertaining the total calcium intake and output. Although of undoubted value, this method has the disadvantage that it does not give any information as to the intermediate metabolism of the calcium, or as to how much calcium there is at any time available for the various parts of the body. It is surprising how little is known about the calcium metabolism, either in normal or in abnormal cases, and especially in cases of tetany.

The metabolism of normal breast babies has been better investigated on account of the ease with which it is possible to obtain a normal breast-fed child. Michel,¹⁵ in a number of infants from 5 to 11 days old, found an absolute retention of calcium of about 0.2 mg., about 60 to 80 per cent. of the intake. In older children, aged 3 to 3½ months, Michel and Perret¹⁶ and Schabad¹⁷ have found slightly less retention, 150 to 200 mg., 40 to 50 per cent. of the intake. Langstein and Meyer¹⁸ give as an average of various observations a retention in breast-fed babies of 176 mg. or 62.44 per cent. of the intake.

As far as bottle-fed babies are concerned, the figures vary from 1 to 5 per cent. retention (Cronheim and Muller¹⁹) to 44 per cent. Blauberg.²⁰ It must be added, however, that as Schabad remarks, the figures of Cronheim and Muller's cases are so low that they do not cover the calcium requirement of the organism. Langstein and Meyer give

14. Gerstenberger: Jour. Exper. Med., Mar. 1, 1911.

15. Michel: L'Obstetrique, Mar. 15, 1896 (quoted by Schabad).

16. Michel and Perret: Bull. Soc. d'Obst., March, 1899.

17. Schabad: Arch. f. Kinderh., lii, 1-3, p. 68.

18. Langstein and Meyer: Säuglingsernährung und Säuglingsstoffwechsel.

19. Cronheim and Muller: Biochem. Ztschr., ix, 79.

20. Blauberg: Ztschr. f. Biol., xl, 19.

the average retention as 44.4 per cent. These figures must be regarded as more or less arbitrary, as not enough cases have been examined nor have the durations of the various experiments been of sufficient length.

CASE REPORT

In a case of tetany which we had the opportunity of observing, the calcium metabolism was studied in three periods of three days each. The history of the case is as follows:

History.—Female child 1 year old, non-instrumental delivery, breast-fed till the age of 10 months; apparently normal until 9 months of age (could stand and made attempts to walk alone), when it suddenly began to have convulsions, which were repeated. For this it was taken to a hospital and remained there two months. Two weeks after it left the hospital it came under our observation. Its condition was as follows:

Physical Examination.—A poorly developed anemic female child with very moderate rachitis, extremities held in typical tetany position, with marked spasticity. Eyes staring, face mask-like; Chvostek extremely marked; Trousseau present. Galvanic irritability showed kathodal opening contraction at 1.0 milliampere. Physical examination of the lungs, heart and other viscera was negative; temperature 102, pulse 120, respiration 30; stools dyspeptic; urine showed a faint trace of albumin.

On admission the child was put in a metabolism bed, and a four-day experiment carried out, the first day being disregarded. It was given in three days 2,300 c.c. of milk, containing by absolute analysis 2.5 per cent. fat, 2.25 per cent. protein and 6 per cent. sugar. During this time and for several weeks afterward the child ran a temperature up to 102. Physical examination including ears, urine, etc., failed to show the cause for this. The Pirquet test was negative.

During the following month the child's food consisted of little milk and plenty of cereal. During this period, although the child took its food badly and lost in weight, the symptoms of manifest tetany improved considerably, so that the child lost its fixed staring expression, Trousseau could no longer be obtained, the Chvostek became less marked and kathodal opening contraction had increased to 3 milliamperes.

May 25 the child was again put in the metabolism bed. It was fed on a cow's milk mixture (fat 3 per cent., protein 2.2 per cent., sugar 6 per cent.), of which it took 1,870 c.c. Its weight at this time was 12 pounds, 14 ounces. After four days the child was removed from the metabolism bed and put on a milk-free diet of soup and cereal for one week. Then it was given cod-liver oil 3i t. i. d., 10 ounces of milk a day, cereals, soup and bread and butter. The milk was then gradually increased. Under this regimen the symptoms rapidly improved, the temperature became normal, and remained so; kathodal opening contraction rising to 6 milliamperes, the only evidence of tetany being a slight Chvostek.

July 21 the third metabolism experiment was begun. During this the child received 2,250 c.c. milk, 120 gm. bread, 150 gm. rice, containing in all fat and protein as seen in the table. The child's weight at this time was again 14 pounds.

During the entire period of observation the stools were one to two a day, unformed, greenish-yellow, dyspeptic. The urine during the first few days of the illness contained a faint trace of albumin and a few hyaline casts. Subsequently the urine was normal.

SUMMARY

A child observed three months.

Experiment 1.—Manifest tetany; kathodal opening contracture 1 milliampere; fever; feeding raw cow's milk, calorically slightly insufficient.

Experiment 2.—Tetany markedly improved, kathodal opening contracture 3; fever; feeding raw cow's milk calorically insufficient through the child refusing nourishment.

Experiment 3.—After milk-free diet and cod-liver oil only symptom of tetany a slight Chvostek; kathodal opening contraction 6 milliamperes.

From Table 1 of the balances in these three experiments, it will be seen that although the child was fed a calorically insufficient mixture, the nitrogen balances were positive, 50 per cent. in the first experiment, and 38 per cent. in the second.

TABLE 1.—FAT AND NITROGEN IN AN INFANT WITH TETANY
—Fatty Acids, K. and S.—

Experi- ment	Intake, gm.	Resorption,		Intake, gm.	Urine and Feces, gm.	Total Nitrogen		Resorption, gm.	Per cent.
		Feces, gm.	gm.			Retention, Per cent.	gm.		
1	50.46	5.72	44.7	88.7	8.13	4.06	4.07	50.0	88.2
2	44.8	1.46	43.34	96.7	6.73	4.12	2.61	38.7	78.0
3	93.6	4.8	88.8	94.8	14.32	7.14	7.185	50.0	95.2

The fat balance obtained by the method of Kumagawa and Suto, showed an intake of 54 gm. in Experiment 1, with resorption of 88 per cent.; the resorption in the second being much better (96 per cent.); in the third about 95 per cent., showing an improvement in the fat resorption in the last two experiments.

TABLE 2.—CALCIUM OXID BALANCE

Experiment Duration, Days,	Amt., c.c.	Food		Intake, CaO, gm.	Amount c.c.	Urine		Feces		Resorption		Retention	
		Composition				CaO, gm.		Amt., gm.	CaO, gm.	Absolute, gm.	Per cent.	Absolute, gm.	Per cent.
1	3	2,300	2.5 F. 2.2 P. 6 S	2.921	635	0.0314	20.0	1.7834	1.376	38.9	1.1062	37.8	
2	3	1,870	3 F. 2.2 P. 6 S	2.917	295	0.0288	7.0	0.8044	2.1128	72.4	2.084	71.3	
3	3		Milk, Rice, Bread	3.918	1,026	0.220	16.0	1.426	2.492	63.6	2.272	58.7	

The calcium metabolism as seen from Table 2 shows that in Experiment 1, with an intake of 2.9 gm. of calcium, there was an absolute resorption of 1.376 gm., or 38 per cent., and an absolute retention of 1.1062 gm. or 37.8 per cent. In the second experiment with practically the same intake there was only 0.8 gm. excreted in the feces, an absolute resorption of over 2.0 gm. or 76 per cent. and a retention of 71 per cent. The amount of calcium excreted in the urine in both of these experiments was about the same. In the third experiment, in which the intake was increased by 1 gm. of calcium, the amount of dried feces being almost the same as in Experiment 1 (16 gm. as compared with 20 gm.), the actual excretion was less than in Experiment 1, the absolute resorption

was 2.4 gm. as compared with 1.3 gm. in Experiment 1, and 2.1 gm. in Experiment 2, the percentage being 63 per cent., almost as large as in Experiment 2 and almost twice as large as in Experiment 1. The retention was 58 per cent. The amount of calcium oxalate in the urine of Experiment 3 is high, due to the unfortunate admixture of some of the feces. However, even if we assume that all the calcium found in this urine in Experiment 3 was derived from this contamination, nevertheless, by adding this to the calcium of the feces we still find the excretion less than in Experiment 1, although the child was getting 1 gm. more calcium by mouth.

It has been shown that the calcium output may be increased by fever,²¹ and it might be argued that the comparatively low retention (37 per cent.) in our first experiment was due to this cause; however, during the second experiment the child ran a similar temperature and the retention had almost doubled.

Concerning the rickets, Schabad²² has shown that as the rickets improves the calcium retention is bettered. In our case it seems hardly probable that the rickets was much of a factor, for the child had no enlargement of the epiphyses, had been able to stand, and had made attempts at walking at 9 months; in fact, the rosary was the only symptom. In a period of five weeks, during which time there had been no especial therapy or diet instituted for rickets (cod-liver oil was given only after the second experiment) and the child having lost weight, the improvement in the calcium retention could scarcely be attributed to improvement in the rickets.

The only cases comparable to ours are that of Cybulski²³ and those of Schabad.²⁴

Cybulski's case was an infant 7 months old weighing 6,100 gm. (13.4 pounds). It was supposedly a non-rachitic infant suffering from manifest tetany. Cybulski did metabolism experiments of three periods of three, three, and four days each. The child received cow's milk in the first and woman's milk in the second and third experiments. From the figures in Table 3 it will be seen that there is a progressive improvement in the calcium retention, the figures showing first 20.8 per cent. retention, then 53.7 per cent., and last 87.2 per cent. The fat resorption, as in our experiment, also improved, but the nitrogen during the first experiment was negative.

The gradual increase in the amount of calcium retained might well be ascribed to the fact that the child received woman's milk, for this in itself ordinarily causes an increase in the calcium retention. Further-

21. Schkarin: *Arch. f. Kinderh.*, 1905, xli.

22. Schabad: *Arch. f. Kinderh.*, liv, Nos. 1-3.

23. Cybulski: *Monatschr. f. Kinderh.*, November, 1906, p. 409.

24. Schabad: *Monatschr. f. Kinderh.*, ix, No. 1.

more, the child during the first experiment was not in nitrogen equilibrium; moreover, it is very improbable that a child of the proletariat weighing only 13.4 pounds at 7 seven months should be free from rickets. In addition, Schabad calls attention to the absence of spastic extremities and the Trousseau sign, doubting as to whether the case is really one of tetany. It seems to us, however, that the electrical reactions undoubtedly classify the case as tetany, and it would seem more than likely that the convulsions could be ascribed to this cause.

TABLE 3.—CYBULSKI'S CASE. CALCIUM OXID BALANCE

Experiment No.	Duration, Days	Intake CaO, gm.	Urine CaO, gm.	Feces CaO, gm.	Resorption		Retention	
					Absolute, gm.	Per cent.	Absolute, gm.	Per cent.
1. . . .	3	1.756	0.0074	1.382		21.4	0.366	20.8
2. . . .	3	0.997	0.0089	0.453		54.7	0.536	53.7
3. . . .	4	1.531	0.031	0.1650		89.3	1.353	87.2

Schabad describes two cases of rickets complicated by tetany, 2½ and 3 years old, respectively, in which the calcium retention had sunk to 4 per cent. in the one and 15 per cent. in the other. By the administration of cod-liver oil and phosphorus he was able to raise the retention in the second case from 15 per cent. to 76.6 per cent., and coincidentally noted the diminution in the electrical excitability — the kathodal opening contraction going from 2 to 6 milliamperes and the Chvostek and laryngospasm disappearing. It is difficult to compare these cases with ours, first, on account of the difference in ages, second, their marked rachitis and, third, the fact that Schabad's metabolism experiments did not include the stage of manifest tetany. It is seen that in his cases also the increase in the calcium retention and the improvement in the symptoms go hand in hand.

TABLE 4.—NITROGEN FRACTIONS IN URINE IN THE AUTHOR'S CASE OF TETANY

Date	Amt. c.c.	Sp. Gr.	Total Nitrogen, gm.	Urea, gm.	Urea N Per cent. Total N	NH ₃ Ni-trogen, gm.	NH ₃ N Per cent. Total N
April 18-19	130	1010	1.07	0.69	64.5	0.0585	5.47
April 19-20	205	1016	1.06	0.73	68.8	0.051	4.81
April 20-21	300	1010	1.08	0.84	77.8	0.072	6.66
May 25-26	95	1020	0.930	lost		0.04	4.3
May 26-27	65	1025	0.740	0.54	73.0	0.044	5.40
May 27-28	135	1012	0.970	0.607	62.6	0.091	9.39
July 19-20	380	1009	2.542	2.086	82.0	0.234	9.21

Haskins and Gerstenberger²⁵ in a child suffering from manifest tetany (negress 14 months old) found the calcium retention 11.7 per cent. Eight months later, after treatment, with the child apparently greatly improved, the calcium retention was 12.8 per cent.

25. Haskins and Gerstenberger: Jour. Exper. Med., March, 1911.

CONCLUSIONS

From the foregoing review of the subject, and analysis of our case, one might conclude as follows:

1. Sufficient data are not available to state definitely the absolute and percentual figures for calcium retention in the normal child.
2. The calcium in our case, as compared with the few normal cases on record, does not seem diminished.
3. From Cybulski's and our cases it appears that the calcium retention improves as the tetany disappears.

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