10917

Influence of Hypochloremia upon the Convulsive Reactivity.*

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Our knowledge of the influence of the chloride content of the blood upon the convulsive reactivity is rather contradictory.

Lennox and Cobb[1] mention findings indicating that increased concentration of chloride in nervous tissues may play a contributory part in seizures. In their tentative list of conditions which may precipitate seizures they mention high chloride, and among the conditions which may prevent seizures, low chloride. These statements were widely accepted, *e. g.*, by Wolff.[2] On the other hand, the convulsive reactivity may be increased in conditions associated with loss of chlorides such as prolonged vomiting in children (Gordon[3]). In view of the practical importance of the question whether the production of hypochloremia in patients with convulsive disorders is desirable or not, in the following series of experiments the influence of hypochloremia upon the convulsive reactivity was quantitatively studied.

The experiments were performed on 8 rabbits and 2 cats. The convulsive reactivity of the animals was determined by electrical stimulation through the eyeballs using an apparatus devised by one of us (Spiegel[4]), that permits one to vary the voltage as well as the duration of the alternating current. After a relative constancy of the threshold was established in daily measurements, hypochloremia was produced by intraperitoneal injection of 10% glucose solution (50 cc per kilo body weight, in some cases repeated after 4 hours following the procedure of Silvette and Britton[5]). Six hours after the first injection the convulsive reactivity was again determined. The chloride content of the serum was determined by the Myers-Whitehorn[6] method before and 6 hours after the glucose injection

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1 Lennox, W. G., and Cobb, St., *Epilepsy, Medicine*, 1928, **7**, 105.

2 Wolff, H. G., *J. Am. Med. Assn.*, 1939, **112**, 1250.

3 Gordon, H. H., *J. Am. Med. Assn.*, 1939, **112**, 1252.

4 Spiegel, E., *J. Lab. and Clin. Med.*, 1937, **22**, 1274.

5 Silvette, H., and Britton, S. W., *Am. J. Physiol.*, 1935, **111**, 305.

6 Myers, V. C., *J. Lab. and Clin. Med.*, 1920, **6**, 17; Whitehorn, J. C., *J. Biol. Chem.*, 1921, **45**, 449.

TABLE 1.

Animal No.	Convulsion threshold: Before hypochloremia Range	Avg	During hypochloremia		Duration of convulsions: Before hypochloremia sec	During hypochloremia sec	Serum Cl (mg/100 cc): Before injection	After injection
							10% glucose, 50 cc/kg intraperitoneally	
	Milliampère-seconds	A	H	*H/A				
Rabbit								
20	12-16	13.6	17.5	1.3	15-60	33	371	349
36	12-16	14.0	14	1.0	11-30	19	337	313
			7	0.5		50		235‡
45	12-17.5	14.0	14	1.0	10-52	10	371	365
			5†	0.36		64		127‡
49	12-14	13.1	7†	0.53	13-32	20	355	217‡
78	19-21	20.6	16	0.77	24-26	16	327	279
81	10.5-16	12.6	14	1.1	12-57	18	325	301
			7	0.55		24		265
702	9-10.5	9.3	21	2.2	24-40	17	343	271
703	12-14	12.8	14	1.09	13-50	34	301	292
Cat								
38	17.5-26	22.2	17.5	0.78	45-94	60	374	205
64	24.5	24.5	19	0.77	34-80	146	343	283

* H: convulsion threshold in hypochloremia; A: average convulsion threshold before hypochloremia.
† The threshold returned some days later to 19 in rabbit No. 45, and to 17.5 in rabbit No. 49
‡ Serum Cl returned some days later to 343 in rabbit 36, to 331 in rabbit 45, to 352 in rabbit 49.

(immediately before the determination of the convulsion threshold).

The results are summarized in Table I in which the convulsion threshold is expressed in milliampère-seconds. In all experiments in which the chloride value of the serum dropped below 265 mg per 100 cc the convulsion threshold was lowered, the ratio of the threshold in hypochloremia to the mean threshold before the induction of the hypochloremia (H/A) dropping below 1. In 2 cases (rabbit No. 78, cat No. 64) a decrease of Cl to 279 mg and 283 mg respectively sufficed to lower the convulsive reactivity; only in rabbit No. 702 the threshold was increased while the Cl was lowered to 271 mg. In this animal, however, the duration of the convulsions was decreased. When the values of the Cl were not lowered below 301 (first experiment in rabbits 36, 45, and 81, rabbit 20) also the threshold was not diminished. The lowest value of H/A was observed in the animal (rabbit 45) with the most marked hypochloremia (127 mg Cl). There is, however, no definite parallelism between degree of hypochloremia and decrease of the convulsion threshold; *e. g.*, in cats No. 38 and 64, the ratio H/A had nearly the same value, while the hypochloremia was more marked in cat 38 than in cat 64. In 3 experiments the increased convulsive reactivity in hypochloremia was also manifested by an increase of the duration of the convulsions, (No. 36, 45, cat 64); in 3 cases the duration of the convulsions elicited during hypochloremia was within the range observed before the hypochloremia (rabbit 49, 81, cat 38) and in one animal it was diminished (No. 78).

As pointed out by Silvette and Britton, intraperitoneal glucose injection lowers both Na and Cl, the loss of these 2 ions showing a straight line relationship. In experiments of Fenn,[7] *et al.*, nervous tissue immersed in isotonic sugar solution lost Na and Cl in approximately equal amounts. The loss of salt from the tissues results in a shift of extracellular water into the cells producing swelling of the cells as was shown on the red blood corpuscles by Gilman.[8] Swelling of the brain, as for instance induced by injection of hypotonic solutions, is associated with increase of the permeability of the cellular surface films for ions (Spiegel and Spiegel-Adolf[9]) thus facilitating those mechanisms upon which excitation depends.

The above mentioned experience that hyperchloremia also may increase the convulsive reactivity is not in contradiction to the

[7] Fenn, W. O., Cobb, D. M., Hegnauer, A. H., and Marsh, B. S., *Am. J. Physiol.*, 1934, **110**, 74.

[8] Gilman, A., *Am. J. Physiol.*, 1934, **108**, 662.

[9] Spiegel, E., and Spiegel-Adolf, M., *Am. J. Psychiat.*, 1936, **92**, 1145; PROC. SOC. EXP. BIOL. AND MED., 1936, **34**, 799.

results of the present series of experiments. As was pointed out by Spiegel and Spiegel-Adolf, the convulsive reactivity may be increased by 2 mechanisms, pericellular increase of the concentration of ions on the one hand, increase of the permeability of the cellular surface films on the other hand. While the effect of hypochloremia belongs to the second group, hyperchloremia probably acts according to the first mentioned mechanism.

Summary. Experiments on rabbits and cats showed that hypochloremia increases the convulsive reactivity

10918

Negative Effects of Cysteine Hydrochloride on Regression of Carcinoma in Line A Albino Mice.

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Cysteine hydrochloride injected directly into the Jensen rat sarcoma has been reported to produce complete regression of the tumor.[1] Recurrence did not occur within a period of 6 months, and reinoculation with the same tumor or with Emge sarcoma[2] was not possible after regression of a cysteine treated tumor. Acids adjusted to the same pH as the cysteine hydrochloride solutions and injected in equivalent volumes were reported to be rapidly absorbed from the tumor and, except for a small area of necrosis, to produce no cytological change.[3]

After the experiments here described had been completed, further work was reported[4] on the treatment of 3 different rat tumors, and on the Brown-Pearce rabbit carcinoma. This confirmed the earlier observations that direct injection of cysteine hydrochloride into Jensen's rat sarcoma and an adenofibroma of rats caused complete regression and cross immunity between the two. Treatment administered by other route was practically ineffective except that it prolonged the average life of rats bearing the Walker tumor by 11.1 days.

1 Connor, C. L., Carr, J. L., and Ginzton, L., PROC. SOC. EXP. BIOL. AND MED., 1936, **34**, 374.

2 Carr, J. L., PROC. SOC. EXP. BIOL. AND MED., 1936, **35**, 341.

3 Carr, J. L., PROC. SOC. EXP. BIOL. AND MED., 1936, **35**, 343.

4 Carr, J. L., Connor, C. L., and Ginzton, L. L., *Am. J. Cancer*, 1936, **34**, 428.