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Experimental Epileptiform Attacks in the Offspring of Alcohol Poisoned Rabbits *).

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Much has already been written concerning epilepsy in the offspring of alcohol poisoned parents. Mostly in all studies on this subject the authors have come to the conclusion, that alcoholism of parents is an important etiologic factor, and the injury to the germ plasm produced by alcoholism in parents is regarded as rendering the offspring more susceptible to the development of convulsions. This conclusion is based on clinical observations. But we know how difficult it is to discuss and to differentiate the importancy of alcoholism of parents as an etiologic factor in epilepsy, while in cases of alcoholism in man we mostly always can find a lot of different degenerative signs, and mostly always we have to do with a psychopatic constitution.

The purpose of this paper is to give some experimental evidences to this question.

On examination of the brains from the offspring of alcohol poisoned rabbits there were found changes in the glial tissue and the bloodvessels, which were similar in their character and distribution to the changes occurring in the brains of epileptic patients. The changes in the rabbits brains were small foci of glial proliferation in the cerebral cortex (Fig. 1—6) and basal ganglia (Fig. 7); these small foci were sometimes closely related to the bloodvessels (Fig. 5 and 6) but more frequently not so. The cells in those foci related to the bloodvessels were always closely packed together whereas in the other foci they were more scattered (Fig. 5 and 7). In some places the walls of the small bloodvessels were thickened, especially in the Ammon's Horn where in one case a totally obliterated vessel was found with hyalin degeneration (Fig. 8). The nerve cells in all parts of the brains showed no definite pathological changes. In many of the brains from the offspring of the alcohol poisoned animals there was found an internal hydrocephalus (Fig. 9) [1]).

These findings were regarded as the result of the alcohol poisoning in the parent animals because in a series of control animals no such changes were found.

As these findings in the rabbits brains are somewhat similar to those in brains of human cases of epilepsy, it was considered possible that these animals might develop sooner or later an illness, which can manifest itself in a similar way to idiopathic epilepsy.

We are fully conscious that in idiopathic epilepsy the relationship between substrate and function is not understood; neither their dependence

*) Preliminarly report read at the XXth International Congress on Alcoholism in London, 1934.

[1]) V. Üprus: Folia Neuropathologica Estoniana Vol. 10, p. 74. 1930.

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on one another, nor their primarity. Neither pathological physiology nor pathological anatomy have explained the cause of epileptic attacks — whether disturbances of function are due to tissue changes, or visa versa.

The disease processes which can result in epileptic attacks have been called by Foerster [2]) „irritative epileptogene Noxen". By idiopathic epilepsy we do not know exactly what are these „irritative epileptogene Noxen", but it would appear however that in idiopatic epilepsy the organism is in general more sensitive and more susceptible to all convulsion producing influences, one of which is the injury to the germ plasm produced by alcoholism in parents.

When we are comparing these clinical considerations with the results of Grant's [3]) experiments in rabbits, we can see some contradictions, while in Grant's experiments the brain of offspring of alcohol poisoned rabbits is less sensitive to electrical stimulation than that of normal rabbits.

To find an explanation for such a contradiction of clinical and experimental observations, a study has been made of experimental epilepsy produced by picrotoxin and monobromide of camphor in the offspring of alcohol poisoned rabbits. The above mentioned toxins were employed for the production of experimental epilepsy because in recent years the toxic theory of idiopathic epilepsy has been more exploited.

Material and Method. For our study were used 28 offspring of alcohol poisoned rabbits of the first generation (AF_1), 13 of the second generation (AF_2), and for control, experiments 20 normal rabbits (NF). They were all reared under similar conditions and seemed to be quite healthy. Of the animals 11 AF_1, 9 AF_2, and 8 NF were used for experiments with picrotoxin, and 17 AF_1, 4 AF_2, and 12 NF for experiments with monobromide of camphor.

Picrotoxin was used as a waterly solution in destilled water 1:1000 and was given subcutaneously 1,0 or 1,5 mgr per kg of body weight.

Monobromide of camphor was used as an oily solution in oleum provinciale 20:100 and was given also subcutaneously 0,5 or 1,0 gr per kg of body weight. Solution of monobromide of camphor at body heat was injected because at room temperature it was not soluble to the extent of 20:100.

The results of experiments were registered visually. All myoclonic manifestations were registered and put into five groups according to the intensity of the myoclonic reaction. Group I: — Very slight myoclonic reaction — positive cases with very delicate clonic movements in ear and face muscles. Group II — slight myoclonic reaction — clonic movements in ear, face, neck and forelimbs muscles. Group III — moderate myoclonic attack — positive cases with general clonic movements in all groups of muscles, but attacks were not compounded from tonic and clonic convulsions. Group IV — strong attack — cases with very strong

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[2]) E. Foerster: Zschr. f. Nervenheilk. Vol. 94, p. 15. 1926.
[3]) F. Grant: Fol. neuropathol. estoniana, Vol. 10. p. 1. 1930.

Fig. 1.

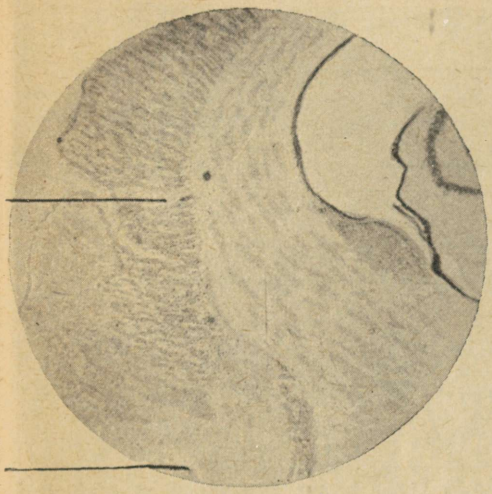
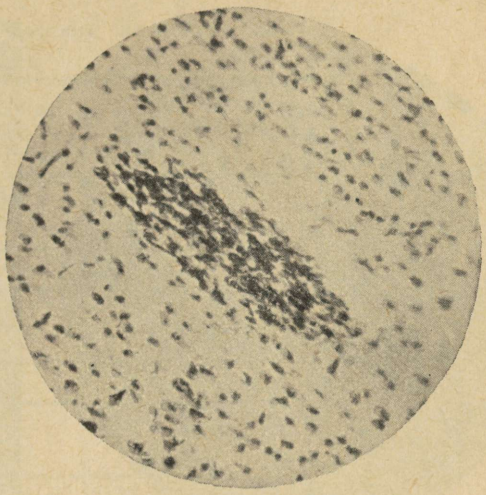


Fig. 2.



myoclonic reaction which started with the tonic and ended with the clonic convulsions, and group V — status myoclonicus — when one strong attack followed after the other over longer or shorter period of time. Most of the cases of status epilepticus ended with death of the animal [5]).

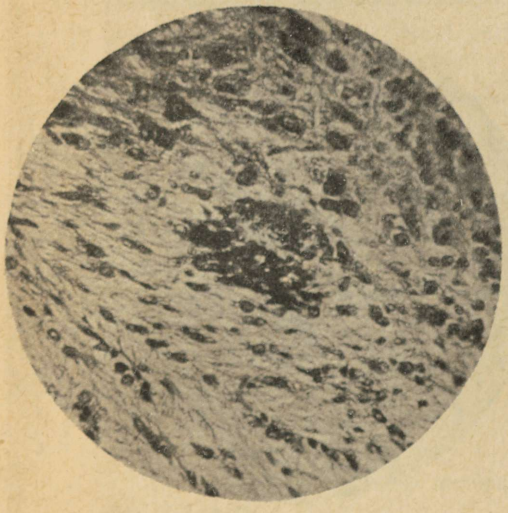


Fig. 3

Fig. 4.

Fig. 5.

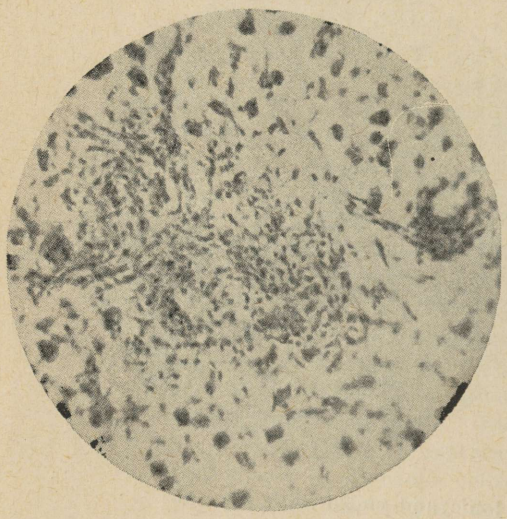
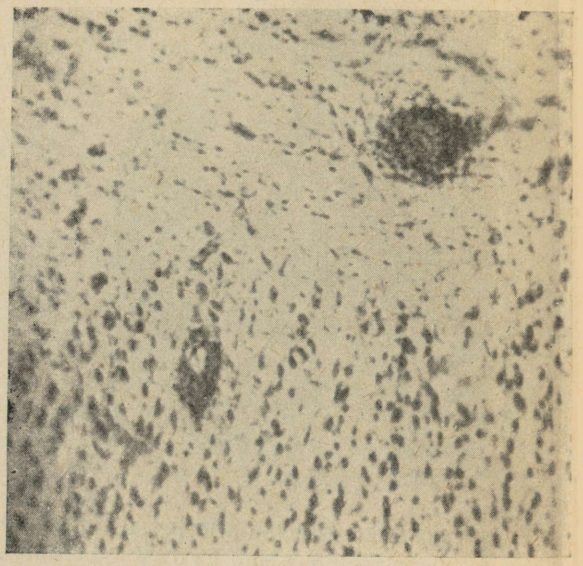


Fig. 6.



Experiments with picrotoxin. 35 experiments were made with 8 NF, 57 experiments with 11 AF_1, and 42 experiments with 9 AF_2. Results of experiments were:

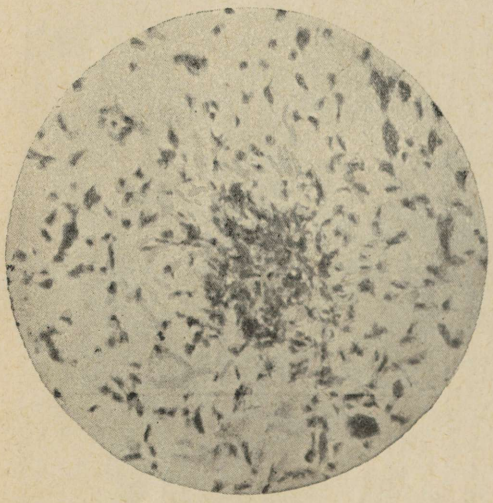


Fig. 7

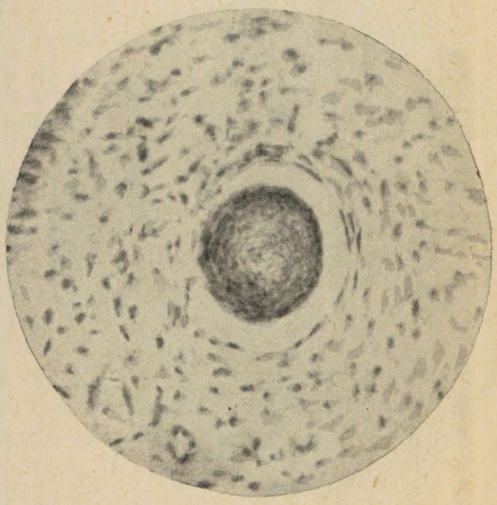


Fig. 8.

Table I.

Absolute number and % of the positive and the negative cases.

Experiments with	Number of animals	Doses of picrotoxine in mg	Number of experiments	+ cases		— cases	
				absol.	%	absol.	%
NF	8	1,0	29	19	65,5	10	34,5
		1,5	6	6	100,0	—	—
	Average		35	25	71,4	10	28,6
AF_1	11	1,0	48	34	70,8	14	29,2
		1,5	9	9	100,0	—	—
	Average		57	43	74,0	14	25,6
AF_2	9	1,0	27	23	85,2	4	14,8
		1,5	15	15	100,0	—	—
	Average		42	38	90,5	4	9,5

Table II.

Latent period of reaction in positive cases.

Experiments with	Number of positive cases	Latent period up to (in minutes)							Dosis of picrotoxine in mg
		15	30	45	60	120	180	<180	
NF	19	—	1	7	7	3	—	1	1,0
	6	—	2	1	1	2	—		1,5
Total	25	—	3	8	8	5	—	1	
AF_1	34	3	11	9	7	4	—	—	1,0
	9	1	2	2	4	—	—	—	1,5
Total	43	4	13	11	11	4	—	—	—
AF_2	23	6	9	5	2	1	—	—	1,0
	15	3	9	2	1	—	—	—	1,5
Total	38	9	18	7	3	1	—	—	—

[5]) Exact description of method by V. Üprus: Fol. neuropath. eston. Vol. XI. 1931.

Table III.

Intensity of myoclonic reaction.

Experiments with	Dosis of picrotoxine in mg	Number of positive cases	I		II		III		IV		V	
			absol.	%	absol.	%	absol.	%	absol.	%	absol.	%
NF	1,0	19	12	63,0	7	37,0	—	—	—	—	—	—
	1,5	6	1	16,7	2	33,3	—	—	2	33,3	1	16,7
	Total	25	13	52,0	9	36,0			2	8,0	1	4,0
AF_1	1,0	34	15	44,1	7	20,6	4	11,8	8	23,5	—	—
	1,5	9	2	22,2	1	11,1	3	33,3	3	33,3	—	—
	Total	43	17	39,5	8	18 6	7	16,3	11	25,6	—	—
AF_2	1,0	23	11	47,8	8	34,8	—	—	4	17,4	—	—
	1,5	15	4	26,7	2	13,3	2	13,3	4	26,7	3	20,0
	Total	38	15	39,5	10	26,3	2	5,3	8	21,0	3	7,9

Experiments with monobromide of camphor: 33 experiment were made with 12 NF, 56 experiment with 17 AF_1, and 10 experiment withe 4 AF_2. Results of experiments were:

Table IV.

Absolute number and % of the positive and negative cases.

Experiments with	Number of animals	Doses of monobromide of camphor in gr.	Number of experiments	+ cases		— cases	
				absol.	%	absol.	%
NF	12	0.5	21	10	47,6	11	52,4
		1.0	12	7	58,3	5	41,7
	Average		33	17	51,5	16	48,5
AF_1	17	0.5	39	15	38,5	24	61,5
		1.0	17	13	76,5	4	23,5
	Average		56	28	50,0	28	50,0
AF_2	4	0,5	7	6	85,7	1	14,3
		1.0	3	2	66,7	1	33,3
	Average		10	8	80,0	2	20,0

Table V.

Latent period of reaction in positive cases.

Experiments with	Doses of monobromide of camphor in gr	Number of positive cases	Latent period in minutes up to								
			15	30	45	60	120	180	300	600	<600
NF	0.5	10	2	2	3	2	1	—	—	—	—
	1.0	7	2	—	3	—	—	1	—	1	—
	Total	17	4	2	6	2	1	1	—	1	—
AF_1	0.5	15	5	2	—	3	2	1	—	1	1
	1.0	13	3	1	2	—	2	—	2	2	1
	Total	28	8	3	2	3	4	1	2	3	2
AF_2	0.5	6	4	—	—	—	1	—	—	1	—
	1.0	2	—	1	1	—	—	—	—	—	—
	Total	8	4	1	1	—	1	—	—	1	—

Table VI.

Intensity of myoclonic reaction.

Experiments with	Doses of monobromide of camphor in gr	Number of positive cases	I		II		III		IV		V	
			absol.	%	absol.	%	absol.	%	absol.	%	absol.	%
NF	0,5	10	2	20,0	2	20,0	—	—	4	40,0	2	20,0
	1,0	7	2	28,6	—	—	—	—	2	28,6	3	42,8
	Total	17	4	23,5	2	11,8	—	—	6	35,3	5	29,4
AF_1	0,5	15	5	33,3	3	20,0	1	6,7	3	20,0	3	20,0
	1,0	13	3	23,1	4	15,7	1	7,7	2	15,4	3	23,1
	Total	28	8	28,6	7	25,0	2	7,2	5	18,4	6	21,4
AF_2	0,5	6	1	17,7	1	17,7	1	17,7	1	17,7	2	33,3
	1,0	2	—	—	—	—	1	50,0	1	50,0	—	—
	Total	8	1	12,5	1	12,5	2	25,0	2	25,0	2	25,0

Resumé. Summarising the results of our experiments we see that the AF_1 and AF_2 animals are relatively more sensitive to picrotoxine intoxication than NF animals. The percentage of positive reaction after picrotoxine injection is in AF_1 and AF_2 animals higher than in NF animals (Table I) and this especially when minimal doses of picrotoxine necessary to produce myoclonic reaction — convulsions, are used. The greater sensitivity to picrotoxine intoxication in AF_1 and AF_2 than in NF animals is expressed also in the latent period of the reaction after picrotoxine injection, (Table II). In NF animals the maximum number of positive cases was observed in the second half of the first hour after picrotoxine injec-

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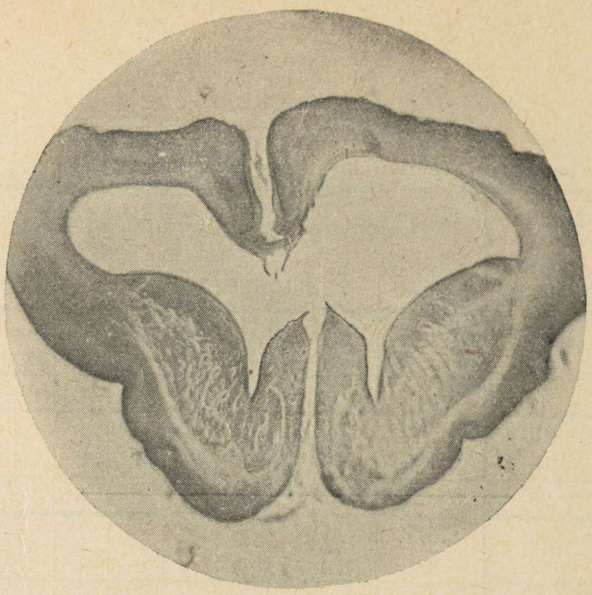

Fig. 9

tion, but in AF_1 and AF_2 animals the highest number of positive cases was observed in the first half of the first hour and never was a positive reaction observed later than two hours after injection. In NF animals the latent period was longer, once over three hours. The intensity of the myoclonic reactions (Table III) also expresses the higher sensitivity of AF_1 and AF_2 animals to picrotoxine intoxication. By using picrotoxine in doses of 1 mg per kg of body weight there was observed in NF animals only a slight myoclonic reaction and only by using higher doses of picrotoxine the strong myoclonic reaction was observed. In AF_1 and AF_2 animals a strong reaction was registered after using both 1,0 mg and 1,5 mg doses of picrotoxine per kg body weight.

In experiments with monobromide of camphor the results are not so clear. Also in these experiments there was registered in AF_1 and AF_2 animals more often a positive myoclonic reaction with a shorter latent period, but the differences are not so great as in the experiments with picrotoxine. An explanation of such difference, we suspect, is due to the slow absorption from oily solution. This finding expresses itself also in the latent period of reaction where sometimes a positive reaction was observed only after ten or more hours from the injection of monobromide of camphor.

Conclusions. 1) In intoxication by picrotoxine and monobromide of camphor with minimal doses for development of myoclonic reaction the offspring of the first and second generation of alcohol poisoned rabbits were more sensitive than the normal controls.

2) Alcohol-poisoning of parents seemed to be a factor in rendering the offspring of the first and second generation more susceptible to the development of convulsions through injury to the germ plasm.

3) Alcohol-poisoning of parents must be taken into consideration by the question of idiopathic epilepsy.

O.-Ü. „Noor-Eesti Kirjastuse“ trükikoda Tartus, 1938