Swabs and membrane of the tonsillar ulcer of each patient, together with his saliva, were rubbed onto the scarified cornea of a rabbit. None of the 12 rabbits developed the acute keratoconjunctivitis characteristic of an infection with the virus of Herpes Simplex,[1] or survived a challenge dose of this virus when given intracerebrally after an interval of about 3 weeks. Neutralization tests done with early and convalescent sera of these patients against a standard (HF) strain of herpes showed that those patients with absence of antibodies during the disease did not develop them in convalescence, while those with neutralizing antibodies in the acute serum did not show a rise of titer in the convalescent serum.

Technics. Those used for virus and for antibody studies were identical with standard methods as used by the authors in a previous study.[1]

Discussion. It has been shown that the common form of acute infectious gingivostomatitis as seen most frequently in children and occasionally in adults is due to a primary infection with the virus of Herpes Simplex. Since the etiology of this disease was in the past frequently ascribed to Vincent's organisms, although it is now known that it is caused by the virus of Herpes Simplex, a study was undertaken to determine whether the so-called Vincent's angina of the tonsil was also caused by this virus with the spirochete-fusiform combination acting as secondary invaders. In the 12 patients with Vincent's angina of the tonsil here studied, neither was the virus demonstrated in the membrane or saliva, nor did neutralizing antibodies against Herpes Simplex virus appear during convalescence. These facts, together with the striking effect of penicillin[2] in this disease, would negate any etiologic role of Herpes Simplex virus and is suggestive of a primary etiological role of the spirochetes themselves.

Summary. A study of 12 typical cases of Vincent's tonsillar angina showed that none of the cases were caused by an underlying infection with the virus of Herpes Simplex.

2 a. Denny, E. R., Stallenberger, P. H., and Pyle, H. D., *J. Oklahoma M. A.*, 1944, **37**, 193; b. Naegeli, F. C., and Morginson, W. J., *J. Am. Dental Assn.*, 1945, **32**, 1393; c. Shellenberger, P. L., Denny, E. R., and Pyle, H. D., *J. A. M. A.*, 1945, **128**, 706; d. Schwartz, B. M., *J. A. M. A.*, 1945, **128**, 704.

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Effects of Some Old and Proposed Anticonvulsants on the Threshold for Electrical Convulsions.

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Desirable improvements on diphenylhydantoin and other anticonvulsants in the treatment of epilepsy have stimulated the investigation of a large number of compounds with the hope of finding some agent which would prevent or mitigate epileptiform seizures without undesirable side effects.

Method. One of the methods used in these studies has been the production of epileptiform convulsions by passing an electrical current of varying amperage through the brains of animals. The threshold in milliamperes (m.a.) for each animal is determined before (control) and after the administration of the drug to be tested, the difference being considered a measure of the effectiveness of the drug as an anticonvulsant. The method has been described in detail by Spiegel,[1] Putnam and Merritt[2] and Tainter

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

2 Putnam, T. J., and Merritt, H. H., *Science*, 1937, **85**, 525.

and associates.[3] We used the technical arrangement described by Tainter and associates.[3]

In this arrangement, a high resistance stimulator and a 110-volt, 60-cycle, alternating current are used. In making a determination of cortical threshold, the transformer is set to give the voltage required for the desired m.a. of current, the electrodes (clamps) are clipped on the ears of the rats, and the stimulus is applied for exactly 10 seconds. In rabbits one electrode is applied to a bit in the mouth, and the other electrode to a small sponge-rubber pad resting on the clipped occipital skin moistened with saline solution. With currents below the threshold level there are generalized muscular contractions, synchronous with the current (tonic phase). At or above the threshold levels the tonic phase passes gradually into the clonic or epileptiform phase. The stimulation in rats is usually begun with a current of 6 m.a. (in rabbits, 14 m.a.), and is repeated at 5-minute intervals increasing the amount 2 m.a. each time until the threshold value is reached. This value remains practically unchanged for the purpose at hand, since it is reproducible within 1 to 2 m.a. when determinations are repeated at intervals of several days. Frequent, *e.g.*, consecutive daily, stimulations, however, tend to produce higher thresholds. Therefore, the animals are always allowed to rest 3 to 5 days before a drug is administered and the threshold redetermined. This procedure has been used routinely for several years in this department on hundreds of animals and with numerous drugs, and therefore, results, even with small groups of animals, are of significance in screening tests.

Employing this technic, a number of old agents and some proposed anticonvulsants were studied and the findings are reported in this paper. The test animals were chiefly adult white rats (total 185) with control thresholds ranging from 6 to 16 m.a. (average, 8 m.a.). A few rabbits (total 25; 3 to a drug) were used for intravenous injections. Their thresholds usually were higher than in rats, ranging from 14 to 28 m.a. (average, 18 m.a.), although the results with the drugs used were similar to those obtained in rats and are described together. The drugs were given by various routes ½ to 1 hour before redetermination of the threshold, a change in which was not considered significant when, because of individual variations, it did not exceed the control threshold by more than 10%. When drugs were given gastrically, food was withdrawn from those animals one day previously. In the majority of tests, 5 rats were used for each drug and each dose, and occasionally up to 20 were used. The results obtained in rats with compounds which gave positive anticonvulsant activity are given in Table I.

Positive Agents. Demerol (isonipecaine, meperidine or pethidine) and propazone[4] were found to be effective only in excessive doses, as was methyl-N-hexylhydantoin (Table I). Of the other new hydantoins* studied, only 2, namely, methyl-N-amylhydantoin and di-isobutyl-hydantoin, showed any promise, and of these the former was effective only in doses which caused slight but definite ataxia. There was less ataxia with higher doses of di-isobutyl-hydantoin, but there was more variability, suggesting that cortical excitability did not decrease proportionately with increase in dosage of the drug. In general, this drug seemed somewhat comparable to diphenylhydantoin.

Negative Agents. Tests were also made with the following drugs of the curare group: curare (2.5 to 5.0 mg per kg intramuscularly), β-erythroidine (10 to 400 mg per kg hypodermically; 50 to 800 mg per kg gastrically), dihydro-β-erythroidine (10 to 100 mg per kg hypodermically; 10 to 30 mg per kg intravenously) and quinine ethochloride (4 to 100 mg per kg hypodermically). These

[3] Tainter, M. L., Tainter, E. G., Lawrence, W. S., Neuru, E. N., Lackey, R. W., Ludueña, F. P., Kirtland, H. B., and Gonzales, R. I., *J. Pharm. and Exp. Therap.*, 1943, **79**, 42.

[4] Luton, F. H., Blalock, J., Baxter, J. H., Jr., and Stoughton, R. W., PROC. SOC. EXP. BIOL. AND MED., 1941, **47**, 245.

* Obtained from Dr. Melville Sahyun, Frederick Stearns & Co., Detroit, Mich.

TABLE I.
Effect of Various Agents on Thresholds for Electrical Convulsions.

Compound	No. of rats	Dose, mg/kg	Route of administration*	Mean change in threshold, m.a.†	S.E. of mean, m.a.†	Avg incr. in threshold, %	Remarks
Demerol	20	5-25	H	+0.6	±0.27	7	No or slight motor depression
"	4	50	H	+2.0	±0.55	28	Coma, fatal
Propazone	8	130-250	IP	+3.2	±0.53	43	Slight ataxia to coma
Diphenylhydantoin	5	40	G	0	±0.25	0	Asymptomatic
"	5	40	IV	+1.0	±0.50	10	"
"	4	100	IV	+3.3	±0.60	41	Slight motor depression
3-indolyl methylene hydantoin	14	100-400	IM	+0.4	±0.42	40	Asymptomatic
Methyl-N-hexyl hydantoin	5‡	25	IV & IM	0	±0.32	0	"
" "	5	50	IV & IM	0	±0.44	0	Motor depression
" "	5	100	IV & IM	+1.2	±0.82	15	" "
" "	10	200	IV & IM	+4.4	±1.45	55	Narcosis
Methyl-N-amyl hydantoin	5‡	50	H	0	±0	0	Asymptomatic
" "	5	50	G	+1.6	±0.71	20	Slight ataxia
" "	5	100	G	+2.4	±0.58	34	" "
" "	5	160	G	+4.4	±0.87	52	" "
" "	5	50	IM	+2.0	±0	25	Asymptomatic
" "	4	80	IM	+3.0	±0.55	37	Slight ataxia
" "	5	160	IM	+7.6	±0.70	95	Moderate ataxia
Di-isobutyl hydantoin	5	50	IM	+2.0	±0	28	Asymptomatic
" "	5	100	IM	+1.2	±1.00	15	Slight ataxia
" "	5	160	IM	+6.4	±0.75	80	" "

* G—gastrically; H—hypodermically; IP—intraperitoneally; IM—intramuscularly; IV—intravenously.
† Milliamperes.
‡ Rabbits.

drugs did not raise the threshold, except in excessive doses which caused incomplete paralysis, or convulsions. With asymptomatic doses thresholds were unchanged or even decreased (possible excitatory action of anoxemia). These results did not support the claim that the curare group of drugs exert a central depressant action.[5]

The beneficial effects of certain dyes on patients, reported by different authors,[6] suggested studies of these agents, but trials with hematoxylin (1.5 g per kg), congo red and vital red (each 50 mg per kg intravenously), neutral red, phenol red and methyl red (each 50 mg per kg intraperitoneally) resulted in no change in threshold.

Other agents which were found to be without anticonvulsant activity were ammonium thiocyanate (0.1 g per kg gastrically), magnesium sulfate (0.7 g per kg intraperitoneally), theophylline sodium acetate (50 mg per kg hypodermically) and glutamic acid (0.1 to 0.2 g per kg hypodermically). Voluntary drinking of dilute acid (0.5% HCl) and of dilute alkali (1% $NaHCO_3$ or 0.01% NaOH) for 6 days, in place of drinking water, also proved ineffective.

A decrease in threshold of about 30% was obtained by depriving rats for 6 days of either water or food or both.

Summary. Over 400 tests were made in 210 animals with 23 different agents on the threshold for electrical convulsions, chiefly in white rats; a few in rabbits. Of 3 new hydantoins studied, di-isobutyl-hydantoin was the most promising, being somewhat comparable to sodium diphenylhydantoin in high doses. Among the ineffective agents were 4 drugs of the curare group, alleged central depressants, and 5 different dyes, including hematoxylin and vital red, alleged antiepileptic agents.

5 Culler, E. A., *Proc. Am. Physiol. Soc.*, 1939, p. 56; Feitelberg, S., and Pick, E. P., PROC. SOC. EXP. BIOL. AND MED., 1942, **49**, 654; Harvey, A. M., and Masland, R. I., *J. Pharm. and Exp. Therap.*, 1941, **73**, 304; Pick, E. P., and Unna, K., *J. Pharm. and Exp. Therap.*, 1945, **83**, 59.

6 Cobb, S., and Cohen, M. E., *Arch. Neurol. Psychiat.*, 1938, **40**, 1156; Osgood, R., and Robinson, L. J., *Arch. Neurol. Psychiat.*, 1938, **40**, 1178; Aird, R. B., *Arch. Neurol. Psychiat.*, 1939, **42**, 700.

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Isopropyl Alcohol, Other Ketogens, and Miscellaneous Agents on Thresholds for Electrical Convulsions and Diphenylhydantoin

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The efficacy but impracticability of a ketogenic diet in the treatment of patients subjected to epileptic seizures suggested the use of products of fat and carbohydrate metabolism and related compounds. With this in mind, the following experiments were carried out.

Method. Clonic (epileptiform) convulsions were produced by passing an electric current for 10 seconds through the brains of white rats, according to a technic described in detail by Tainter and associates.[1] A summary of the essential features of this method, adapted to rats, is given in a previous paper by Chu and Driver,[2] and need not be repeated here.

The control threshold, which ranged from 6 to 16 milliamperes (m.a.) (average, 8 m.a.),

1 Tainter, M. L., Tainter, E. G., Lawrence, W. S., Neuru, E. N., Lackey, R. W., Ludueña, F. P., Kirtland, H. B., and Gonzales, R. I., *J. Pharm. and Exp. Therap.*, 1943, **79**, 42.

2 Chu, W. C., and Driver, R. L., PROC. SOC. EXP. BIOL. AND MED., 1947, **64**, 245.