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.

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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.

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TABLE I.
Isopropyl Alcohol and Ketogens on Thresholds for Electrical Convulsions and Diphenylhydantoin.

Compound*	No. of rats	Dose, mg/kg	Route of administration†	Hr before test	Mean change in threshold, m.a.§	S.E. of mean, m.a.§	Avg incr. in threshold, %
Acetone	5	1250	G	1	+ 4.4	±0.80	46
"	5	"	G	4	+ 1.2	±0.55	14
Acetophenone	3‡	"	G	1	+ 7.3	±0.60	87
Ethyl acetoacetate	5	"	G	1	+ 1.6	±0.75	15
Methyl alcohol	5	"	G	1	+ 4.4	±0.82	41
Ethyl "	5	"	G	1	+ 2.8	±0.80	26
Propyl "	5	"	G	1	+ 3.2	±1.10	26
Isopropyl "	5	"	G	1	+ 7.2	±0.85	82
" "	5	"	G	2	+ 4.8	±0.62	57
" "	4	"	G	4	+ 7.0	±1.40	75
" bromide	5	"	G	1	+ 2.8	±0.87	32
Diacetone alcohol	5	"	G	1	+ 4.8	±0.51	55
" glycol	5	"	G	1	+ 6.0	±0.65	71
Sodium diphenylhydantoin	5	40	G	1	+ 0	±0.25	0
" "	5	150	G	2	+ 1.2	±0.53	13
" "	5	40	IV	1	+ 1.0	±0.50	10
" "	4	100	IV	1	+ 3.3	±0.60	41
" "	4	40	IM	2	+ 0	±0	0
" "	5	100	IM	2	+ 1.0	±0.45	11
" "	5	150	IM	2	+ 2.0	±0.70	23
" "	5	40	G	1	+ 4.4	±0.42	40
+ ethyl alcohol		1250	G	1			
Sodium diphenylhydantoin	5	40	G	1	+12.2	±2.02	115
+ isopropyl alcohol		1250	G	1			

* An insoluble compound was administered as a suspension or emulsion.
† G—gastrically; IV—intravenously; IM—intramuscularly.
‡ 2 rats died.
§ Milliamperes.

was established for each rat at least 4 days before testing the effect of a compound. The substance was administered at a given time before the test, and the threshold redetermined. The difference in the thresholds so obtained was taken as a measure of the effectiveness of the medication, and, because of individual variations, had to exceed 10% to be considered significant. Food was withdrawn from all animals the night before the day of the test. The results (average % changes) including the standard errors (S.E.), with a number of positive agents and combinations are given in Table I. A total of 265 rats was used, in groups of 5 for each agent or combination in the majority of tests.

Isopropyl Alcohol and Other Ketogens. The results in Table I indicate that a number of compounds excelled sodium diphenylhydantoin as an anticonvulsant. Of particular interest were the compounds closely related to acetone in chemical structure. Of these, isopropyl alcohol, which exerted a tremendous anticonvulsant effect without ataxia or narcosis, proved to be one of the most promising. The dosage used, *i.e.*, 1250 mg per kg, was only about one-fourth the anesthetic dose. The animals were somewhat quieter than normals, but their reflexes and voluntary locomotion were preserved. Three months later all were alive and in good condition. The safeness of this agent for oral use has been reported by Harris.[3,4] Boughton,[5] comparing the relative toxicity of ethyl alcohol and isopropyl alcohol in rats given 5% solutions of these alcohols for 9 months, concluded that isopropyl was only slightly more toxic than ethyl alcohol. Lehman and Chase,[6] studying the acute and chronic tox-

[3] Harris, L. E., *Drug and Cosmetic Ind.*, 1944, **54**, 44.

[4] Harris, L. E., *J. Am. Pharmaceutical Assn., Pract. Pharm. Ed.*, 1944, **5**, 38.

[5] Boughton, L. L., *J. Am. Pharmaceutical Assn.*, 1944, **33**, 111.

[6] Lehman, A. J., and Chase, H. F., *J. Lab. and Clin. Med.*, 1944, **29**, 561.

icity of isopropyl alcohol given to, and drunk voluntarily by rats reported no evidence of delayed toxic effects and no suggestion of harmful intermediate products, while the acute effects were similar to those of ethyl alcohol. These reports are typical of many on the toxicity of isopropyl alcohol. Its superiority to ethyl alcohol as an anticonvulsant is, according to biochemical evidence, probably due to its partial transformation to acetone in the body.[7-11] This may also be the explanation of the beneficial effects of a ketogenic diet in epileptics, although, of course, the ultimate mechanism remains unsolved.

Beta-hydroxy-butyric acid and acetoacetic acid were not tried, but diacetone alcohol* (4-hydroxy-2-keto-4-methylpentane) and diacetone glycol* (2,4-dihydroxy-4-methyl pentane) were quite effective, while ethyl acetoacetate was slightly so. The difference in activity between isopropyl alcohol and acetone was possibly due to differences in rate of absorption and excretion.[7] Acetone, after 4 hours, caused only a small increase in the threshold, presumably because this agent was rapidly eliminated from the body due to its volatility. The positive effect of isoprophyl bromide could conceivably have been due to 2 things: (1) liberation of bromide and (2) formation of acetone. Acetophenone was quite effective but was too toxic because it caused fatalities. Aside from acetophenone, in this group of ketogens, only diacetone alcohol caused demonstrable ataxia.

Isopropyl Alcohol and Diphenylhydantoin Combined. Since the available evidence favored isopropyl alcohol as the least hazardous and most desirable of all the agents tested, it was tried in combination with diphenylhydantoin. A greater effect than summation of activity, perhaps a sensitization, was obtained by combining sodium diphenylhydantoin in doses of 40 mg per kg with isopropyl alcohol, given gastrically, because diphenylhydantoin itself caused no significant increase in threshold, while the combination of the 2 drugs exceeded considerably the depression caused by isopropyl alcohol itself (Table I). Ethyl alcohol, combined the same way, only moderately exceeded the threshold for the alcohol itself, thus indicating that isopropyl alcohol was more specific in this respect. Here again, raising of the cortical threshold with the combinations of isopropyl alcohol and diphenylhydantoin occurred without demonstrable evidence of ataxia or narcosis, and all the animals recovered. It is suggested that the isopropyl group (or isopropanol), in view of its relative nontoxicity and close correlation with the ketogenic mechanism, would seem to offer possibilities for developing new, or improving old, antiepileptic agents.

Ineffective Agents. The following compounds were found to be ineffective: the sugars—glucose, fructose, galactose, sucrose and triose (each 1.5 g per kg); the organic acids—lactic, pyruvic, acetic, propionic, butyric, palmitic, citric, malic, succinic, malonic and fumaric (each 0.5 g per kg); iodoacetic acid (0.02 g per kg); the alcohols—butyl, isobutyl and isoamyl (each 1.25 g per kg); insulin (2.5 units per kg), isopropyl ether and ethyl acetate (each 1.25 g per kg). All these agents were given gastrically, except insulin and iodoacetic acid, which were injected hypodermically.

Summary. The majority of certain compounds tried, and related in chemical structure to acetone, particularly isopropyl alcohol, were found to raise considerably the threshold for electrical convulsions in rats. Isopropyl alcohol increased the cortical depressant efficiency of diphenylhydantoin without demonstrable motor depression or narcosis. Some other alcohols and certain sugars and organic acids were ineffective. The possible significance of the isopropyl group

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* These and some other related agents were supplied by the Shell Development Co., Emeryville, Calif.

(or isopropanol) for benefits from ketogenic agents in epilepsy and for developing new or improving old antiepileptic agents is discussed.

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Hydropic Changes in Pancreatic Ductules and Islets in Alloxan Diabetes in the Rabbit.*

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Several investigators have described hydropic degeneration of the pancreatic islets and ductules in dogs rendered diabetic by partial pancreatectomy[1,2] and by anterior pituitary extracts.[3-5] In dogs made diabetic by alloxan, hydropic degeneration of islet cells has not been observed even in the presence of extreme vacuolation of the epithelium of the intralobular pancreatic ducts.[6] Hydropic changes have been observed in the islets of cats that had become diabetic following partial pancreatectomy[2] or treatment with anterior pituitary extract[7] but the pancreatic ductules were not affected. While such alterations in occasional islet cells have been described in rabbits treated with alloxan[8,9] the duct epithelium is said to remain normal.[10] The only description of alterations in the epithelium of pancreatic ductules in diabetic rabbits is that of Ogilvie[11] who found slight vacuolation of the lining cells of "newly formed" intralobular ducts in 1 of 28 rabbits treated with anterior pituitary extract. It is interesting, therefore, to report a high incidence of moderate to extreme hydropic degeneration of both the ductules and islets of the rabbit's pancreas following diabetes of long duration induced by alloxan.

Materials and Methods. Each of 56 white domestic rabbits obtained from several different dealers received intravenously 200 mg of alloxan (Eastman) per kg of body weight in a 5% aqueous solution. They were treated with protamine zinc insulin and glucose for a period of not more than 14 days following alloxan injection. In all of these animals and in a control group of 26 untreated rabbits, repeated determinations were made of fasting blood sugar and urinary sugar and acetone. Surviving animals of the experimental group were killed with corresponding control animals at various intervals up to one year after injection of alloxan.

Observations. Of the 56 rabbits treated with alloxan, 53 became persistently diabetic

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† Medical Research Fellow of the National Research Council, Canada.

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