muscle. Although the response of muscle to direct stimulation has commonly been described as due to the direct excitability of muscle fibers, it seems possible that the spread of the electrical pulse through the entire muscle may excite the nerve fibers which innervate it to play an important role in eliciting the response of muscle.

Separate experiments (unpublished data) have been carried out to determine the effect of curare upon the ability of the muscle to sustain responsiveness to faradic stimulation. If it were possible to completely block the myoneural junction without unfavorable effects upon respiration and circulation, the structures involved in the response to the stimulus could be further elucidated. Normal rats were given continuous subcutaneous injections of curare for periods up to 48 hours In these experiments curare did not affect work output in any dosage which did not cause respiratory failure. It was also shown that doses which failed to cause respiratory symptoms also failed to completely block the myoneural junctions in the stimulated muscle.

Summary. Male rats (310 to 350 g) were subjected to direct faradic stimulation of the gastrocnemius muscle following the cutting of the sciatic nerve, and their work performance was compared to that of sham-operated controls. When stimulation was started immediately following the operation the rate of work of denervated muscle was normal for several hours but was depressed below normal by 24 hours and continued to decrease rapidly, whereas the control animals sustained a high rate of work. When stimulation was delayed for 24 and 48 hours following denervation, the initial contractions were subnormal and decreased rapidly during continued stimulation. When the intensity of the pulse was increased from 12 to 20 milliamperes, at the end of each experiment there was a striking recovery in the rate of work of denervated muscle but it remained below that of the sham-operated controls.

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Rodenticidal Action of 2-Chloro-4-Dimethylamino-6-Methylpyrimidine (Castrix).*

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At the close of the European phase of the war it was revealed that German scientists had developed a new rodenticide (2-chloro-4-dimethylamino-6-methyl-pyrimidine) which was known as "Castrix." Since no data on the toxicity of Castrix were available in this country and no antidote against accidental poisoning in man and domestic animals was known the present investigation was undertaken to ascertain the toxicity of Castrix to several species, to examine its efficacy as a rodenticide, and to find an effective antidote for the treatment of accidental poisoning. The results of this preliminary study demonstrated the high toxicity of Castrix and the effectiveness of pentobarbital sodium as an antidote against Castrix poisoning.

Experimental. In all of the species examined Castrix produced symptoms typical of central nervous system stimulants. Convulsions occurred after a latent period of 15 to 45 minutes following either oral or intraperitoneal administration. The head retracted and the fore-legs and hind-legs were tetanically extended. After the tonic phase

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TABLE I.
Acute Toxicity of Castrix.

Species	Route of administration	$LD_{50} \pm$ S.E. (mg per kg)	No. of animals
Rat	Oral	1.25 ± 0.10	30
Rat	Intraperitoneal	1.00 ± 0.06	132
Mouse	"	0.42 ± 0.05	82
Guinea pig	"	2.66 ± 0.10	65
Rabbit	"	*ca.* 5	13
Dog	"	*ca.* 0.5	8

clonic movements spread over the entire body increasing in intensity for several seconds and then subsided. Several convulsive seizures occurred intermittently terminating with death after lethal doses or complete recovery after sublethal doses.

The high toxicity of Castrix† to 5 species is shown by the data in Table I. No differences in toxicity were observed when either aqueous or aqueous ethanol solutions (10% ethanol) were employed. A comparison of the toxicity of Castrix to 20 male and 20 female rats indicated that there was no sex difference in susceptibility. No evidence of tolerance was obtained when rats were given sublethal doses for varying periods and then given a lethal dose (2 mg/kg) of Castrix. The toxicity data shown in Table I were obtained during the summer months. Subsequent tests have shown some seasonal variation in the toxicity of this rodenticide to rats since the LD_{50} of Castrix to Sprague-Dawley rats increased to 2.5 mg/kg during the winter months.

To test the acceptability of Castrix when offered to rats in the food 3 groups, each containing 5 rats, were fed Wayne Dog Blox *ad libitum* and were then offered the same diet ground and mixed with varying amounts of Castrix. The acceptability and high lethality of Castrix offered in the diet are shown in Table II.

TABLE II.
Acceptability of Castrix to Rats.

% Castrix in diet	Mortality	Time of death (hr)
1.00	5/5	2
0.50	5/5	<12
0.25	5/5	<12

† We are indebted to Dr. J. R. Stevens of the Baker Chemical Co., Phillipsburg, N.J., for the Castrix used in these experiments.

The symptoms of Castrix poisoning suggested that anti-convulsants might be effective antidotes. Sodium pentobarbital (Nembutal) was chosen for the present studies. Since convulsions constitute the first observable sign of poisoning, an antidote would have no practical value in man and domestic animals unless it were effective when administered during or after the onset of convulsions. Therefore, in these experiments Nembutal was never administered until the first convulsion began in about 25 minutes after administration of the rodenticide.

The data in Table III show the antidotal action of Nembutal in Castrix-poisoned rats. It is apparent from these results that at least 10 LD_{50} doses of Castrix can be effectively counteracted by Nembutal. Since the animals which succumbed to 20 mg/kg of Castrix died in extreme central depression it is possible that more careful regulation of the dosage of the barbiturate might result in complete protection against 20 LD_{50} doses.

Preliminary experiments with dogs have shown that Nembutal is effective in counteracting at least 15 to 20 LD_{50} doses of Castrix. Since it was necessary to prolong the treatment for at least 13 hours when 10 mg/kg were given to dogs it appears that Castrix is detoxified more slowly in dogs than in rats.

Summary and Conclusions. A powerful convulsive agent, Castrix (2-chloro-4-dimethylamino-6-methylpyrimidine) is more toxic to rats than is either alpha-naphthylthiourea[1] or sodium fluoroacetate[2] by oral

[1] Richter, C. P., *J. Am. Med. Assn.*, 1945, **129**, 927.

[2] Kalmbach, E. R., *Science*, 1945, **102**, 232.

TABLE III.
Treatment of Castrix Poisoning in Rats with Sodium Pentobarbital.

Dose of Castrix (mg/kg)	No. of rats	Pentobarbital initial dose (mg/kg)	Schedule of pentobarbital treatment Hr after Castrix 1	1.5-2	3	6	% survival
5	5	45	30	20			100
5	5	45	30		20		100
10	5	45	30	30		30	100
20	5	30	30		15		60
20	5	30		30	20	15	60

and parenteral administration. Diets containing 0.25% to 1% of Castrix are readily eaten by rats and are highly toxic. No perceptible sex difference in susceptibility and no noticeable tolerance were observed in rats but some seasonal variation in susceptibility was noted. Sodium pentobarbital is an effective antidote against at least 10 LD_{50} doses of Castrix in rats and dogs even when administered after convulsions have begun.

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Lack of a Hypoglycemic Response to Intrathecal Injection of Glucose.*

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Marinelli and Giunti have recently presented data which clearly indicated that an increase in the glucose concentration of the spinal fluid of dog and man induced a rapid and pronounced reduction in the peripheral blood sugar level.[1] Lackey failed to obtain similar results in dogs.[2] In view of the paucity of evidence concerning the mechanisms whereby the central nervous system exerts its influence on the regulation of the blood sugar level, it was considered advisable to attempt to confirm the observations of Marinelli and Giunti in man. Consequently, we studied the influence of an increase in the cerebrospinal fluid glucose concentration on the blood sugar level.

Methods. Subjects suffering from a variety of cerebrovascular and psychiatric disorders were studied after a preliminary fast of approximately 12 hours. Samples of blood were obtained from the antecubital vein before and at intervals after the intrathecal injection of glucose. Spinal fluid samples were obtained throughout the period of observation by means of an inlying needle inserted into the lumbar subarachnoid space. Glucose was injected into the spinal fluid in quantities of 5 to 10 ml of a 5% sterile solution in distilled water (250-500 mg) by way of either the cisternal or lumbar routes. The glucose concentrations of both blood and spinal fluid were determined by the Nelson modification[3] of the Somogyi method.

Results. The data obtained in this study are listed in Table I. In no instance was there noted any significant change in the blood sugar level in spite of the marked increase in the cerebrospinal fluid glucose content. It will

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1 Marinelli, L., and Giunti, V., PROC. SOC. EXP. BIOL. AND MED., 1947, **65**, 23.

2 Lackey, R. W., *Science*, 1947, **106**, 618.

3 Nelson, N., *J. Biol. Chem.*, 1944, **153**, 375.