antibodies for these cells after the numerous infusions is indicative that the present donors will remain compatible with the sensitized dogs.

Inasmuch as dogs, for all practical purposes, are of the same group, so that any dog may be a suitable donor for another, the development of the incompatibilities in this species bears a striking similarity to the clinical picture obtained in some cases with humans. Wiener[6] states that "in cases where the same patient is to be given more than one transfusion, the cross match should be repeated before each transfusion, even if the same donor is used again. Several cases have been reported in which, although the first transfusion was successful, reactions took place during subsequent transfusions where the same donor was used. . . . . This subject has not been investigated thoroughly and deserves further study."

8473 C

Comparative Minimal Hypnotic Effects, Toxicity, and Pathology, Produced by Sodium and Magnesium Salts of Phenobarbital.

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Gilman and Barbour[1] have shown that the minimal hypnotic dose (M.H.D.) and the minimal lethal dose (M.L.D.) of magnesium phenobarbital when administered orally to rats are approximately 25 mg./kilo and 275 mg./kilo, respectively. According to the criterion of Issekutz[2] this would suggest a "hypnotic range" of 250 mg./kilo in the rat, or 10 times the M.H.D.

In a series of 232 rats we have found that when sodium phenobarbital and magnesium phenobarbital in freshly made 4% solutions are administered subcutaneously to rats in parallel experiments that there is no essential difference in the toxicity of either salt. The M.L.D. of both salts for rats by the subcutaneous route is close to 215 mg./kilo.

In dogs, the M.L.D. of both the sodium and the magnesium salts

1 Gilman, A., and Barbour, H. G., PROC. SOC. EXP. BIOL. AND MED., 1935, **32**, 1634.

2 Issekutz, B., *Therap. Monatshefte*, 1915, **29**, 379.

of phenobarbital, when administered orally, is in the neighborhood of 115 mg./kilo, and the M.H.D. of each salt is approximately 20 mg./kilo. However, in a series of 28 dogs a comparison was made of the minimal hypnotic response to the intravenous administration of both salts. By the intravenous route we found the M.H.D. to be 15 mg./kilo. No difference in degree of hypnosis was observed in dogs administered less than 30 mg./kilo, but at this dose level magnesium phenobarbital produced a more profound hypnosis than sodium phenobarbital. The dogs administered sodium phenobarbital would nod, or sleep lightly after onset of hypnosis, but were sensitive to noises and would come when called. On the other hand, the dogs administered magnesium phenobarbital would sleep soundly when left alone, and would neither come when called nor respond to noises of the same pitch and intensity as the dogs administered sodium phenobarbital. Further, the excitement state, manifested by struggle, muscular tremors, and rigidity appeared to be somewhat more depressed in the latter than in the former. The depressing effect of the magnesium ion as opposed to the stimulating effect of the sodium ion, when administered intravenously, may be a factor.

Twenty-eight dogs were used in comparative chronic toxicity experiments extending over a period of 60 days. Fourteen dogs of the group were administered daily doses of sodium phenobarbital by stomach tube and 14 dogs of the group were administered daily doses of magnesium phenobarbital in like manner. Details are shown in Table I. The tissues of dogs dying from chronic poisoning before the end of the 60-day period were examined histologically. One dog of each series that survived was sacrificed at the end of the period for histological studies. Although diffuse and diversified tissue changes were frequently observed in the tissues of dogs dying before the end of the experiment, all of the tissue changes observed could be explained on the basis of a profound vascular disturbance, and no constantly occurring lesion which might be characteristic of chronic poisoning by either the sodium or the magnesium salt of phenobarbital could be established in the nervous system or elsewhere.

Following the chronic toxicity experiments outlined in Table I, 7 dogs were administered orally by stomach tube 25 mg./kilo of sodium phenobarbital daily for 30 days, and 7 dogs were likewise administered 25 mg./kilo of magnesium phenobarbital for the same length of time. All dogs survived the 30-day period without constant weight loss or weight gain. Toward the end of the experiment it was evident that a marked degree of tolerance in both groups of

TABLE I.
Comparative Toxicity of Sodium Phenobarbital and Magnesium Phenobarbital when Administered by Stomach Tube in 4% Solutions.

Dose Sodium Phenobarbital mg./kilo	No. Dogs	Deaths
10	2	1 death in 28 days; 1 death in 30 days.
15	3	1 " " 26 " 2 dogs survived.
20	3	All dogs survived.
25	2	" " "
35	2	1 death in 5 days; 1 death in 10 days.
50	2	1 " " 3 " 1 " " 4 "
Dose Magnesium Phenobarbital mg./kilo		
10	2	All dogs survived.
15	3	1 death in 18 days; 2 dogs survived.
20	3	1 " " 16 " 2 " "
25	2	All dogs survived.
35	2	1 death in 4 days; 1 dog survived.
50	2	2 deaths in 3 days.

dogs had developed. At the end of the 30-day period 2 dogs of each group were taken off the drugs in order to study withdrawal symptoms. The withdrawal symptoms were essentially as described by Seevers and Tatum[3] in chronic experimental barbital poisoning, but the 4 dogs made a complete clinical recovery. The daily doses of the remaining dogs, 5 dogs of the sodium phenobarbital series and 5 dogs of the magnesium phenobarbital series, were raised to 35 mg./kilo. After 4 days the daily doses of each series were increased to 50 mg./kilo, which was survived by all dogs in both series for 14 days. In Table I it is shown that none of the 4 dogs survived the initial 50 mg./kilo dose for over 4 days. None of the dogs survived in either group when an attempt was made to build up the tolerance of the animals beyond the latter dose level.

Conclusions. There is no essential difference in the toxicity of the sodium and magnesium salts of phenobarbital when administered orally to rats and dogs. When magnesium phenobarbital is administered intravenously to dogs in doses of 30 mg./kilo it produces a more pronounced hypnotic effect than sodium phenobarbital likewise administered at the same dose level. It is apparent that the additive depressing effect of the magnesium ion, as opposed to the stimulating effect of the sodium ion, is responsible for the difference in degree of hypnosis of the 2 salts. No such effect was observed when the 2 salts of phenobarbital were administered orally.

[3] Seevers, M. H., and Tatum, A. L., *J. Pharmacol. and Exp. Therap.*, 1931, **42**, 217.

In a final paper it will be shown that while the nervous system and other tissues of dogs dying from chronic phenobarbital poisoning contains no constantly occurring lesion typical of phenobarbital poisoning, phenobarbital produces a profound vascular disturbance in those tissues. In dogs a marked degree of tolerance to phenobarbital may be built up. After a period of pronounced irritability and sleeplessness, following withdrawal of the drug, clinical recovery takes place. The question of whether histological recovery parallels clinical recovery remains to be studied.

8474 C

Inoculation of Mice with Poliomyelitis Virus.

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Nungester[1] demonstrated that when poliomyelitis virus was combined with mucin and injected intraperitoneally into 76 mice, death occurred in 22, muscular weakness in 13 and flaccid paralysis in 2 animals. The brains and cords of 12 of the 22 mice that died and 7 controls were examined by Weil.[2] In 2, the picture seen closely resembled the histopathology found in *M. rhesus* monkeys that died of poliomyelitis. These results were sufficiently important to encourage further work along the same line.

Commercial gastric mucin powder was sterilized dry by autoclaving, a 5% emulsion prepared and used as a diluent to make up a 2% suspension of potent poliomyelitis virus. All injections were made the same day that the mixture was prepared and each mouse received 1 cc. intraperitoneally. The results are tabulated in Table I. In controls, the diluent was either normal saline, normal cord in mucin, or mucin in saline. In one group, the diluent for the mucin and virus was convalescent poliomyelitis serum.

All mice of group I that died following the inoculation of virus and mucin showed a small amount of clear, straw-colored fluid in the peritoneal cavity. The upper part of the small intestine was swollen and yellow reddish brown in color. There was slight or

* Crile Fellowship Scholar.

1 Nungester, W. J., PROC. SOC. EXP. BIOL. AND MED., 1933, **30**, 1128.

2 Weil, W., PROC. SOC. EXP. BIOL. AND MED., 1933, **30**, 1242.