were sacrificed and the thyroids removed. The tissue was fixed, embedded in paraffin, and the sections stained with haematoxylin and eosin for histological study. The sections were cut in such a manner that from each of the 3 thyroids a portion of the parathyroid gland was included.

Results. Photomicrographs of the sections from the control, 10 μc, and 50 μc studies are shown in Fig. 1, 2 and 3 respectively. At the 10 microcurie dosage level it is apparent that there was a marked degree of injury to the thyroid follicles as evidenced by their diminished size, loss of colloid, and increase in size of the follicular epithelium, Fig. 2. The general thyroid architecture is distorted to such a degree that it would seem probable that in this instance the degree of radiation injury approached a level of being totally irreversible even if a recovery period of from six months to a year had been allowed. The adjacent parathyroid tissue did not reveal any observable changes that would suggest radiation injury to this organ. The thyroid tissue in the rat which received 50 microcuries of astatine^{211} is not recognizable as such. Here there is complete obliteration of the follicles, colloid, and follicular epithelium. The thyroid tissue has been replaced by fibrous tissue with some infiltration of lymphocytes and fat cells. In this instance it appears that a complete and irreversible destruction of the thyroid gland took place, as a result of an extreme degree of radiation injury. It is significant to note that there was no histological evidence of manifest radiation injury in the adjoining parathyroid tissue.

Summary. The results from this preliminary study demonstrate the capacity of astatine to induce an extreme degree of radiation injury of the thyroid gland in the rat without apparent involvement of the adjoining parathyroid gland.

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Prevention of Procaine Convulsions by Presidon and Sodium Pentobarbital. (17573)

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While the use of procaine is extensive and relatively safe, an occasional subject is found sensitive to the drug. The toxic reactions to subcutaneous procaine are caused by stimulation of the central nervous system resulting in restlessness and tremors which may proceed to convulsions. There is also an initial period of respiratory stimulation followed by depression of the medullary centers resulting in dyspnea and respiratory collapse. The use of hypnotics in the prevention and treatment of toxic reactions to local anesthetics is based on animal studies which show that hypnotics, especially the barbiturates, depress the convulsive effects of local anesthetics.(1,2) Presidon (Pyrithyldione; 3,3-diethyl-2,4-dioxotetrahydropyridine) is a relatively short acting hypnotic with a wide margin of safety.(3,4) It was shown to inhibit the convulsions produced by caffeine,(3) picrotoxin and Metrazol.(4) It was found to be an effective hypnotic in human subjects.(5) We have extended the studies on the anticonvulsive properties of Presidon to the prevention of pro-

1. Tatum, A. L., Atkinson, A. J., and Collins, K. H., *J. Pharm. and Exp. Therap.*, 1925, v26, 325.
2. Knoefel, P. K., Herwick, R. P., and Loevenhart, A. S., *J. Pharm. and Exp. Therap.*, 1930, v39, 397.
3. Krautwald, A., Kuschinsky, G., and Riedel, H., *Arch. Exp. Path. Pharmacol.*, 1939, v193, 219.
4. Koppanyi, T., Herwick, R. P., Linegar, C. R., and Foster, R. H. K., *Arch. intern. pharmacodynamie*, 1940, v64, 123.
5. Freed, S. C., *J. Lab. and Clin. Med.*, 1946, v32, 895.

caine convulsions in various species. The comparative hypnotic and anticonvulsive properties of Presidon and pentobarbital have been determined in mice, guinea pigs, rabbits and dogs. Similar studies in rats were abandoned because of the high resistance of the rat to procaine intoxication.

Methods. The convulsive dose of procaine administered subcutaneously was determined for each species. The toxic symptoms included excitability, nervousness, tachycardia, dyspnea, clonic convulsions and terminal respiratory failure. In addition, rabbits and guinea pigs displayed opisthotonos and tonic extension of the limbs; tonic extension was common to the dogs as well. The dose which produced these toxic effects in 95% of the animals was calculated from a log dose-probit graph and the standard errors also calculated.(6) The hypnotic dose for pentobarbital and Presidon administered intraperitoneally was determined as the dose which produced sleep in 50% of the animals. The endpoint of hypnosis was the loss of righting reflexes *i.e.* the animal was unable to right itself when placed on its side. The hypnotic doses and standard errors were calculated by the probit method.(6) The protective doses of pentobarbital and Presidon were determined as the doses which prevented convulsions in 50% of the animals which had received the 95% convulsive dose of procaine. The hypnotic drugs were given intraperitoneally 10 minutes prior to the subcutaneous administration of procaine. The endpoint was the prevention of the convulsive movements in the various species. The protective doses were calculated by the graph probit method.(6)

In order to compare the relative effectiveness of pentobarbital and Presidon, protective indexes were calculated as the ratio of the hypnotic dose to the protective dose.

Results. The results summarized in the table show that Presidon in comparison with pentobarbital administered intraperitoneally is an effective anticonvulsant. The protective index for Presidon is higher than for pentobarbital in the four species studied. The dose

TABLE I.
Hypnotic and Anti-convulsant Effects of Presidon and Pentobarbital.

Treatment		Mice, mg/kg	Guinea pigs, mg/kg	Rabbits, mg/kg	Dogs, mg/kg
Procaine HCl	Convulsive dose—CD95 ± s.e.	1000 ± 250	140 ± 8.0	225 ± 20.3	410 ± 62
Pentobarbital sodium	Hypnotic " —HD50 ± s.e.	38 ± 3.2	6.5 ± 1.2	11.3 ± 1.2	5.1 ± 5.0
Presidon	" " —HD50 ± s.e.	178 ± 3.6	87 ± 4.4	87 ± 12.2	35 ± 14
Pentobarbital sodium	Protective " —PD50 ± s.e.	40 ± 12.0	2.95 ± 1.6	5.5 ± 2.1	2.9 ± 0.6
Presidon	" " —PD50 ± s.e.	42 ± 18.5	28 ± 14.6	22.5 ± 14.8	13 ± 1.5
Pentobarbital sodium	" index—HD50 / PD50	95	2.2	2.06	1.75
Presidon	" " —HD50 / PD50	4.2	3.1	3.7	2.70

Procaine was administered subcutaneously; pentobarbital and Presidon were administered intraperitoneally.

6. deBeer, E. J., *J. Pharm. and Exp. Therap.*, 1945, v85, 1.

of Presidon which protects mice from procaine convulsions is about one-fourth the hypnotic dose but the protective and hypnotic doses of pentobarbital are almost identical. In the other species the protective dose of Presidon is about one-third the hypnotic dose whereas the protective dose of pentobarbital is about one-half the hypnotic dose. There is large species variation in the sensitivity to procaine convulsions and also to the hypnotic and anticonvulsive potency of pentobarbital and Presidon. The mouse is most resistant to both procaine and the hypnotics. The dog is more resistant than the guinea pig or rabbit to procaine convulsions but is most sensitive to the hynotics. The smallest protective doses of the hypnotics were required by the dog.

Discussion. In cases of procaine intoxication, there is an initial period of respiratory stimulation which is followed by depression which may lead to terminal respiratory failure(2,7,8). Most deaths following the subcutaneous administration of procaine were caused by respiratory failure even though, in some instances, the convulsions had been controlled.(9,10) In view of the strong depressant action of the barbiturates upon respiration, it would seem more feasible to employ a prophylactic drug which could abort the convulsive effects of procaine HCl without causing additive effects on the already depressed respiration. Presidon and pentobarbital have been compared as central nervous system depressants using hypnotic activity as an index. That Presidon has a wider margin of safety than representative barbiturates has been previously reported.(3,4) It is important to note that pentobarbital confers protection against the convulsive effects of procaine HCl only in doses which are considerably more depressant than equally protective doses of Presidon. It would seem, therefore, that the ability of a drug to prevent local anesthetic intoxication does not parallel its degree of depressant action on the central nervous system.

Summary. Presidon and pentobarbital administered intraperitoneally, prevent the convulsions produced by procaine in dogs, rabbits, guinea pigs, and mice.

Presidon confers protection against the convulsive effects of procaine at one-fourth to one-third the hypnotic dose, whereas the protective dose of pentobarbital is from one-half to the full hypnotic dose.

7. Dragstedt, C. A., and Long, V. F., *J. Pharm. and Exp. Therap.*, 1928, v32, 215.

8. Beutner, R., *Anesthesia and Analgesia*, 1943, v22, 121, 205.

9. Mayer, E., *J. A. M. A.*, 1928, v90, 1290.

10. Martin, E. G., *J. A. M. A.*, 1928, v91, 555

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Relationship of Type of Growth of *M. tuberculosis* to Antituberculous Activity of Subtilin.*† (17574)

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In the course of an investigation of the antimicrobial activity of subtilin it was observed that although this substance possessed a high degree of inhibitory activity on tubercle bacilli *in vitro*, it failed to afford protection to mice experimentally infected with tuberculosis,

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