anoxia, b) that the temporary anoxia produced by large doses of cysteine can explain only partially the radioprotective action of the substance.

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Effect of Chlorpromazine on Emesis after Radiation. (21076)

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Radiation sickness is an ever present danger when ionizing radiations are employed for diagnostic, therapeutic, or experimental purposes. The importance of this syndrome clinically is abundantly evident from the impressive number of references in the radiological literature. Nausea and vomiting are among the most characteristic symptoms of this disorder and numerous medications have been employed for their relief with equivocal results. Various antihistamines(1,2), vitamin (3), and hormonal(4,5) preparations, as well as other miscellaneous compounds(6,7,9) have been advocated. Recently, (dimethylamino-1-n propyl-3) - N - (2-chloro) - phenothiazine HCl (chlorpromazine) has been reported to give striking relief of nausea and vomiting in a large series of clinical patients(9). To our knowledge, no preparation has been shown to protect animals from vomiting after irradiation. In fact, such protection has only been reported(10) after destruction of the chemoceptive trigger zone described by Borison and Wang(11). Since chlorpromazine protects dogs against other emetic stimuli acting upon this area (apomorphine(12), hydergine(13), motion(14)), it was of obvious interest to test its effectiveness against radiation emesis as well.

Methods. As controls, 12 normal mongrel dogs, weighing from 7 to 13 kg, were fed commercial dog food and 30 minutes later irradiated with 800 r. A Picker deep therapy x-ray unit was employed with 260 KVP and 18 MA. The external filtration was 1 mm Al and 0.50 mm cu plus 0.25 mm cu inherent filtration. The target-to-object distance was 118 cm and the dose rate 13 r/minute in air. The dog received half the radiation dose on one side of the body, at which time he was turned and given the remainder of the dose. After irradiation, the dogs were observed from 4 to 6 hours, unless vomiting occurred earlier. Another group of normal dogs within the same weight group received subcutaneously 5 or 10 mg of chlorpromazine†/kg body weight freshly prepared in 0.9% saline. They were immediately fed and 30 minutes later irradiated with 800 r as described above. On one occasion, a solution of chlorpromazine was not used for 2 hours, during which time it assumed a slightly brown color. To test the effect of such standing, 5 dogs received 10 mg/kg of a chlorpromazine solution allowed to "age"

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TABLE I. Radiation Emesis in Dogs after Chlorpromazine or Cysteinamine.

Medication	Dose, mg/kg	Dogs vomiting/dogs tested	Latent vomiting period after radiation (min.)	Survival (days)
0	—	12/12	32.4	3.8
Chl.*	10	2/10	72.5	5.7
" ("aged")	10	4/ 5	66.2	5.8
"	5	4/ 5	69.8	4.3
Cys.* (before rad.)	200†	5/ 5	25.0	5.0
" (after ")	"	4/ 5	22.3	5.2
" (during ")	"	8/11	55.1	6.2

* Chl. = Chlorpromazine; Cys. = Cysteinamine.
† Total dose given to all dogs regardless of weight.

for 2 hours at room temperature in an open flask. Since cysteinamine has been reported to control vomiting clinically after x-ray therapy(8), it was included in the present investigation for comparative purposes. Its ability to prevent vomiting in animals has not been previously investigated. At first 5 dogs received 200 mg of cysteinamine‡ intravenously immediately prior to the start of irradiation. Injection at this time has been shown(15) to allow greatest survival in smaller animals. The duration of action of cysteinamine is short and injections *after* irradiation have failed to increase or prolong animal survival. Nevertheless, clinically, intravenous injections have been reported to relieve or eliminate the symptoms (vomiting, nausea, diarrhea, etc.) resulting from prior irradiation. For this reason, a second series of dogs(5) were given 200 mg of cysteinamine intravenously immediately *after* irradiation. Finally, a third group(10) received the same dose intravenously *during* irradiation. The dogs received 400 r whole body radiation, were injected with cysteinamine and then immediately received the remaining 400 r. It was hoped by these variations in timing that optimal conditions would be realized in one group.

Results. The relative effectiveness of the various preparations is compared in Table I. It can be seen that freshly prepared chlorpromazine (10 mg/kg of body weight) affords good protection against vomiting after irradiation. All controls vomited within 2 hours after radiation was completed and 9 of the 12 within 30 minutes. With chlorpromazine, only 2 out of 10 vomited, one after 56 and the other after 89 minutes. However, when the solution of chlorpromazine in saline was allowed to stand for 2 hours before injection, all but one dog vomited after radiation although the latent vomiting period was increased. The lowered dose of chlorpromazine (5 mg/kg) gave almost identical results, with little, if any, protection against vomiting but an apparent increase in the latent period. Cysteinamine given before or after 800 r x-radiation neither prevented nor delayed the vomiting beyond that of the controls. However, of 11 dogs receiving cysteinamine immediately interposed between 2-400 r exposures, 3 failed to vomit and the average latent vomiting time of the remaining animals was increased.

The apparent increased survival times with both chlorpromazine and cysteinamine is suggestive, but the series are too small to permit conviction on this point.

Discussion. The effective dosage of chlorpromazine used here was larger than that necessary to prevent vomiting in dogs after the injection of apomorphine(16,17), ergot(16), or after swinging(17). As has been pointed out previously(9,16,17), subcutaneous injections of 10 mg/kg produces some degree of depression. This raises the question whether the protection noted was due to a specific effect on the chemoceptive emetic trigger zone or a non-specific effect due to depression of the vomiting center. Glaviano and Wang(13) have pointed out that 2.0 mg/kg or more of chlorpromazine significantly increases the threshold to oral $CuSO_4$. This indicates a depression of the reticular vomiting mechan-

‡ Generously supplied by E. R. Squibb & Sons, New Brunswick, N. J.

ism. It is probable, therefore, that the doses employed in the present study produced some central depression. Whether this depression was adequate to account for the decreased sensitivity to radiation cannot be stated. However, preliminary results utilizing other depressants have failed to demonstrate a comparable protection against radiation vomiting. The lowered effectiveness of solutions allowed to stand for 2 hours is not in accord with reports on its stability for 24 hours(9). No explanation is available for this discrepancy.

The apparent increase in survival time after chlorpromazine requires confirmation with larger series of animals. Studies with mice and guinea pigs have failed to confirm this prolonged survival following x-radiation(18). Additional dogs have not yet been studied.

Summary. Chlorpromazine-(dimethylamino-1-n propyl-3) - N - (2-chloro) - phenothiazine HCl in doses of 10 mg/kg injected subcutaneously protected dogs against vomiting after 800 r x-radiation. Injections of 5 mg/kg were ineffective as were 10 mg/kg prepared from solutions allowed to stand for 2 hours at room temperature before injection. Cysteinamine (200 mg intravenously) had no or questionable protection whether given before, during, or after radiation. Increased survival time was noted with both chlorpromazine and cysteinamine. The mechanism of protection is discussed.

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Esterification of Soybean Sterols *in vitro* and their Influence on Blood Cholesterol Level. (21077)

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It has been reported recently(1,2) that the feeding of soybean sterols to rats resulted in a lowering of the blood and lymph cholesterol. The decrease was mainly in the ester fraction. An explanation offered(2) for these effects is that the plant sterols interfere with the esterification of cholesterol in its passage from the lumen of the intestine to the lymph. In connection with studies being carried out in these laboratories it has been demonstrated that the enzyme cholesterol esterase and bile salts play an important role in the esterification of cholesterol and in cholesterol absorption(3,4). It became of interest to determine