cause of current interest in these substances, and because little if any report of animal studies has appeared in the American literature. A report of results with an older type of dextran has appeared(3). The Swedish dextran has been stated to cause no lesions in animals(2), and we found very little effect. The lesions observed by us following periston injections are of the type and order of magnitude already reported. The foam cell accumulations caused by periston are said to disappear after several weeks(4). Periston in our material did not cause the arterial alterations, in addition to foam cell storage, noted with some previously tried plasma substitutes(5).

Summary. Seventeen rabbits were each given 16 intravenous injections of 10 cc/kg of one or another plasma substitute over a 2-month period. The solutions used were 6% dextran in distilled water, 3½% periston (polyvinylpyrrolidone) in distilled water, and 10% dextrose in physiological saline solution. No effects of treatment on behavior or body weight were noted. At autopsy, there was slight enlargement of the spleen, on the average about 70%, in the periston animals. Kidney and liver weights were not affected except for a possible slight increase in kidney weight with dextrose. On detailed microscopic examination, the one outstanding lesion was a foam cell storage of periston or some near derivative. Certain other and minor lesions were caused by periston and dextran, and none by dextrose.

3. Goldenberg, M., Crane, R. D., and Popper, H., *Am. J. Clin. Path.*, 1947, v17, 939.

4. Barfuss, F., and Eichler, O., *Arch. f. exp. Path. u. Pharm.*, 1949, v206, 346.

5. Hueper, W., *Arch. Path.*, 1942, v33, 267.

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Chronic Toxicity of a Purified Extract of *Veratrum viride*.* (18627)

JAMES GOURZIS AND ROBERT O. BAUER. (Introduced by George L. Maison)

From the Department of Pharmacology, School of Medicine, Boston University.

Examination of available literature failed to reveal long term chronic toxicity studies on *Veratrum viride* or its extracts. Perdue *et al.* (1) reported a short term (8 week) paired feeding study using powdered root of *Veratrum viride* in Long-Evans rats. They concluded severe toxicity was not encountered until about 3% was included in the diet, and that the toxicity could be related to inanition.

Since clinical use of veratrum preparations in the treatment of hypertension requires the ingestion of the drug over a period of years it seemed desirable to observe the effects of feeding this drug over 12 months to rats and dogs. The use of the purified extract of *Veratrum viride* (Veriloid†) for the present study offered the first opportunity to feed mixtures of hypotensive potency known to be uniform(2).

Method. Rats: Albino rats (Wistar Strain), 30 days of age, weighing 64.6 ± 12.9 g were divided into 5 groups of 30 (15 females and 15 males) animals. The rats were fed a modified Steenbock's diet(3) and water *ad libitum*. The drug was incorporated in the diet of the first 4 groups while the fifth group served as the control. In 3 of the experimental groups (low, medium and high dose) the drug concentration was gradually increased over a 4- to 10-week period until 7.3, 11 and 19 mg % had been attained in the respective diets. The fourth group (intensive group) were, from the beginning, given diet

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1. Perdue, Adaline S., Bell, Francis, Stearnes, W. R., Hitchcock, Philip and Teague, R. S., *J. Am. Pharm. A.* (Scient. Ed.) 1950, v39, 91.

† Trademark of Riker Laboratories, Los Angeles, Calif. A purified reproducible hypotensive extract of *Veratrum viride* assayed in the dog.

2. Maison, G. L. and Stutzman, J. W., *Arch. internat. de pharmacodyn. et de therap.*, 1951, v85, 357.

3. Steenbock, H., *Science*, 1923, v58, 449.

such that the daily dose of drug would be in the region of the acute oral LD50 for the rat (12.25 (10.6-14.2) mg/kg)(4). During the first 6 months this latter group ate a diet containing 11 mg % of drug and during the last 6 months the diet contained 19 mg %. Body weight, food and drug consumption, appearance and behavior of the rats were recorded weekly. Complete blood counts and hemoglobin determinations were recorded for ⅓ of the animals in each group before the experiment, at six months and at termination. Dogs: Mongrel dogs (8 female and 7 male), weighing 9.8 ± 2.4 kg (between 6.8 and 15.4 kg), separately caged, were given 15 g/kg ground horse meat three times daily and allowed water *ad libitum*. After a 28-day control feeding period the standard Veriloid powder was incorporated into the diet of 12 animals while 3 continued as controls. The diet was prepared fresh for each meal, the drug being mechanically dispersed through the meat. The quantity of Veriloid added to each meal was determined on the basis of the individual animal's recent history of emesis and diet refusal. Daily recording of food and drug consumption, incidence of emesis and the general behavior of the dog were made. The animals were weighed weekly. Complete blood counts, hemoglobin determinations, routine urinalysis and serum bilirubin values were obtained during the control period, at six and twelve months. A female and two males were maintained as dietary, weight and pathological controls.

Pathologic examination. At 6 months, 25 rats (5 animals from each group) and 5 dogs (1 female control, 2 female and 2 male Veriloid fed dogs) and at twelve months 36 surviving rats and 7 dogs (1 male control, 1 male and 5 female Veriloid fed dogs) were sacrificed‡ for macroscopic and microscopic examination. Weights of the body, brain, lungs, heart, liver, spleen, kidneys and testes were recorded. Histologic sections of the following organs were made at random: brain, lung, heart, liver, pancreas, adrenals, spleen, gastro-intestinal tract, kidneys, testes, ovaries, sternum, muscle, skin and thymus.

Results. Rats: A progressive failure to gain weight (depressed growth) resulted in the 4 experimental groups ingesting graded doses of Veriloid (Fig. 1). Food and drug consumed and mortality in the 4 experimental groups as well as the control groups are recorded in Table I. In the experimental groups, almost three-quarters of the mortality occurred in the first 12 weeks during which time the animals were in their active phase of growth. Animals dying in the drugged and control series were indistinguishable. These animals stopped eating, lost weight, lost the pink ear color; their coats became shaggy and unkempt. Death followed in a few days.

Dogs. The animals fed the drug lost weight during the first 6 months of the experiment, (from 10.0 ± 2.0 kg to 8.0 ± 2.2 kg). During the second 6 months greater care was taken to reduce emesis and food rejection by individual dosage control. At the conclusion of 12 months the 5 surviving dogs had recovered and exceeded their starting weight. The 3 control dogs consistently

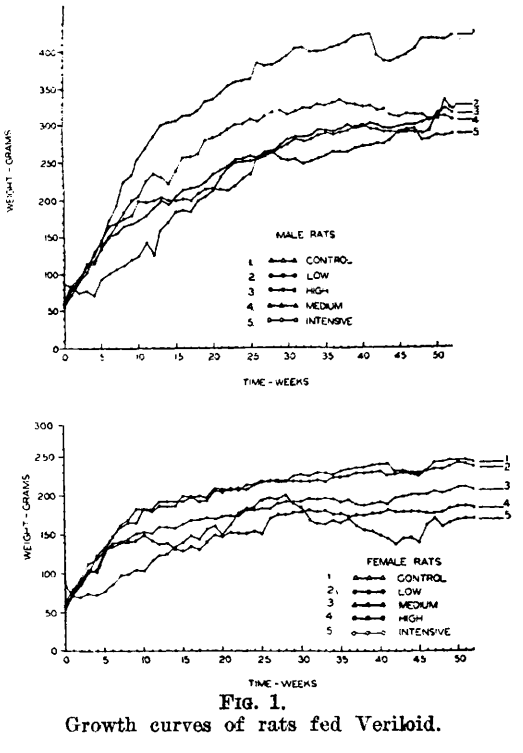

FIG. 1.
Growth curves of rats fed Veriloid.

4. Bauer, R. O., *Fed. Proc.*, 1950, v9, 1.

‡ Dogs sacrificed by exsanguination during pentobarbital anesthesia, rats by guillotine.

TABLE I. Summary of Weight, Mortality, Food and Drug Intake of Rat Groups Fed Veriloid for 12 Months.

Group	Sex	Start		1st 6 mo.			2nd 6 mo.					
				No. animals			No. animals					
		No. animals	Mean wt S.D., g	Dead*	Surviving	Mean wt with S.D. (g)	Dead*	Surviving	Mean wt with S.D. (g)	Drug in diet, mg %	Mean food intake and S.D., g/rat/day	Mean drug intake and S.D., mg/kg/day
Control	M	13	55 ± 6	4	9	364 ± 25	0	7	424 ± 17	—	15.2 ± 2.4	—
Low	M	16	63 ± 9	3	13	308 ± 22	1	9	323 ± 74	7.3	13.5 ± 1.7	3.2 ± 0.2
Medium	M	16	61 ± 6	2	14	258 ± 51	0	12	311 ± 52	11	12.5 ± 1.6	5.0 ± 1.2
High	M	16	59 ± 4	3	13	233 ± 44	1	10	319 ± 32	19	11.9 ± 1.6	8.0 ± 2.4
Intensive	M	15	87 ± 2	13	2	252 ± 14	0	2	291 ± 11	11–19†	14.9 ± 4.2	10.2 ± 2.1
Control	F	16	56 ± 9	1	15	219 ± 14	1	11	249 ± 24	—	12.0 ± 1.3	—
Low	F	13	65 ± 11	1	12	218 ± 23	0	10	244 ± 28	7.3	10.6 ± 0.9	3.2 ± 0.2
Medium	F	14	60 ± 5	1	13	187 ± 27	1	9	211 ± 19	11	10.7 ± 1.0	5.9 ± 1.6
High	F	14	60 ± 4	7	7	151 ± 28	0	4	189 ± 62	19	9.8 ± 1.7	9.9 ± 3.2
Intensive	F	17	83 ± 1	11	6	196 ± 8	4	2	175	11–19†	10.8 ± 2.9	10.5 ± 3.0

* Does not include rats sacrificed for pathologic section.
† Explanation in text.

gained weight during the period of observation (2 for 6 months, 1 for 12 months). In general the daily food consumption was smaller and more variable for the drugged than for the control dogs (Table II).

Pathologic findings. Macroscopic or histologic changes attributable to Veriloid administration were not observed. Liver changes were seen in both control and experimental rats and dogs. These consisted of peri-portal round cell infiltration and portal congestion. Thickening of pulmonary alveolar walls by round cell infiltration was observed in sections from control as well as drugged rats and dogs. These changes were regarded as non-specific inflammation. All other organs observed displayed normal histologic structure. Organ weights of the experimental animals did not differ significantly from those of the controls. There were no hematologic or urinary abnormalities at six or twelve months.

Discussion. The graded depression of the weight-growth curves of the rats resulting from graded doses of Veriloid suggested the presence of chronic toxic properties in the drug. The failure to show progressive pathologic changes with increasing doses implies that these toxic properties are non-specific.

These findings are in accord with the hypothesis of deficient nutrition advanced by Perdue *et al.*(1). The lower food consumption of the drugged animals is concordant. In the dogs the failure to eat was correlated with occurrence of emesis and in the dogs which died severe inanition preceded death.§

The mean daily drug intake of the several groups of rats (low, medium, high and intensive) approximated 30, 50, 80 and 100 times the average daily dose/kg for patients as reported by Wilkins *et al.*(5). These data then suggest a respectable margin of safety for the agent. Excessive quantities of the drug apparently would be required to produce this non-specific toxicity in man and the produc-

§ This statement describes all cases except No. 4A which died after only 3 weeks exposure to drug. Post mortem was not obtained because of autolysis.

5. Wilkins, R. W., Stanton, J. R., Freis, E. D., PROC. SOC. EXP. BIOL. AND MED., 1949, v72, 302.

TABLE II. Summary of Weight, Mortality, Food and Drug Consumption in Dogs Fed Veriloid.

Dog	Wt, kg: Control	6 mo.	12 mo.	At death	Duration drug exposure, days	Mean food intake, g/kg/day	Mean drug intake, μg/kg/day	Remarks
Control	15.2*	17.2*	—	15.8*	(273)	36.3 ± 4.9	Control	Death from acute gastric perforation and hemorrhage
"	10.4*	10.4*	—		(200)	42.8 ± 5.8	"	
"	6.8*	8.7*	9.5*		(378)	40.8 ± 6.2	"	
4a	7.3†	—	—	7.7	21	36.0 ± 7.8	110 ± 23	Delivered pups after 30 days drug exposure
4b	8.3†	—	—	5.3	45	16.1 ± 17.0	59 ± 50	
5	8.6	6.4	8.6	—	350	51.4 ± 26.4	203 ± 68	
6	8.0†	—	—	5.2	138	36.7 ± 6.8	220 ± 53	
7	12.0†	10.9	—	6.0	350	37.6 ± 8.9	195 ± 59	
8	10.9†	6.8	—	6.1	190	33.5 ± 12.3	173 ± 36	
9	7.9	6.4	8.4	—	350	39.9 ± 8.9	223 ± 62	
10	6.8	6.0	8.4	—	350	41.4 ± 10.9	227 ± 57	
11	8.8	7.9	10.9	—	350	40.0 ± 13.2	158 ± 45	
12	11.4	7.8	—	—	172	28.0 ± 12.7	114 ± 39	
13	12.1	7.8	11.6	—	350	33.6 ± 8.6	143 ± 56	
14	12.0	12.3	—	—	172	34.9 ± 6.8	198 ± 57	
Mean	9.8	8.0	9.6	—				
S.D.	2.4	2.2	1.6	—				
Mean†	9.3	—	—	6.1				
S.D.†	2.0	—	—	1.0				

* Not included in mean or S.D.
† Animals which died in course of experiment.

tion of emesis would prevent such occurrence.

Summary. (1) A purified extract of *Veratrum viride*, Veriloid, was fed to growing rats and adult dogs for 12 months. (2) A graded retardation of growth was observed in the rats consuming 3, 5, 8 and 10 mg kg per day of the drug. No such gradation of pathologic change was found. (3) Weight loss and emesis resulted in the dogs. The mean daily intake for this species was limited to 0.19 mg/kg by emesis and failure of animals to eat. (4) No specific organ toxicity was found in either species.

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Effect of ACTH on Decreased Serum Inorganic Phosphorus Induced by Insulin and Glucose. (18628)

FRANCISCO DE VENANZI.*

From the Departmento de Patologia General y Fisiopatologia. Instituto de Medicina Experimental, Universidad Central de Venezuela, Caracas.

The mechanism of the diabetogenic action of ACTH (adrenocorticotropic hormone) and of 11 oxi-cortico-steroids is little known. Ingle and Thorn(1) have been able to secure evidence against the possibility of a simple increase in neoglucogenesis. Ingle(2), demonstrated the decrease in peripheral utilization of glucose determined by adreno-cortical extracts in the eviscerated rat treated with insulin and his experiments were in harmony with the inverse phenomenon of the facilitation of utilization induced by adrenalectomy in the eviscerated rat as described previously

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1. Ingle, D. J., and Thorn, G. W., *Am. J. Physiol.*, 1941, v132, 670.

2. Ingle, D. J., *Ann. New York Acad. Sci.*, 1949, v50, 576.