cannot postulate further on the uniqueness of the first 6 rare earths in their biochemical effects.

Summary. Lactate, isocitrate, malate, glutamate, and glucose 6-phosphate dehydrogenases and aldolase were examined in the absence and presence of 9 lanthanide chlorides. All these enzymes were inhibited, although not to the same extent. The forward direction of the glutamate dehydrogenase reaction (glutamate deamination) apparently is not sensitive to the lanthanides, although marked inhibition is observed when α-ketoglutarate is substrate (reverse direction). The results reveal that all the lanthanides tested (atomic numbers 57-71) can inhibit enzymes sensitive to metals, whereas the fatty-liver response *in vivo* is elicited only by lanthanides with atomic numbers 57-62. The experimental data reveal that lanthanide inhibition *in vitro* is probably a typical heavy-metal effect.

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Respiratory Excretion of Selenium.* (31638)

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The methylation of selenium and the excretion of $(CH_3)_2$ Se,(1) in the respiratory gases comprise one of the pathways by which selenium may be eliminated from the animal body(2-6). It appears from the wide range of respiratory values (% dose) reported in the literature that the quantity of selenium exhaled in the respiratory gases increases with the increase in the amount of selenium administered. In order to examine more thoroughly the dose-excretion concept, experiments were performed to determine the correlation between the amounts of selenium administered as either selenite ($^{75}SeO_3^{=}$) or L-seleno-75 methionine, and that excreted in the respiratory gases.

Materials and methods. Young adult male rats were injected subcutaneously with a single dose of selenium either as selenite ($^{75}SeO_3^{=}$) or L-seleno-75 methionine (Squibb, Sethotope) to which was added amounts of the correspondent stable selenium compound as indicated in Table I. Following selenium injection, the animals were placed in the Delmar† glass metabolism apparatus which permitted the collection of respiratory gases and urine.

A steady stream of dry air was drawn through the system with a water pump, and the expired air was absorbed in a series of 3 gas washing traps. The first 2 traps contained 10% bromine in HBr (V/V) and

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TABLE I. Respiratory Excretion of Selenium.

Type compound	Selenium injected: mg Se/kg	Cpm × 10^3	μc	% Dose Exhaled: 0-3 hr	3-6 hr	6-24 hr	Total	Urine, %
A. $H_2{}^{75}SeO_3$	0.005	53.3	51	.01	.03	.2	.2	32.9
	0.913	47.6	43	6.00	2.9	1.7	10.6	23.2
	2.146	42.8	42	22.4	12.9	6.5	41.8	22.0
	3.102	66.9	61	25.6	14.4	4.6	44.6	5.0
	3.473	57.3	52	20.6	12.5	7.9	41.0	3.1
	3.893	41.7	38	14.7	18.4	14.5	47.6	10.2
	4.504	40.7	37	30.7	14.6	13.0	58.3	12.5
	4.593	23.1	23	30.2	11.0	21.0	62.2	7.4
	5.164	36.2	35	18.0	27.7	15.0	60.7	14.4
	5.410	34.7	34	26.2	13.5	12.3	52.0	1.9
B. L-seleno-75 methionine	0.001	0.103	.3	.5	.1	.7	1.3	27.10
	1.065	0.929	1.2	1.8	1.5	2.8	6.1	35.80
	2.452	0.926	1.1	10.8	6.8	8.4	26.0	22.30
	3.082	0.775	.7	10.5	4.6	2.4	17.5	14.52
	3.509	0.790	.7	12.9	8.2	6.5	27.6	12.48
	4.145	0.790	.7	15.0	10.3	4.9	30.2	9.35
	5.048	0.371	.3	15.4	7.9	6.4	29.7	11.13
	5.583	0.710	.6	14.6	11.0	10.3	35.9	6.82

the third trap contained water. Nearly all of the selenium in the experimental runs was found in the first absorption chambers. Collections were made at 3, 6 and 24 hours. After the collection period, the bromine:HBr solution containing the ^{75}Se was made to volume and an aliquot was taken for radioactive assay. The radioactivity determinations for ^{75}Se were made in a well-type scintillation counter NaI (TL) with a Picker gamma-ray spectrometer(7). The efficiency of ^{75}Se assay was found to be 43%.

Results and discussion. It is shown in Table I that small amounts of selenium of the order of 1% or less of the administered dose were excreted in the respiratory gases when trace amounts of selenium were injected as $^{75}SeO_3^=$ (0.005 mg Se/kg) and L-seleno-75 methionine (0.001 mg Se/kg). Conversely, when larger amounts of selenium were administered as $^{75}SeO_3^=$ (5.4 mg Se/kg) and L-seleno-75 methionine (5.6 mg Se/kg), 50% ($^{75}SeO_3^=$) and 35% (L-seleno-75 methionine) of the administered dose were found in the respiratory gases. About 70% of the total amount of ^{75}Se exhaled within 24 hours was excreted during the first 6 hours. It is interesting to note in previous studies that when sodium selenate was administered to rats, 75% of the total amount of ^{75}Se exhaled within 24 hours was excreted during the first 6 hours(3). The percent of dose excreted in the respiratory gases for a 24-hour period was 5 to 20% greater when administered as $^{75}SeO_3^=$ than with L-seleno-75 methionine. The only exception was when trace amounts of the compounds were administered. Along with an increase in the total amount of selenium administered there is a decrease in urinary excretion of selenium for both $^{75}SeO_3^=$ and L-seleno-75 methionine.

Summary and conclusions. The current experiments demonstrate that the formation and excretion of volatile selenium compounds occur soon after administration of $^{75}SeO_3^=$ and L-seleno-75 methionine. The rate of excretion of volatile substances through the lungs when administered either as inorganic ($^{75}SeO_3^=$) or organic (L-seleno-75 methionine) selenium is more rapid during the first 6 hours than during any subsequent 6-hour period up to 24 hours. On the basis of mg selenium per kg body weight, larger amounts of selenium are excreted when administered as inorganic than as organic selenium. It is apparent that the mechanism of methylation and rapid excretion *via* the respiratory gases assumes a more significant detoxification role when amounts of selenium approaching the lethal levels are administered.

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Possible Teratogenic Effects of Veratramine. (31639)

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We reported previously on the production of ovine fetal cyclopia by the plant *Veratrum californicum*(1) and by fractions and crystalline alkaloids preparations derived therefrom (2,3,4). Because of similarities in structure between veratramine and these alkaloids and because veratramine is present in members of the *Veratrum* genus, we tested the teratogenicity of this compound. The unexpected teratogenic effects are reported here.

Materials and methods. Twenty-one crossbred ewes were given veratramine either by capsule or injection on the 13th or 14th day after breeding. Individual doses are recorded in Table I. The doses were estimated from previous experience with veratrosine, the glycoside of veratramine(4). Four ewes died from overdose while the survivors had some toxic signs, such as increased salivation and respiration, cardiac weakness and convulsions. These signs were similar to those reported(5) for other species.

The lambs were examined at birth for gross abnormalities and at intervals later for evidence of improvement or increasing severity of abnormality.

Results and discussion. The effect of veratramine on offspring of experimental ewes is shown in Table I, along with the dosage schedule. Photographs of lambs of a high degree of abnormality, selected from among the abnormals, are shown in Fig. 1. It is evident that a significant incidence of abnormalities resulted in offspring from veratramine-dosed ewes. Excluding ewes that died of overdosage and the single nonpregnant ewe, 37.5% of the ewes dosed produced abnormal lambs or fetal deaths.

The abnormalities included slight lateral or medial bowing of the front legs, slight to marked flexure of knee joint, apparent loss of muscle tone that caused marked looseness of the hock and stifle joints, and/or complete lack of skeletal muscular control (inability to rise). No gross lesions in musculature or other systems were evident on post mortem examination of the single lamb of ewe 404 that died. Surviving abnormal animals showed marked improvement within 3 weeks after birth in all respects with the exception of the bowing of the legs.

The nature of the abnormalities apparently produced by veratramine were completely unexpected. Veratramine is a C-Nor-D-homopregnane modification of the usual steroidal ring system with an additional terminal piperidine ring and is a member of the steroid class of the veratrum alkaloids. Results of other experiments in our laboratory(2,3,4) have suggested that compounds of this general structural class are the compounds responsible for ovine fetal cyclopia. It was expected that if veratramine proved to be teratogenic it too would produce cyclopia. It was inactive in this respect, producing rather the effects described above.

The selection of the 13th and 14th days after breeding as the days for dosing was based upon the fetal insult period for production of fetal cyclopia by *Veratrum californicum*(6). Since limb buds are not formed, although the embryo is in the pre-somite stage (7) by the 14th day, the apparent effect on the limbs might possibly be due to an effect on the central nervous system. The complete lack of skeletal muscular control in some of