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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

TABLE I. Ewes Dosed with Veratramine During Gestation and the Resultant Effect on Their Offspring.

Ewe No.	Lamb No.	Oral capsule dose schedule (g) 13th day	14th day	Injected dose schedule on 14th day	Resultant effect on offspring	
368	134 ♂ 135 ♀	.6	.3	—	Normal	Male and female lambs
404	147 ♂ 148 ♂	.9	.4	—	Abnormal	148 was normal, 147 had no skeletal muscular control—unable to stand, very rapid breathing, died 2 days after birth.
306	—	.8	.4	—	Nonpregnant	
286	150 ♀ 151 ♀	.7	.4	—	Abnormal	151 was normal, 150 had looseness of hock and stifle joints of both rear legs.
390	—	.5	.5	—	"	Abortion or fetal death. Ewe died at 130 days gestation and showed evidence of recent uterine activity.
359	116 ♀ 118 ♀	—	1.1	—	Normal	Female lambs
370	101 ♂ 102 ♀	—	1.0	—	Abnormal	Both 101 and 102 had bowed front legs and looseness of hock and stifle joints.
412	121 ♀	.9	—	—	Normal	Female lamb
432	99 ♂ 100 ♀	—	—	40 mg I.V. + 120 mg I.M.	"	Male and female lambs
319	110 ♂ 112 ♀	—	—	200 mg I.M.	"	*Idem*
382	—	—	—	160 mg I.M.	—	Ewe died from overdose (too rapid dosing).
411	108 ♀ 109 ♂	—	—	300 mg I.M.	Abnormal	109 was normal, 108 had no skeletal muscular control in rear limbs, unable to stand.
249	168 ♂ 169 ♀	—	1.0	—	Normal	Male and female lambs
371	—	—	1.2	—	—	Ewe died from overdose (excessive dose).
407	—	—	1.4	—	—	*Idem*
267	—	—	1.0	—	Normal	Male fetus, ewe killed at 37 days gestation.
429	53 ♀ 52 ♂	—	1.0	—	"	Male and female lambs
401	80 ♀	—	1.0	—	"	Female lamb
149	79 ♂	—	1.0	—	"	Male lamb
323	—	—	1.4	—	—	Ewe died from overdose (excessive dose).
383	131 ♀ 132 ♂ 133 ♂	1.0	—	—	Abnormal	All 3 lambs had looseness of hock and stifle joints and lamb 131 also had bowed front legs.

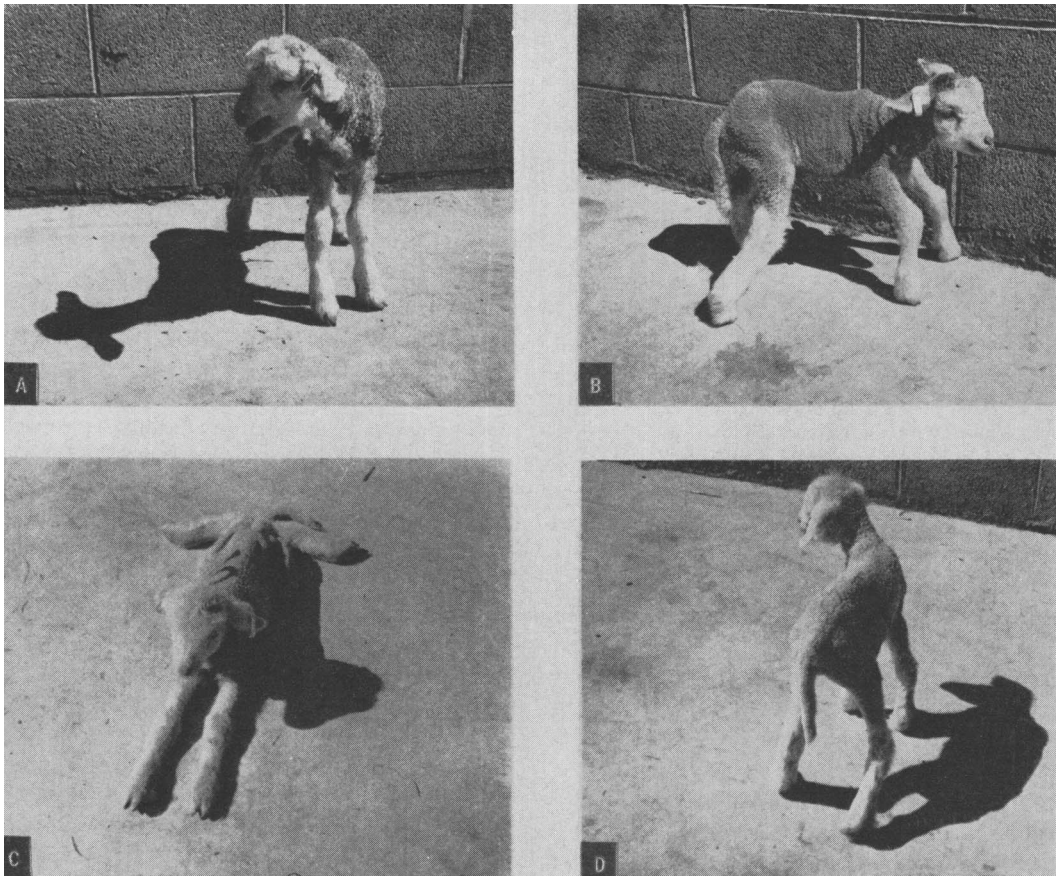

FIG. 1. Photographs of selected lambs born to ewes given veratramine on 13th or 14th day after breeding. (a) Lamb 102 with one front leg bowed laterally and one bowed medially. (b) Lamb 101 with marked flexure of knees and looseness of hock and stifle joints. (c) Lamb 108 with no muscular control in rear limbs. (d) Lamb 131 with bowed front legs and looseness of hock and stifle joints.

the lambs suggested central nervous system involvement, especially since no gross lesions were seen in musculature or other systems on post mortem examination. Further, the rapid post-natal recovery is suggestive of a central nervous system lesion wherein alternate nervous pathways for skeletal muscular control are rapidly developed replacing those damaged by the veratramine fetal insult.

Summary. The alkaloid veratramine, a parent alkamine of the steroidal class of veratrum alkaloids, produced congenital abnormalities in lambs. It did not produce the expected cyclopian deformities but rather abnormalities which included slight lateral or medial bowing of the front legs, slight to marked flexure of knee joint, looseness of the hock or stifle joints, or complete lack of skeletal muscular control (inability to rise).

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