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# Observations of *Lupinus sulphureus*-induced "crooked calf disease"

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## Abstract

**Lupine-induced "crooked calf disease" occurred in a fall calving herd of cows in Northeastern Oregon. Sixty-seven calves from a herd of 131 cows (51%) were born with congenital skeletal malformations primarily of the front limbs, neck, or spine and a few had cleft palates. Because of the nature of the malformations, lupine was suspected, and investigation of the ranch and pastures where cows grazed revealed 2 species of lupine (*Lupinus sulphureus*; Douglas ex. Lindl. and *Lupinus leucophyllus*; Douglas ex. Hooker) and poison-hemlock (*Conium maculatum*). Poison-hemlock was not grazed and therefore eliminated as the teratogenic plant. Extensive grazing of the *Lupinus sulphureus* especially the seed pods was evident. Chemical analysis of the 2 lupine species demonstrated that *L. sulphureus* was likely the cause of the birth defects because it contained high levels of the quinolizidine alkaloid anagyrine, a known teratogen. *Lupinus sulphureus* is a yellow-flowered lupine and contained 1.84% anagyrine in the seed, whereas *Lupinus leucophyllus*, a purple-flowered lupine, contained other quinolizidine alkaloids but no anagyrine. The seed pods of *L. sulphureus* were high in total alkaloids (42 mg/g of dry seed), of which 45% was anagyrine. After a review of breeding records, grazing patterns and growth stage of plants, it was determined cattle probably ingested *L. sulphureus* in the seed pod stage during critical fetal developmental periods of gestation. Epidemiologic studies suggested the critical gestational period included day 21 to day 100; 70% of the malformed calves were born to cows that were exposed to the plant during gestation days 60 to 80. The risk of deformities was markedly increased in fetuses exposed during this interval. A few malformations occurred in cows exposed to the lupine as early as gestation day 21 and as late as day 100. We conclude that *L. sulphureus* was the teratogenic species, and producers should prevent cows from grazing *L. sulphureus* during gestation days 40 to 100 and consider herbicide control of this lupine species.**

**Key Words: lupine, anagyrine, skeletal malformations, cleft palate, arthrogryposis**

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Ingestion of lupine by pregnant cows induces congenital malformations in calves, a condition named "crooked calf disease" (Wagnon 1960, Shupe et al. 1967a, 1967b, 1968). The malformations are characterized by twisted or bowed limbs (arthrogryposis), twisted or deviated spine (scoliosis or kyphosis), twisted neck (torticollis), occasional cleft palate, or any combination of these. The malformations may be minor contractions which resolve spontaneously or they may be severe resulting in dystocia, delivery by Cesarean, or death of the neonate. A similar condition of genetic origin is reported in Charolais calves from an inherited simple autosomal recessive trait (Nawrot et al. 1980).

Lupine species previously implicated in crooked calf disease include *L. sericeus*, *L. caudatus* (Shupe et al. 1967a, 1968), and *L. laxiflorus* (Wagnon 1960). *Lupinus latifolius* was implicated in dog and human malformations when milk from goats eating this lupine was ingested by the mothers during pregnancy (Kilgore et al. 1981). The quinolizidine alkaloid anagyrine was implicated as a teratogenic alkaloid in this and in earlier studies of lupine-induced "crooked calf disease" (Keeler 1976). Anagyrine was demonstrated to pass into the goat's milk after ingestion of the lupine and all lupines containing anagyrine are believed to be potentially teratogenic if eaten during critical periods of gestation. Although plant extracts rich in anagyrine induced crooked calves (Keeler 1976), the pure compound has yet to be tested. Fifteen *Lupinus* species containing anagyrine have been identified in the western United States (Davis and Stout 1986) but *L. sulphureus* was not listed among those examined.

Quinolizidine alkaloid absorption from the gut is rapid (alkaloids appear in the blood within 15 minutes after gavage) and the serum elimination half life for anagyrine is about 5 to 10 hours (Gardner and Panter 1993). Repeated dosing or continuous low level ingestion of small amounts over time may result in cumulative intoxication and/or teratogenesis. Currently, the minimum number of days ingestion must occur for malformations to result is unknown.

The mechanism of action of these alkaloids is associated with reduction in fetal movement during critical stages of gestation (Panter et al. 1990). If the critical stage of pregnancy includes early gestation (up to day 38 in sheep and goats and day 56 in cows; Evans and Sack 1973), cleft palate may be induced (Panter and Keeler 1992). Specific alkaloid-induced cleft palate is believed to result from the mechanical interference of palatal shelf closure and fusion by the tongue due to reduction in fetal movement (Panter and Keeler 1992). If the critical period of ges-

tation is later, then skeletal contracture type malformations may also occur.

The purpose of this report is to describe a clinical case of lupine-induced "crooked calf disease" implicating *Lupinus sulphureus* as the teratogenic plant. Alkaloid levels are reported for *L. sulphureus* and *L. leucophyllus* at various growth stages and related to epidemiologic records of gestational stages of exposure. Management recommendations to reduce losses are also reported.

## Materials and Methods

### History

An outbreak of "crooked calf disease" in a fall calving herd of cattle in Northeastern Oregon was reported in the fall of 1992. Cows were Hereford and Hereford crossbreds in good body condition. Ranch history of crooked calves included 10 to 12 deformed calves born in a 27-day period from 20 November to 17 December, 1991. Before 1991 crooked calf disease was rare on the ranch. The foothill pastures are 16 km east of Pendleton, Ore. in the Blue Mountains and have been a part of this ranching operation for several decades. Stocking rates of 1.6 cows per hectare had not been changed in recent years and pasture rotation was similar to that of past years.

Cows were exposed to bulls on 5 February through 5 April 1992, and were turned out on the foothill pasture containing good quality grass and abundant *Lupinus sulphureus* (Fig. 1) on 28 April 1992 for 22 days. Forage availability and quality were not specifically evaluated but shortage of grass did not appear to be a factor in increased consumption of *L. sulphureus* pods. At the end of the 22 day grazing period cows were transferred to an adjoining pasture with some *L. sulphureus* in isolated areas, but a predominance of *L. leucophyllus*. One-hundred-thirty-one mature cows were placed on the foothill pasture with lupine and 28 first-calf heifers were placed on neighboring irrigated pastures without lupine. The calving season began on 28 October 1992, and extended to 25 January 1993. By 1 January 1993, 142 calves had been born.

**Fig. 1. Prevalence of lupine (*Lupinus sulphureus*) in the east pasture before flowering.**

In the spring of 1993 the ranch and foothill pastures were examined and types of vegetation noted. Three pastures contained improved grasses with few forbs except 2 species of lupine and poison-hemlock. Plant samples were collected at different phenological stages from different pastures for alkaloid analysis and for plant identification at the Intermountain Herbarium at Utah State University, Logan. The lupines were identified as *L. sulphureus* (yellow lupine) and *L. leucophyllus* (purple lupine).

### Chemical Analysis

Lupine plant samples were submitted for identification to the Intermountain Herbarium and then air-dried. Either the whole plant or individual plant parts were ground to pass a 2 mm screen. One-hundred mg samples were extracted in duplicate according to the protocol previously described (Gardner and Panter 1993). The isolated alkaloid fraction was weighed to determine total alkaloid content. Individual alkaloids were identified by GC analysis comparing alkaloid retention times with a sample of *L. caudatus* with known and verified alkaloid profiles. Individual alkaloid concentration was calculated using area under the curve as a relative percent of the total alkaloid weight as measured from gas chromatogram (GC) analysis and reported in Tables 1–3. Identification of anagyrine was verified by GC/mass spectrometer (MS) analysis.

### Epidemiology

Review of calving dates and time of entry and exit from the pastures provided the information for the epidemiology studies. Fetal age was back calculated using birth dates and a 283 day gestation length. Gestational age-specific incidence as determined by the gestational age at the onset of exposure was plotted with the fetal age divided into 10 day periods (Figs. 2 and 3). Data from the *L. sulphureus* were further analyzed by a LOWESS program for smoothing scatter-plots (Fig. 4; Cleveland 1981). One calf with severe malformations was submitted for pathological examination.

### Herbicide Treatment

Herbicide treatment included 18.25 ml Ally, 1.18 liter Curtail and 4.75 liter of M-90 spreader sticker per hectare applied by fixed wing airplane (total cost of $46.75 per hectare). Herbicide treated and untreated *L. sulphureus* plants were also submitted for alkaloid analysis 6 days after herbicide application (Table 1). Herbicide was applied 26 April 1993.

## Results and Discussion

Sixty-seven calves from 131 cows grazing pastures containing lupines were born with skeletal deformities and 50 either died or were humanely killed because of the severity of their deformities. Many of the 17 calves with moderate deformities that survived were not marketable commercially (Figs.5 and 6). Of the 67 deformed calves, 60 had front limb involvement (6 of which had some neck deviations), and 4 or 5 had palate defects. One calf had cleft palate only without any skeletal defects suggesting brief exposure early in gestation. Palates were not checked until late in the calving season and death of some of the earlier calves may have been related to cleft palates. One severely deformed calf was taken to the diagnostic lab at Washington State University

**Table 1. Total and individual alkaloid concentrations (mg alkaloid/ 100 mg dry plant of *L. leucophyllus* (A) and *L. sulphureus* (B) collected on 6-2-93 in different pastures, and before and after herbicide treatment for *L. sulphureus* (C). *L. Sulphureus* in the east pasture had senesced and was not analyzed. Note: No anagyrine was detected in *L. leucophyllus*.**

| | (mg Alkaloid/100 mg Dry Plant) | | | | | | |
|---|---|---|---|---|---|---|---|
| *L. leucophyllus* (A) | | | | | | | |
| Pasture | Total | A | F | H | L | | |
| West | 1.38 | 0.20 | 0.43 | 0.03 | 0.72 | | |
| Top | 0.86 | 0.05 | 0.34 | TR | 0.42 | | |
| East | 0.51 | 0.06 | 0.19 | TR | 0.25 | | |
| *L. sulphureus* (B) | | | | | | | |
| Pasture | Total | J | K | C | L | E | |
| West | 1.08 | 0.08 | 0.07 | 0.54 | 0.07 | 0.27 | |
| Top | 1.25 | 0.08 | 0.27 | 0.25 | 0.02 | 0.59 | |
| *L. sulphureus* (flower stage) (C) | | | | | | | |
| | Total | J | K | C | L | E | % anagyrine in total |
| Untreated | 0.73 | 0.09 | 0.08 | 0.13 | TR | 0.44 | 61 |
| Treated | 0.95 | 0.06 | – | 0.39 | 0.02 | 0.37 | 43 |

A = Tetrahydrorhombifoline
C = Lupanine
E = Anagyrine
F = 13-Hydroxylupanine
H = 13-Angeloyloxylupanine
J = 5, 6-dehydrolupanine
K = Lamprolobine
L = Unidentified Alkaloids (represents a total of 4 chromatographic peaks for *L. leucophyllus* and 1 peak for *L. sulphureus*)
Note: Letters represent peaks on the chromatogram.

for necropsy and histopathologic evaluation. The 28 replacement heifers on irrigated pastures without lupine did not have any deformed calves.

Gross necropsy findings on the calf submitted for pathological examination included arthrogryposis and valgus deviation of the left forelimb, varus deviation of the right forelimb, left torticollis, and scoliosis of the thoracic spine. No histologic abnormalities were seen in multiple samples of skeletal muscle, brain, and spinal cord. Both the physical abnormalities observed in the live calves and the findings at necropsy of the sacrificed calf are consistent with a diagnosis of lupine-induced congenital disease.

Lupine samples were collected for identification and screened by chemical analysis for the presence of possible teratogenic alkaloids (piperidines or the quinolizidine alkaloid anagyrine). *Lupinus sulphureus* and *L. leucophyllus* were identified and chemical analysis revealed high anagyrine levels in *L. sulphureus* but none in *L. leucophyllus* (Tables 2 and 3). No teratogenic piperidines were detected in either species. Anagyrine was identi-

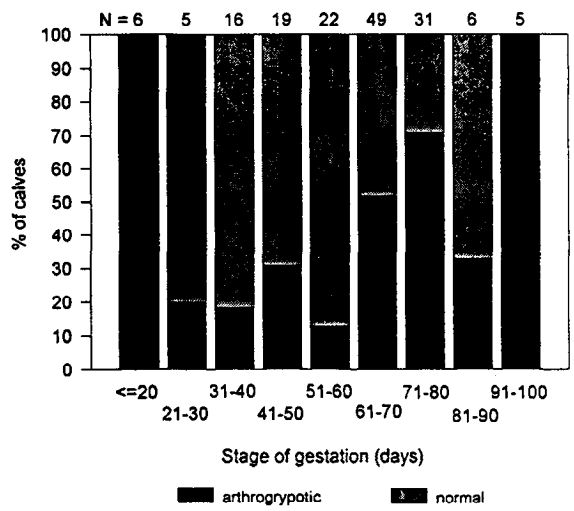


**Fig. 2. Epidemiologic data of fetal stage of development at time of exposure to yellow lupine (*Lupinus sulphureus*). N= number of cows in each 10 day gestational block including days 20 to 100. Stage of gestation was based on a 283 day parturition.**

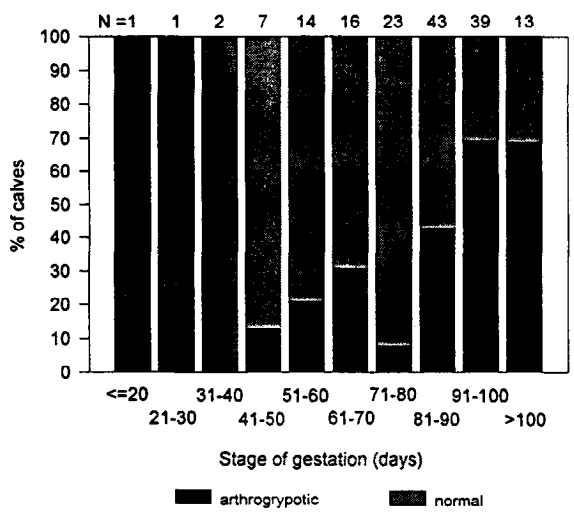


**Fig. 3. Epidemiologic data of fetal stage of development at time of exposure to purple lupine (*Lupinus leucophyllus*). N= number of cows in each 10 day gestational block including days 20 to 100. Stage of gestation was based on a 283 day parturition.**

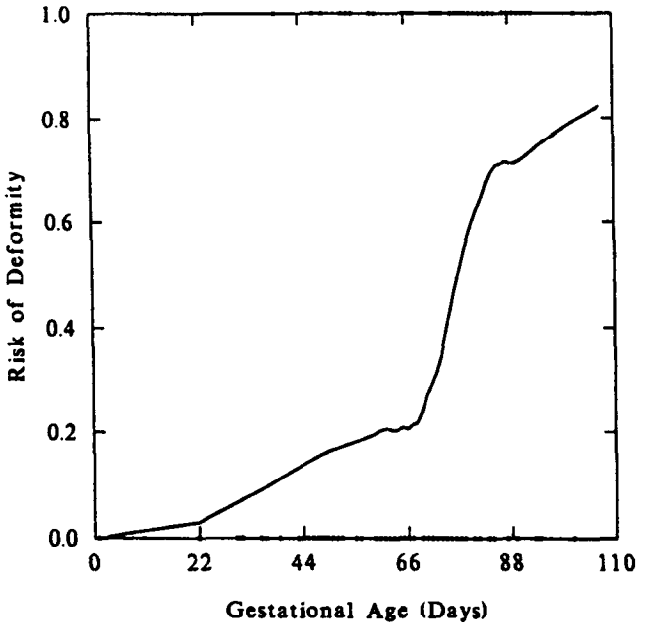


**Fig. 4. LOWESS smoothed plot (Cleveland, 1981) of the risk of fetal deformity versus gestational midpoint in days for fetuses during 22 day exposure to *L. sulphureus*. Stage of gestation was based on a 283 day gestational period.**

fied as the probable teratogen in other lupines (Keeler 1976) and is believed to be the key factor in this case. *L. sulphureus* is high in anagyrine at all stages of growth until after seed shatter (Table 2). Seed was very high in total alkaloid and anagyrine at 4.17% and 1.84% of dry seed, respectively. Herbicide treatment slightly increased total alkaloid and lupanine content but reduced anagyrine levels (Table 1). While herbicide treatment was of questionable value in control of the lupine, these data indicate some changes in plant alkaloid profiles resulted.

Epidemiologic investigations showed that cows likely grazed *L. sulphureus* in the pod stage during the susceptible fetal period of gestation. Previous research has shown that cattle begin grazing lupine, locoweed, and larkspur when in the pod stage (Keeler et al. 1977, Ralphs 1987, Pfister et al. 1988). This particular year, plant growth was early because of good residual soil moisture and warm temperatures early in the season. Weather data from the Oregon Climate Service, Oregon State University, for the Pendleton area showed increased annual precipitation in 1991 of 34.3cm (average 31cm). In the first 3 months of 1992 when cows were grazing the *Lupinus sulphureus* pasture precipitation was decreased by an average of 1.9cm per month while temperatures were increased by an average of 2.2°C per month for the same period.

Seed pods of this particular species are apparently palatable and the plant in the seed pod stage is considered a teratogenic threat as reported in the literature (Keeler et al. 1977) and as demonstrated here by the high anagyrine content (Table 2). The preference of cattle for lupine relative to grasses is unknown; however, grasses were not depleted when the cows were grazing lupine pods. While the plant and pods may have negative qualities for grazing such as bitterness and toxicity, they also have nutritional value, for example seed pods with 30-40% seed shatter and pure seed from *Lupinus argenteus* collected near Twin Falls, Ida. had protein values of 19.4 and 48% respectively (Panter, unpublished data 1996). We still don't understand all the factors that influence livestock grazing habits and why they graze poisonous plants when they do.

When plants were collected for chemical analysis, phenological stage was different for the 2 lupine species as *L. sulphureus* matured early in the season and was drying whereas *L. leucophyllus* was just entering the seed pod stage. This was evident by the 23 June 1994 collections in which *L. sulphureus* was mature with about 75% seed shatter and *L. leucophyllus* was in the mid to late flower/early pod stage (Tables 2 and 3). It appeared that *L. leucophyllus* seedlings were increasing in the grass community whereas the *L. sulphureus* had been a significant part of the vegetation for many years. We concluded initially that *L. leucophyllus* was the most likely lupine; however, alkaloid analysis and subsequent risk analysis incriminated *L. sulphureus* not *L. leucophyllus*.

The gestational age-specific incidence of arthrogryposis for exposure to *L. sulphureus* during the first 100 days of gestation is shown in Figures 2 and 4, and supports the conclusion that *L. sulphureus* was the causative lupine. The period of grazing *L. sulphureus* was 22 days and the majority of the calves born with arthrogryposis experienced the onset of exposure during 60 to 80 days of gestational age. The risk for arthrogryposis increased dra-

**Table 2. Total and individual alkaloid concentrations (mg alkaloid/100 mg dry plant) in *L. sulphureus* at different stages of plant growth.**

| Plant stage | Date | Total | J | K | C | L | E | % of E[1] |
|---|---|---|---|---|---|---|---|---|
| | | | (mg Alkaloid/100 mg Dry Plant) | | | | | |
| Pre bud | 4–02–93 | 1.55 | TR | - | 0.43 | TR | 1.11 | 70% |
| Early bud | 4–16–93 | 1.25 | 0.06 | 0.26 | 0.21 | TR | 0.73 | 58% |
| Early bloom | 4–28–93 | 1.43 | 0.08 | 0.05 | 0.35 | 0.03 | 0.91 | 64% |
| Full bloom | 5–04–93 | 0.98 | 0.10 | 0.15 | 0.13 | 0.01 | 0.59 | 60% |
| Late flower/early pod | 6–15–93 | 0.80 | 0.08 | 0.09 | 0.28 | 0.03 | 0.30 | 36% |
| Mature 75% Seed shatter | 6–23–93 | 0.24 | 0.06 | 0.02 | 0.05 | – | 0.13 | 54% |
| Flowers | 5–04–93 | 1.68 | 0.12 | 0.09 | 0.15 | 0.02 | 1.30 | 78% |
| Leaves | 5–04–93 | 1.23 | 0.13 | 0.12 | 0.22 | 0.02 | 0.73 | 59% |
| Stems | 5–04–93 | 0.24 | 0.06 | 0.02 | 0.04 | – | 0.14 | 61% |
| Seed | 6–23–93 | 4.17 | 0.68 | 0.23 | 1.26 | 0.02 | 1.84 | 44% |

[1] = % of E in the total alkaloid content
E = The teratogen anagyrine
J = 5, 6-Dehydrolupanine
K = Lamprolobine
C = Lupanine
L = Unidentified Alkaloid (represented by 1 chromatographic peak)
Note: Letters represent peaks on the chromatogram.

**Table 3. Total and individual alkaloid concentrations (mg alkaloid/100 mg dry plant) in *L. leucophyllus* at various stages of plant growth. Note: no anagyrine was detected.**

| Plant stage | Date | Total | A | F | H | I |
|---|---|---|---|---|---|---|
| | | | (mg Alkaloid/100mg Dry Plant) | | | |
| Early growth | 4–02–93 | 1.30 | 0.11 | 0.17 | 0.26 | 0.75 |
| Pre bloom | 4–28–93 | 1.44 | 0.17 | 0.32 | 0.15 | 0.75 |
| Mid-late bloom | 6–23–93 | 0.94 | 0.11 | 0.25 | 0.05 | 0.53 |
| Late bloom/early pod | 6–23–93 | 0.89 | 0.15 | 0.27 | 0.04 | 0.44 |
| Mature seed heads | 7–09–93 | 1.42 | 0.04 | 0.38 | TR | 1.00 |
| Seedlings | 7–09–93 | 1.31 | 0.40 | 0.24 | 0.07 | 0.59 |

A = Tetrahydrorhombifoline
F = 13-hydroxylupanine
H = 13-angeloyloxylupanine
I = Unidentified Alkaloids (represents a total of 4 chromatographic peaks)
Note: Letters represent peaks on the chromatogram.

matically between gestational midpoints of 66 to 88 days (Fig.4). The analysis also caused us to believe that some risk may occur with an onset of exposure as late as 90 to 100 days of gestation. These data suggest that the "window of susceptibility" proposed by Shupe et al. (1967b) of 40 to 70 days gestation may now include days 22 to 100, although they did report slight to moderate front limb contractures in calves exposed at gestation days later than 70. Certainly, maternal dose of anagyrine and fetal size would be important determinants. In controlled feeding trials in cows there was no evidence of shortened gestation periods in cows carrying malformed fetuses induced by lupine (Keeler and Panter 1989).

## Conclusions and Recommendations

This case implicates an unreported *Lupinus* species that apparently causes crooked calf disease and further supports evidence that anagyrine is perhaps the key teratogen in these quinolizidine alkaloid-containing lupines. This report also supports the need for chemical analysis in management decisions discerning teratogenic lupines from non-teratogenic lupines. Management recommendations include herbicide treatment of pastures and rotating pastures: putting cows into pastures without the *Lupinus sulphureus* during the critical periods of gestation and monitoring

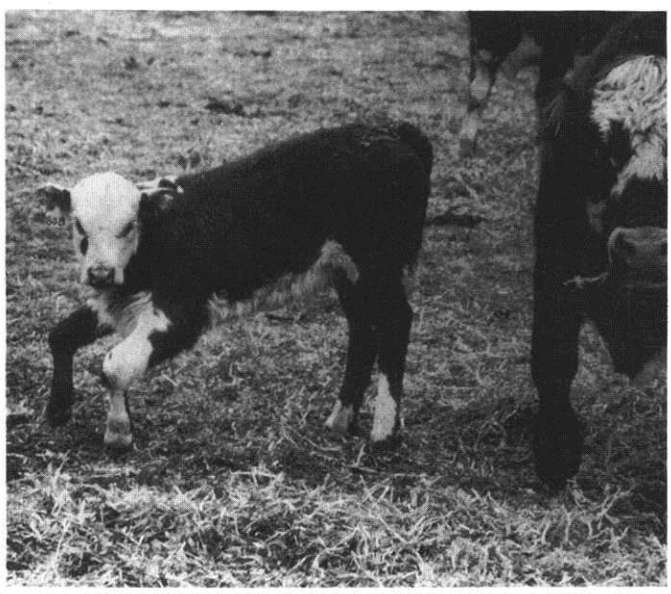

**Fig. 5. A moderately deformed calf showing the bowed legs. These calves grew as demonstrated in Fig. 6 but were not marketable to a feeder or packer because of the condition.**

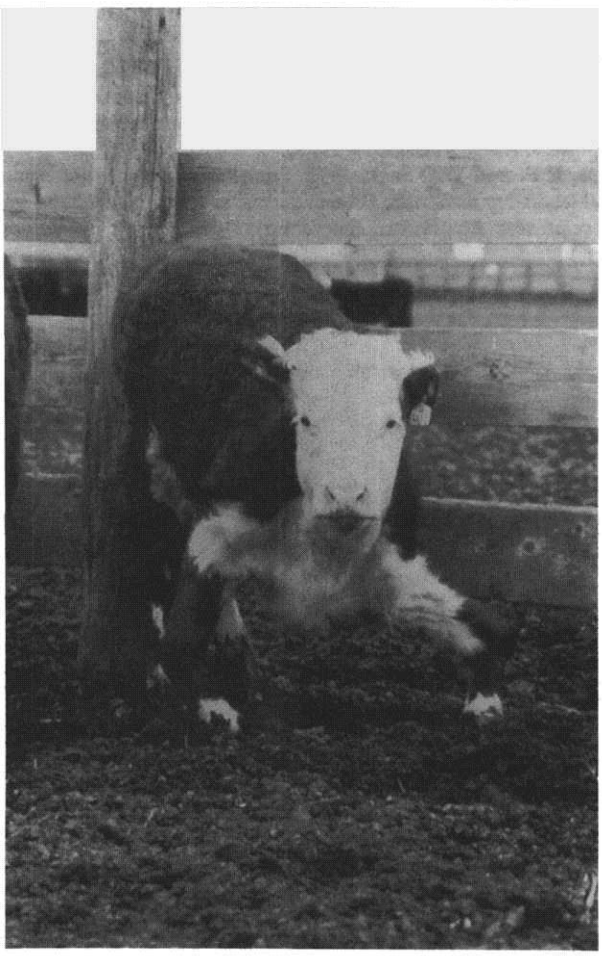

**Fig. 6. A moderately deformed yearling demonstrating that these moderate contractures do not resolve but generally worsen as the size of the calves increase.**

plant growth stages. These recommendations have prevented deformed calves in this herd of cows in recent years.

Earlier management recommendations to reduce losses from lupine included altering breeding dates with adjusted grazing patterns to prevent cows from grazing teratogenic lupines during 40 to 70 days gestation and avoid grazing lupines during high alkaloid content (early growth and pod stage) (Keeler et al. 1977). This recommendation suggested that fall calving schedules were beneficial in reducing losses; however, this study demonstrates that cows bred for fall calving may also be at risk, especially if the cows are bred to calve in late fall as these were. If this herd had been bred for calving to occur in early fall beginning in September the critical periods of gestation would for the most part have been avoided. However, lack of malformations before 1991 suggest this calving schedule was acceptable during most years. The early, warm, spring-like conditions in January and February of this particular year caused the plant to grow and mature earlier than usual. This scenario is a reminder that successful management strategies to prevent poisoning need to be flexible and should consider the stage of plant growth as well as the stage of pregnancy of the cows.

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