

Toxic plants as possible human teratogens

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Circumstantial evidence points to lupine toxin in goat's milk as cause of human birth defects.

Teratogens are substances that cause birth defects. Although nongenetic deformities have been recorded throughout human history, evidence that they could be caused by exposure to toxic chemicals did not appear until the 1930s, and it was the 1961 Thalidomide episode that generated today's public concern over teratogenic chemicals. Compounds as chemically diverse as vitamin D, quinine, aspirin, marijuana cannabinoids, and 2,4-D have shown some evidence of teratogenicity in laboratory rodents. We now suspect that toxic constituents of common plants may contribute to human birth defects.

Birth defects in domestic animals are commonplace. In 1960, Wayne Binns and his USDA co-workers discovered that a severe skull deformity known as "monkey-faced lamb," which had been thought hereditary, could be produced by feeding a toxic range plant, *Veratrum californicum*, to the dams during early pregnancy. Another deformity commonly observed by ranchers was "crooked-calf disease," characterized by bone abnormalities in the forelimbs and, to a lesser extent, spine and skull (scoliosis and cleft palate); K.A. Wagnon proposed that range lupines (*Lupinus* species) might be the cause, and Binns later proved it with feeding experiments in pregnant cows. More detailed investigation by Richard Keeler over the past few years shows that crooked-calf disease can be directly attributed to ingestion of a specific lupine alkaloid, known as anagryne, by the mother at some time during the second or third month of pregnancy.

In September 1980, a baby boy born in the mountainous backcountry of northwestern California (Trinity County) was brought to the U.C. Medical Center in Sacramento with severe bone deformities in his arms and hands, including a partial absence of forearm bones (radial aplasia) and absent thumbs. Extensive medical histories and genetic analyses of his parents indicated that the probable cause was environmental rather than hereditary, and his mother feared that somehow exposure to 2,4-D spraying was responsible; popular association of forest spraying and a reportedly high incidence of birth defects in northwestern California and south-

ern Oregon has been highly publicized in recent years and has become controversial. Indeed, it appears likely that this herbicide had been applied to a forested ridge several miles distant from the mother's home more than a year before the child's conception, but no closer. She provided the evidence that her goats also gave birth to kids stillborn or with deformed legs during and after the period of her pregnancy, and that puppies born to a dog fed the goat's milk during pregnancy were likewise deformed. (Local goat's milk has become a common food item in the area, and the child's mother drank it regularly herself throughout pregnancy.)

Our examination of the animals' deformed bones revealed a distinct similarity to those of calves born with crooked-calf disease and to those of the little boy. A thorough survey of nearby areas where the goats had regularly browsed at the time of the mother's early pregnancy showed that a perennial lupine, identified as the widely distributed *Lupinus latifolius*, often formed the principal low-growing forage. Gas chromatographic analysis of seeds and dry foliage from these plants showed them to be very high in anagryne.

Other alkaloids, such as those from tansy ragwort (*Senecio*), already have been shown to transfer readily into the milk of animals to which they or their plant source have been fed. When we fed the lupine seeds to a lactating goat, anagryne and other alkaloids were detected almost immediately in the milk by gas chromatography/mass spectrometry.

Today, the presence at that time of 2,4-D in the mother's environment cannot be proved or disproved. However, the circumstances rule out significant exposure, and an alternative explanation of these simultaneous deformities is needed. We propose the possibility that anagryne or a similar alkaloid from the lupines was the teratogen, that it was transferred to the mother in milk of the foraging goats, and that the embryo was exposed at the critical time for limb formation during the second month of development.

This hypothesis has some analogy in the well-known "milk-sickness" of the last century, in which the toxic tremetol in snake-root (*Eupatorium rugosum*) poisoned many people who drank milk from foraging cows

that had fed on the plant. Keeler demonstrated through feeding tests the teratogenicity of wild tobacco (*Nicotiana*), poison hemlock (*Conium*), and skunk cabbage (*Veratrum*) in sheep or cattle, and all three were found in browsing areas near the child's home. *Lupinus latifolius* has not previously been indicated to be teratogenic, although the crooked-calf disease has been found within its geographic range, but a number of other perennial lupine species cause deformities in cattle. Goats seem especially prone to browse on toxic plants, and, in winter, the perennial lupines may make up a substantial part of the available forage.

Admittedly, our evidence is circumstantial. Anagryne-containing milk cannot be fed experimentally to human mothers, and the high potency of the teratogen during a short period early in pregnancy almost certainly precludes its analytical detection by the time any defects could be recognized. Epidemiological correlation of specific deformities with the incidence of toxic plant species or dietary peculiarities might produce positive leads, but adequate proof may be long in coming.

Possible harm might have been largely circumvented by avoiding milk products from foraging cows and goats during the first trimester of human pregnancy or by restricting the foraging of milk-animals during that period. The extent of the hazard is not known at present—if it had not been for chance and the striking deformity, even this case would have escaped investigation. However, the ease with which some alkaloids and other substances apparently can pass into milk suggests that an important route of prenatal exposure to plant toxins has been previously overlooked.

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