

A Brief Review of Poisonous Plants Affecting Reproduction

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When Dr. Franz called me at the end of June to inform me that I had been selected to receive this prestigious honor and that I was to deliver the Bartlett address, I was completely surprised and more than a little apprehensive about the prospect. Dr. Franz explained that I would soon receive a letter explaining what was entailed. As I was leaving for a brief vacation the next day, I quickly copied all the previous Bartlett lectures to gain an understanding of what might be expected. During my stay in the woods of Canada, I was reminded of why the national bird of Canada is the mosquito, and, as I read those papers, I was filled with awe and a deepening feeling of apprehension and inadequacy.

I returned on July 9th to find a letter requesting that I submit a copy of my address to the Society for Theriogenology office by July 18th. I was already uncomfortable facing the prospect of preparing a talk and speaking before the group which I am sure includes many members who are more accomplished and more deserving of this award than I. Apprehension turned to panic! I called Dr. Franz and was granted a few more days, but in my case not enough time to prepare the Bartlett lecture as I would have liked. In spite of my initial misgivings, I would like to thank the committee that nominated me for this singular award, and I hope that the membership will forgive them, as everyone makes mistakes.

I would like to start by expressing my gratitude to all my friends and colleagues who inspired, mentored, and assisted me throughout my career. First I must acknowledge and thank my wife Beverly who has always stood by and supported me through some difficult times. We were married in mid July, and when we returned from our honeymoon in August I learned that due to Dr. Fincher's retirement I would be in charge of the large animal medicine course which at that time was taught to all senior students from 8 to 9 every morning. Daily lecture preparation, in addition to a full day of ambulatory calls, made for some very long days and nights and got our marriage off to a challenging start. I'm sure it made Beverly wonder what she had gotten herself into. Somehow she stayed the course, taking on the lion's share of raising three exceptional children, landscaping our homestead, training a championship Dog World obedience dog, and raising and training a Grand Prix dressage horse from a homebred thoroughbred. All in her spare time. I have been blessed by her help and love throughout our marriage.

Having been raised on a dairy farm in the days when we milked the cows by hand and did our field work with a team of draft horses, my love and respect for animals was deeply embedded. I wanted to be a veterinarian for as long as I can remember. When I was about eight years old, I observed our local veterinarian, Dr. Greenman, treat one of our draft horses for colic. The aroma emanating from his medicine case as he tubed that mare with his seemingly magical medications (probably pine oil and turpentine) fueled my aspirations to become a veterinarian. Dr. Greenman welcomed my interest and encouraged me to follow my dreams. I owe him a deep debt of gratitude.

I attended New York State College of Veterinary Medicine at Cornell when there was no tuition for in-state residents—only a laboratory fee of approximately \$150.00 per semester. This enabled me to work my way through school and emerge debt-free. Today, many of our new graduates are exiting with debt loads of \$60,000-100,000 dollars. This is an intimidating and discouraging outlook for prospective students. If we want to continue to attract the best and brightest students, we must find ways to reduce this burden.

After graduation I spent two interesting years in the Army Veterinary Corps fulfilling my ROTC obligations before joining Dr. Ed Leonard in his general practice in Tully, NY. Dr. Leonard was one of the first practitioners in his area to embrace the herd health approach, and he maintained herd records in his office, all transcribed by hand in those pre-computer days. The following year I was offered an internship at Cornell's Ambulatory Clinic, where I joined Doctors Fincher, Roberts, and Fox. Dr. Fincher was the head of the Large Animal Medicine Department and allowed me to collect skate mares and stable them in straight stalls in the clinic without charge so I could start an equine palpation class for interested students. We met at 5:00 a.m. each morning to tease, palpate, and eventually breed this band of mares. As the band expanded, it became necessary to write grants and use the mares for research projects in order to support them. Over the years, the quality of the equine donations improved, and today we maintain a group of about twenty-five registered mares and four to six stallions. The addition of Warmblood stallions has greatly increased the value of our foals, which helps sustain the group. Now all phases of equine reproduction are available for the students to observe and participate in.

In those early days of my tenure at Cornell, we were encouraged to bring interesting, unusual cases into the clinic without charge for students to observe and examine. For instance, we could bring in a cow with a mummified fetus so many students could palpate her. In most cases those cows would only be in the clinic for a short time because most of them passed their mummies within a couple of days following the numerous rectals with no other treatment. Presumably, the repeated massaging of the uterus stimulated the release of enough prostaglandin to lyse the corpus luteum and lead to the delivery of the mummy.

In the days before prostaglandin became available, we also utilized uterine massage during herd health checks to assist herd managers in finding cows in estrus. Cows that were due to be bred but had not been observed in estrus were palpated for the presence of a corpus luteum, and we tried to determine the stage of their cycle. When a firm, mature corpus luteum was found, the uterus would be massaged for an extra 15-20 seconds, and the headsman would be told to watch that cow carefully for heat in 3-4 days. The combination of the massage and the focused observations resulted in many cows being caught in estrus three-four days after a herd check.

Working with Dr. Roberts was an awesome opportunity. He taught the obstetrics course, took ambulatory calls, played polo, and coached the Cornell polo team to several national championships. He was an avid reader and had an encyclopedic memory for facts relating to all phases of reproduction, as those of you who have fathomed his obstetrics textbook can readily appreciate. Dr. Fox taught and is a master of physical diagnosis. He emphasized the need to use your powers of observation and is still revered as a most astute diagnostician. Each of these men was an exemplary mentor early in my career.

Over the years I have had the opportunity and privilege to meet and benefit from working with many of the leaders of theriogenology. I worked with Dr. Bartlett while serving on the Sire Health Committee of the National Association of Animal Breeders, where I represented Eastern AI Cooperative. Dr. Bartlett was a consummate gentleman and always impressed me with his ability to articulate his ideas precisely and with remarkable clarity. Dr. Ken McEntee was chairman of my graduate committee when I studied for my Masters Degree in Reproductive Pathology. Dr. Hansel was also on my graduate committee and I wound up taking his excellent endocrinology course. His teaching assistant at that time was Dr. Lloyd Faulkner, who was pursuing a PhD doing research with rats. This research involved transplanting the pituitary gland from the base of the brain to a location under the renal capsule and evaluating the effects this had on endocrine functions. For one hour of laboratory credit, Dr. Faulkner had us also operating on rats, transplanting the pituitary under the renal capsule and then castrating one half of the survivors to study the effects on endocrine function. I have never put in so much time and effort for one credit. Dr. Faulkner was always there to encourage our efforts and keep us on the straight and narrow. I thank all of these men for their help and guidance.

During a sabbatic at the University of Kentucky, I worked with Dr. Bob Loy as well as Dr. John Hughes, who was also on a sabbatic from U.C. Davis at that time. I consider those two to be among the giants in the field of equine reproduction, and it was a privilege to have the opportunity to work with them. During this period I also went on farm calls with Dr. Ed Fallon and Dr. Walter Zent. When I arrived to start my sabbatic in July, the breeding season had just ended, so the clinicians were “letting down.” By the end of July I wasn’t sure I would survive a full year—I knew I couldn’t if the partying continued all year at the July pace. Fortunately, sanity returned by August. The following spring, as I became acutely aware of the long and busy hours the equine reproductive veterinarians are required to put in, I could better understand the need for a “let down” period. All in all it was a most enjoyable as well as educational year.

I spent a second sabbatic at Colorado State University, where I had the golden opportunity to work with Dr. Les Ball helping with the instruction of fetotomy labs. Dr. Ball had recently returned from a sabbatic in Utrecht, and I profited immensely from his expertise. I spent the majority of my time in Colorado at the Animal Reproduction Laboratory assisting Doctors Ed Squires and Bill Pickett with a number of research projects. It was also during this tour of duty that I made time to study for the ACT written examination, which qualified me to sit the oral examination in Mobile in 1979 and experience first-hand the power of hurricane Frederick!

I had two six month sessions at UC Davis where I benefitted from exchanging ideas and techniques with Dr. Irwin Lui and Dr. Matts Troedsson. I have been privileged to be one of a group of nine individuals who have been able to attend all eight International Symposia on Equine Reproduction and to interact with leading scientists as they convened every four years at various locations throughout the world. There have also been many colleagues and visiting clinicians at Cornell who mentored and assisted me over the years including Bob Kenney, Don Lein, Ingemar Settergren, Maarten Drost, Rob Gilbert, Mary Smith, Barry Ball, Peter Daels, and Gordon Woods. I have been blessed to have worked with so many gifted professionals throughout my career and I thank them for their help and guidance.

In the late spring of 2001 the mare reproductive loss syndrome (MRLS) struck central Kentucky resulting in an estimated loss to the equine industry of approximately 350 million dollars. Epidemiological studies pointed toward involvement of an environmental toxin rather than an infectious agent. The list of proposed possible sources of toxins included insecticides, cyanide originating from cherry leaves, mycotoxins and phytoestrogens as well as eastern tent caterpillars (ETC) and their frass. Due to the prominence of plant sources on this list and because I help teach a course on poisonous plants, I felt a brief review of some of the plants that impact reproduction would be appropriate.

From the onset of the investigation of MRLS the overwhelming number of ETC present in central Kentucky in the spring of 2001 were thought by many to be involved. The preferred diet of ETC's is cherry leaves which contain cyanogenic glycosides. It was proposed that after ingesting cherry leaves, the ETC and /or their frass would contain enough cyanide to cause an intrauterine hypoxia and induce MRLS. Intensive studies have been unable to demonstrate toxic levels of cyanide in ETC or their frass, and the MRLS affected mares failed to demonstrate any symptoms of cyanide toxicity. Cyanide intoxication causes a histotoxic anoxia by paralyzing the enzyme system that transports oxygen from the blood into tissues. In acute cases signs appear within 15 minutes of ingesting the toxic material and death may ensue within two to three minutes. The mucous membranes are bright red in color. The animals exhibit dyspnea, anxiety, restlessness and terminal convulsions. Less acute cases show depression, staggering and muscle tremors. While ETC remain the prime suspect as the source of MRLS, it appears that the presence of cyanide from the cherry leaves does not have a prominent role in the syndrome. In spite of this a large number of cherry trees in central Kentucky have been cut down as one strategy to reduce the numbers of ETC.

The suspicion of mycotoxins being involved in MRLS was prompted by the unusual spring weather conditions in Kentucky in 2001. An early period of exceptionally warm and damp weather stimulated lush growth of pasture plants. This was followed by several days of hard frosts which damaged the plants, making them susceptible to fungal invasion with the likelihood of mycotoxin production. Investigations have been unable to substantiate mycotoxin involvement in MRLS, but here are several mycotoxins that are known to have detrimental effects on reproduction. Zearalenone (ZEN) is a mycotoxin that is produced by *Fusarium spp.* which commonly invade many grains and crops throughout the world. Corn is the most commonly affected grain but ZEN has been found in barley, oats, wheat, corn silage and even hay. Prepubertal gilts ingesting infected feedstuffs develop vulvovaginitis, mammary enlargement, atrophy of the ovaries, enlargement of the uterus and occasionally vaginal and /or rectal prolapse.

Pregnant sows on a ZEN contaminated diet have high levels of stillbirths, neonatal mortality, fetal mummification, splay-leg of piglets, abortion and abnormal return to estrus. Boars consuming moldy corn demonstrated inflammation of the prepuce, reduced testicular weight, enlargement of the mammary glands and reduced libido. Cattle are less sensitive to ZEN than swine but increased levels have been associated with infertility, reduced milk production and hyperestrogenism. Prepubertal heifers developed enlarged mammary glands with secretory activity.

Claviceps spp invade cereal grain plants and produce toxins called ergot alkaloid. Ingestion of heavily infected feed can produce a nervous syndrome with staggering, convulsions and posterior paralysis. Chronic ingestion of lower levels results in weight loss, rough hair coat and gangrene of extremities due to the vasoconstrictive effects of the ergot alkaloids. Ergotism has also been shown to lower reproductive efficiency and promote agalactia in swine, sheep and cattle. Ergopeptide alkaloids produced by the *Neotyphodium* endophyte in tall fescue produce similar syndromes. Cattle grazing infected tall fescue have reduced calving rates and have been shown to have poor luteal function with low levels of circulating progesterone. Mares grazing toxic tall fescue at more than 300 days gestation may abort but the more common result is a prolonged gestation terminating in dystocia with large, weak foals. The mares are agalactic. Normal parturition ensues if mares are removed from toxic fescue by day 300 of gestation.

Several other mycotoxins, including aflatoxins, deoxynivalenol and ochratoxin, impact reproduction indirectly by reducing feed intake, altering rumen function, damaging vital organs such as the liver and kidney, or by depressing the immune system.

Phytoestrogens are present in many legume forages with peak levels attained primarily during periods of rapid growth. The estrogenic activity of legumes is due to the presence of isoflavones and coumestans. The level of isoflavins in clover varies with the species and strain of clover, stage of growth, and soil conditions. The clover with the most extensive involvement with impairment of livestock reproduction is subterranean clover (*Trifolium subterranean*). This clover has been planted extensively on sheep pastures in Australia and in northwestern United States to increase pasture productivity but it has resulted in decreased fertility in many flocks. Infertility is associated with poor sperm transport due to alterations in cervical mucus consistency as well as structural changes in the cervix. Early removal from phytoestrogen exposure resolves the infertility but repeated or prolonged exposure can result in permanent infertility. In spite of reducing the level of infertility by developing varieties of subterranean clover with lower levels of phytoestrogens and implementing pasture management practices to limit exposure at times of peak levels, it has been estimated that about 4 million sheep fail to lamb each year in Australia due to phytoestrogen exposure.

Ladino clover, a variety of white clover (*Trifolium repens*), may contain elevated levels of coumestol during periods of lush growth. Exposure at this time can lead to cornification of vaginal epithelium and infertility in ewes. Ewes grazing a toxic variety of red clover (*Trifolium pratense*) have a reduced conception rate. Prompt removal from exposure resolves the infertility but prolonged exposure results in permanent sterility due to cystic hyperplasia of the endometrium.

Alfalfa (*Medicago sativa*) contains increased levels of coumestans during periods of lush growth which have been reported to reduce fertility in dairy cattle due to cystic ovaries and irregular estrus cycles.

There are many poisonous plants that can cause embryonic death, fetal abnormalities, and abortion. *Veratrum californicum* (Western false hellebore) is a wild lily growing in moist areas in the western mountain ranges that is responsible for several congenital birth defects in sheep. Ingestion of this plant by a pregnant ewe on day fourteen of gestation results in cyclopia and

monkey faced lambs. A high incidence of early embryonic deaths occurs at this time and at days nineteen to twenty-one of gestation as well. Ingestion between days 27 and 32 results in limb defects (shortened metacarpal and metatarsal bones) and tracheal stenosis. Prolonged gestation can occur due to lack of a pituitary gland. Those lambs remain in the uterus and continue to grow and may reach a size of 20 to 30 pounds, which usually results in the death of both the lamb and the ewe. *Veratrum* contains many alkaloids, three of which have been shown to be teratogenic. *Veratrum viride*, the eastern false hellebore, has not been proven to be teratogenic as experimental trials have resulted in death of the ewes. Grazing management (avoiding exposure to *Veratrum* during early pregnancy) has greatly reduced the incidence of losses from this condition.

Lupinus spp (lupines) occur throughout North America and encompass about 100 species. Many species are not toxic and serve as high-protein food sources. Some species contain the quinolizidine alkaloid anagyrine or the piperidine alkaloid ammodendrine which are teratogenic. Ingestion of toxic species of *Lupinus* by cows pregnant 40 to 70 days results in “crooked calf disease”. The malformations produced include severe arthrogryposis (twisted legs and immobility of the joints) scoliosis, kyphosis, torticollis and cleft palate. These malformations usually result in dystocia. Toxic lupines are most teratogenic during early growth or at the seed pod stage. Range management to limit exposure of cattle at 40 to 70 days gestation to the most teratogenic stages of lupine growth has greatly reduced the incidence of “crooked calf disease.”

Astragalus and *Oxytropis spp* are referred to as locoweeds. This is a large group of legume plants many of which are poisonous but many are nontoxic and provide excellent forage. Toxic locoweeds can produce several different syndromes depending on the species of plant. The name locoweeds comes from the bizarre nervous signs some species precipitate. Selenium poisoning can occur following ingestion of some species which grow best on seleniferous soils and concentrate selenium. Some species contain compounds which when metabolized can produce nitrate poisoning as an acute poisoning while chronic toxicity causes a weakness in the hindquarters with knuckling of the fetlocks called “cracker heels”. Locoweeds can impact reproduction by causing fetal malformations, interfering with placental function and by causing hydrops amnii and abortion. Congenital deformities most commonly produced include contracted tendons, lateral deviation of forelimbs, flexure of the carpus and rigidity of joints. Abortion rates can be as high as 60%.

Conium maculatum (poison hemlock) grows in barnyards, along roadsides and at the edges of grain and alfalfa fields. It contains piperidine alkaloids which produce a nervous syndrome that is often fatal in acute poisonings. Repeated sublethal doses cause teratogenic effects in cattle, sheep, goats and pigs which include cleft palate and multiple contracture-type skeletal malformations similar to those seen in “crooked calf disease.” Poisoning has occurred most often when feeds are contaminated with *Conium* seeds, when fields containing *Conium* are made into hay or silage or, in early spring, when *Conium* is often the first green forage to emerge.

Nicotiana tabacum (cultivated tobacco) induced teratogenic changes when sows ingested waste tobacco stalks during the first trimester of pregnancy. Tree tobacco (*Nicotiana glauca*) produced similar changes in cattle, swine and sheep. The induced skeletal changes include arthrogryposis, lordosis, torticollis and cleft palate. These changes have proven to be due to the presence of the

alkaloid anabesine not nicotine in the tobacco. Feeding studies with *Nicotiana*, and *Conium* and *Lupinus* employing ultrasound to monitor fetal movement has shown that the alkaloids in these plants cause an inhibition of fetal movement. The lack of motion and fetal repositioning results in the development of limb ankylosis, spinal deformities and cleft palate.

Any of the previously mentioned plant poisonings can produce fetal loss. Cattle ingesting the needles and /or buds of ponderosa pine (*Pinus ponderosa*) experience abortion or deliver premature calves which seldom survive without intensive care. In most cases fetal membranes are retained, often followed by septic metritis, toxemia and occasionally death if no treatment is provided. The principal compound causing premature parturition or abortion is isocupressic acid. Ponderosa pine is a valuable source of lumber and covers millions of acres in western United States. Cattle grazing ranges containing ponderosa pine suffer yearly losses estimated at from \$4.5 million to \$20 million. Two other trees that contain isocupressic acid and can cause abortion are Utah juniper (*Juniperus spp*) and Monterey cypress (*Cypressus macrocarpa*), which is found in New Zealand.

Gutierrezia microcephala (Snakeweed, Broomweed, turpentine weed) is a small western shrub which can cause abortions in cattle, sheep and goats at any stage of gestation. The plant contains numerous potentially toxic compounds. In addition to abortion, affected cattle demonstrate anorexia, weight loss, digestive upsets and jaundice. Some cattle exhibit edema of the vulva and udder.

Nitrates have been incriminated as a cause of abortion in cattle. The mammalian fetus is normally in a selectively hypoxic state in as much as its lungs are full of fluid and it must acquire oxygen through the placenta. Any reduction in the oxygen supply can lead to the demise of the fetus. Excess dietary nitrate is converted to nitrite in the rumen. Nitrite converts hemoglobin into methemoglobin which reduces the blood's ability to transport the oxygen necessary to maintain the fetus. Chronic nitrate poisoning also decreases progesterone production which can lead to abortion. Many plants can acquire excess amounts of nitrate due to over fertilization and/or adverse growing conditions. Common weeds such as *Chenopodium* (lamb's quarters), *Amaranthus* (pigweed), *Ambrosia* (ragweed) and canadian thistle (*Cirsium*) as well as some crops (corn, oats) can contain toxic levels of nitrates.

Dr Bartlett concluded his inaugural address in 1984 by stating that at that time the future of theriogenology depended on how it was chauffeured by the Society for Theriogenology and the American College of Theriogenologists. I know he must be proud, and as I am, more than a little bit in awe of the progress that has been achieved since his lecture. We have been blessed with many hard working, visionary leaders who have been dedicated to promoting our speciality and advancing education in theriogenology. Dr. Roberts stated in his Bartlett address that he felt he had lived in the "Golden Age" of Theriogenology. I am filled with the same feelings but I do have some concerns about how we can attract more applicants for both equine and food animal positions and how we can reduce the debt load of our graduating students. I hope we can find ways to surmount these challenges so we can increase our membership and provide some relief for our members in those fields. Also while I appreciate the value of computer based teaching for the saving lecture time and allowing the availability for re-visiting the presentations, I fear we may be drifting away from the personal contact and hands on experience that is so valuable in

mentoring our students. I feel ample personal contact is vital not only to teach technical skills but also to encourage empathy for patients and to demonstrate a professional manner and attitude when dealing with clients. I am proud to be a member of this fraternity and eagerly anticipate future advances in all phases of theriogenology. I thank you for your attention and for the privilege of presenting this Bartlett address.