



# Myotoxic Plants

## Poisonous Plant Class ADVS 586

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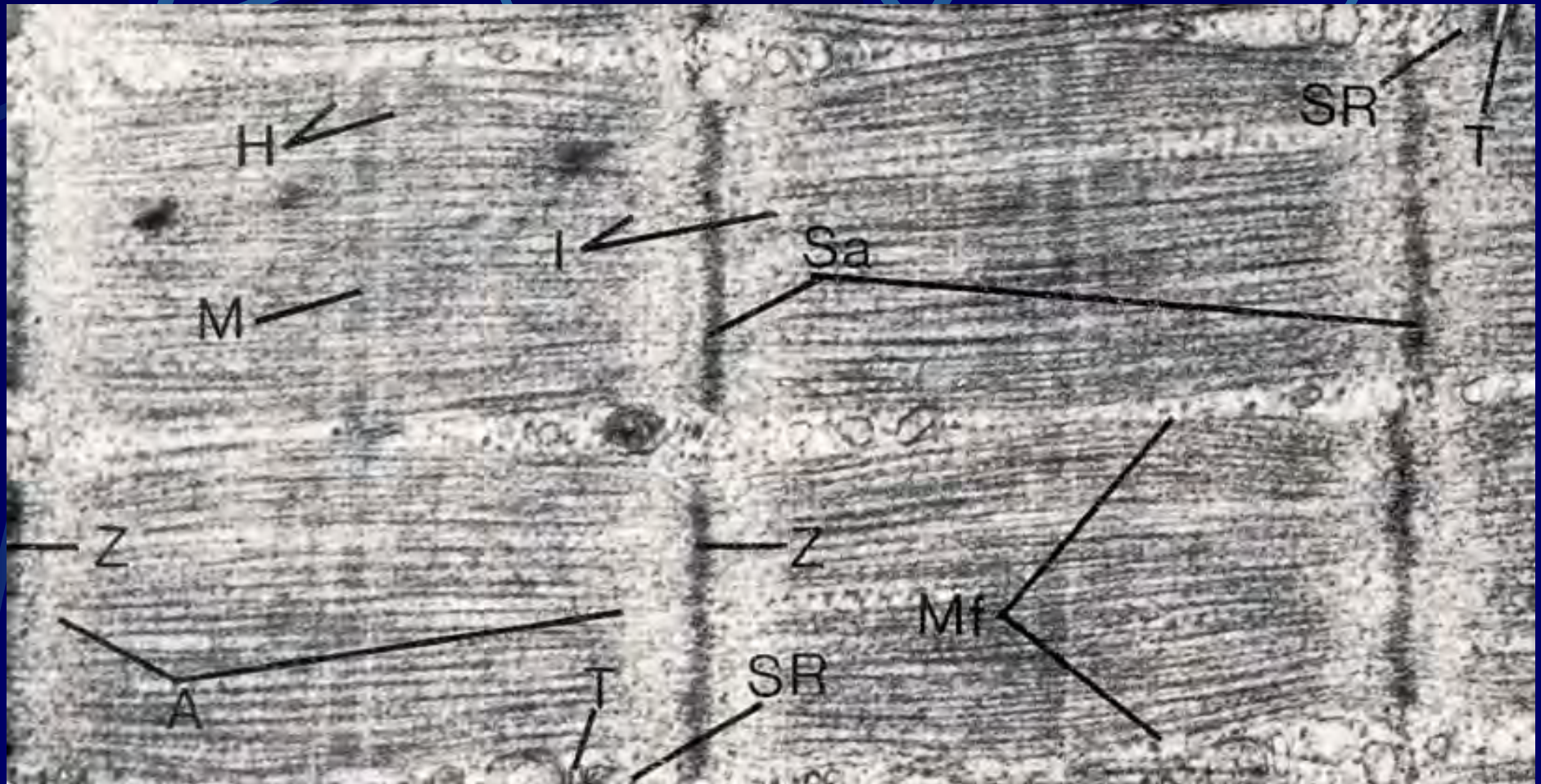
March 11, 2010

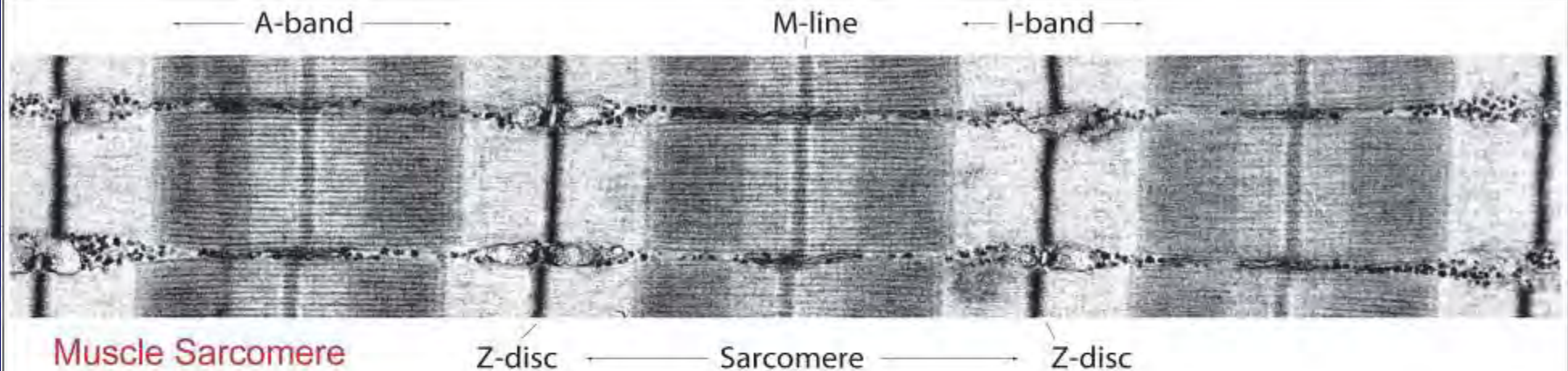
# Striated Muscle

- Types of muscle
- Mitochondria
- Sarcolemma

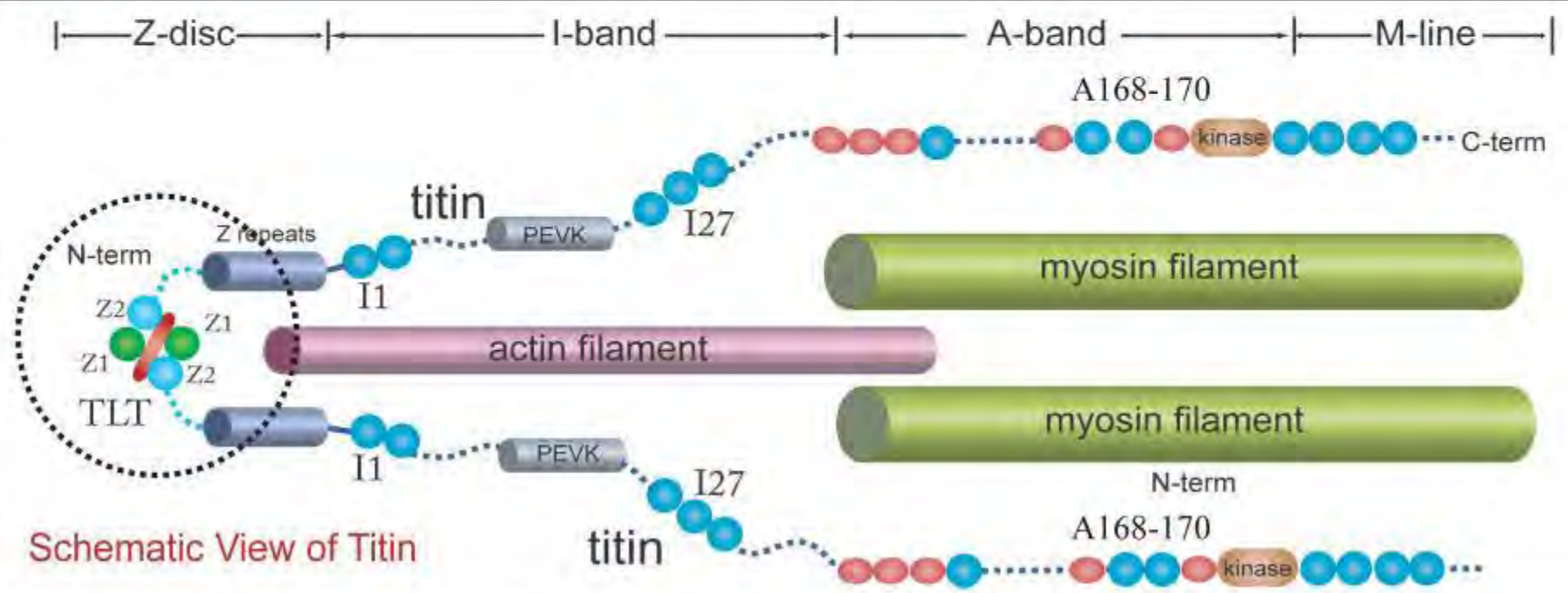


# Ultrastructure

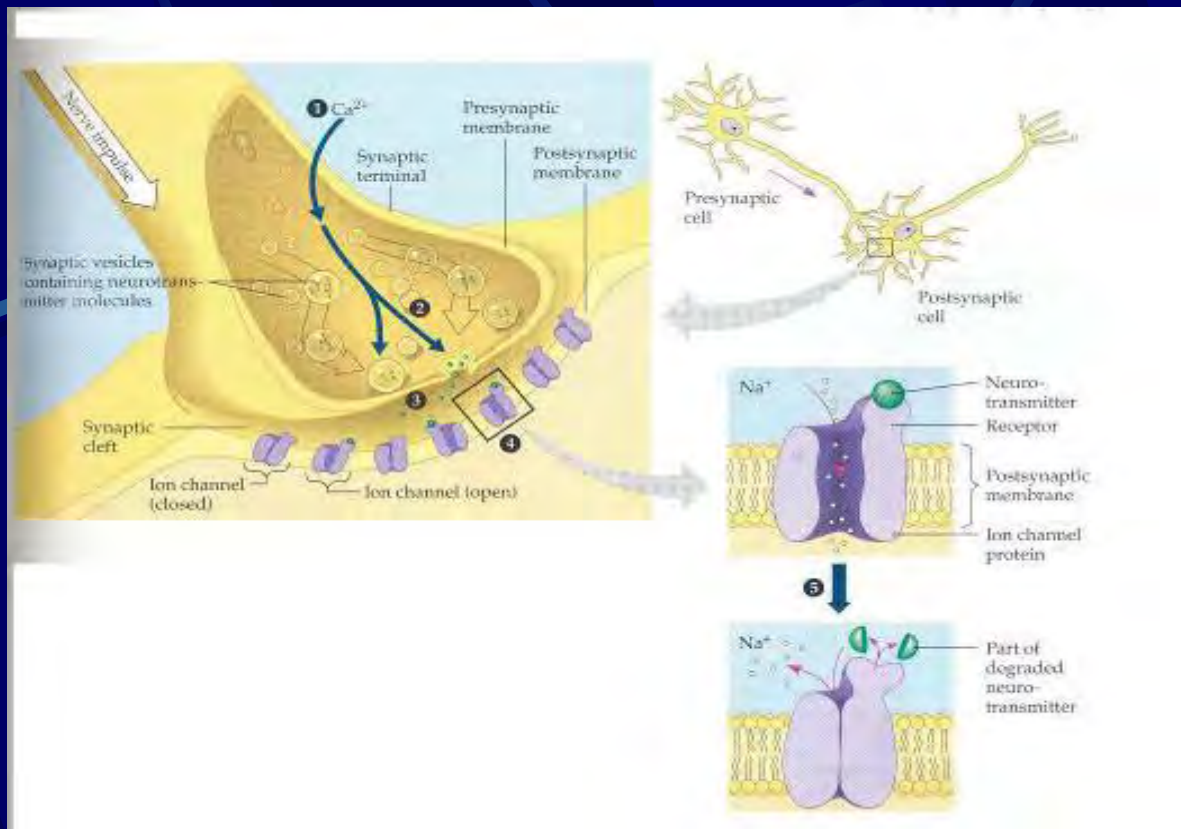




Muscle Sarcomere

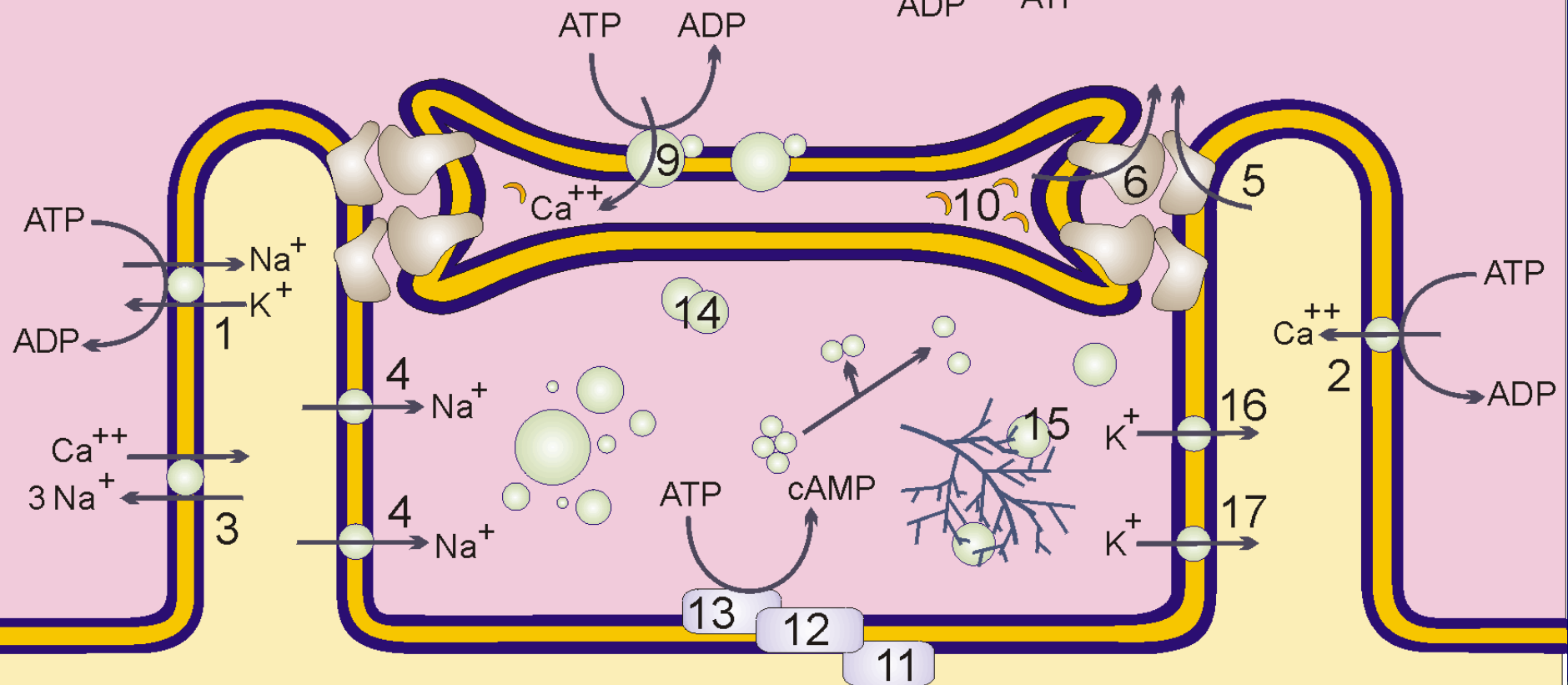
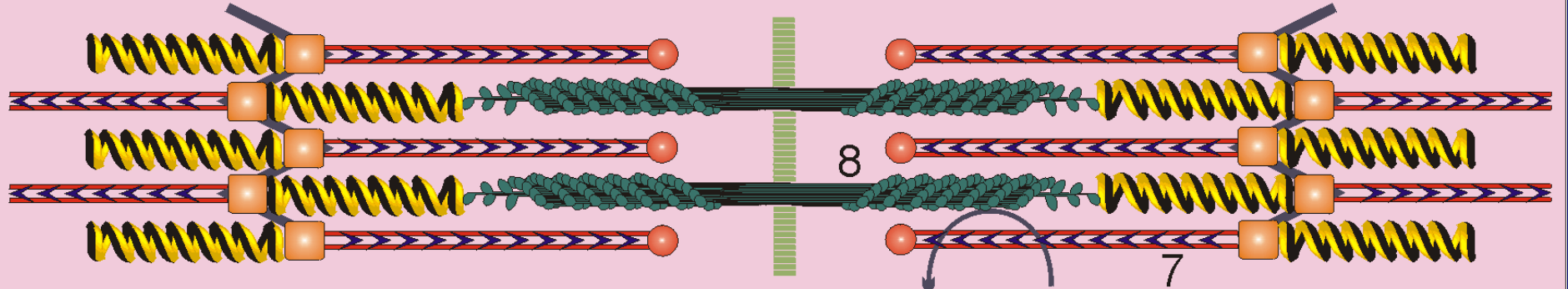


Schematic View of Titin



## Striated Muscle Toxins

- **Larkspur** (MLA block AchR)
- **Monkshood** (Aconitum inhibits Na channels)
- **Botulism** (cleaves synaptobrivin, syntaxin and SNAP-25 blocking cholinergic tx)
- **Tetnus** (tetanospasmin blocks glycine inhibition)
- **Cardioglycosides** (Inhibits Na/K ATPase enzyme)



# Myotoxic Plants

- Muscle structure and physiology
- Clinical and histologic lesions
- Myotoxic Plants
  - *Thermopsis montana*
  - *Eupatorium rugosum*
  - *Haplopappus*, *Aplopappus* or *Isocoma* spp.
  - *Cassia occidentalis* *O. obtusifolia*
  - *Kwarwinskia humboldtiana*
  - *Gossypium* spp.
  - *Lathyrus* spp.
  - *Vicia villosa*
  - *Solanum* spp. (enzootic calcification)
- Cardioglycoside Containing Plants
  - *Digitalis purpurea*
  - *Nerium oleander*
  - *Convallaria majalis* and *C. montana*
  - *Apocynum* spp.
  - *Adonis aestivalis*
  - *Pieris japonica* and *P. floribunda*
- Grayanotoxins
  - *Rhododendron* spp.
  - *Kalmia* spp.
- Other potential myotoxic plants



# Clinical Signs

- Anorexia, depression, droopy ears
- Reluctant to stand or move
- Swollen hard muscle
- Walk with slow, labored gait
- Weakness, trembling, ataxia
- Recumbency, coma, death





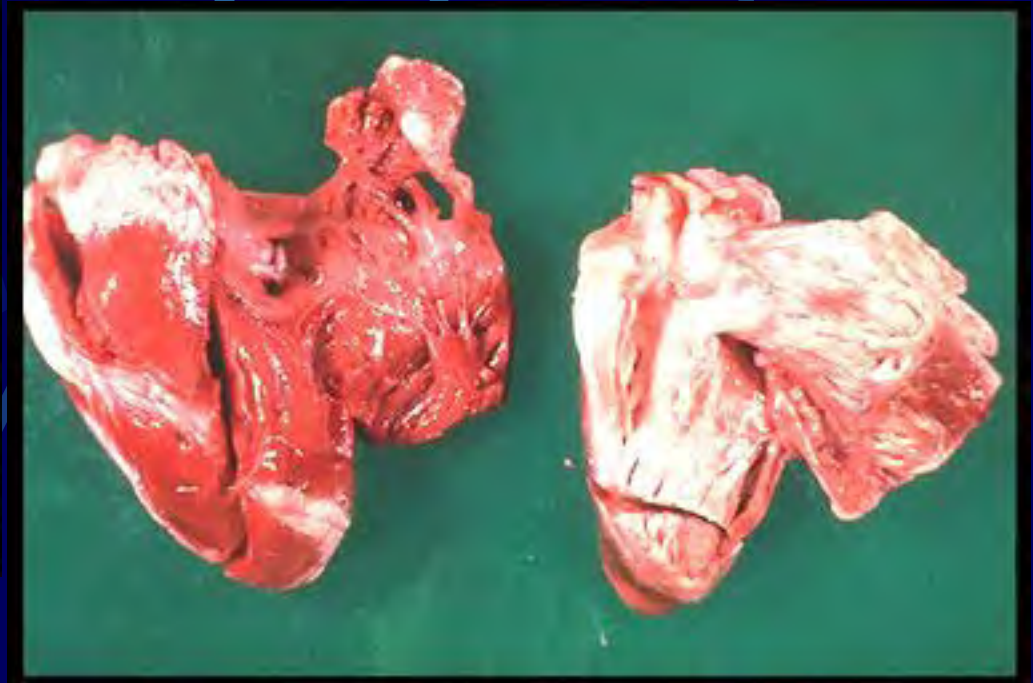
# Biochemical Changes

- AST
- CPK
- K
- Myoglobinuria
- Secondary changes

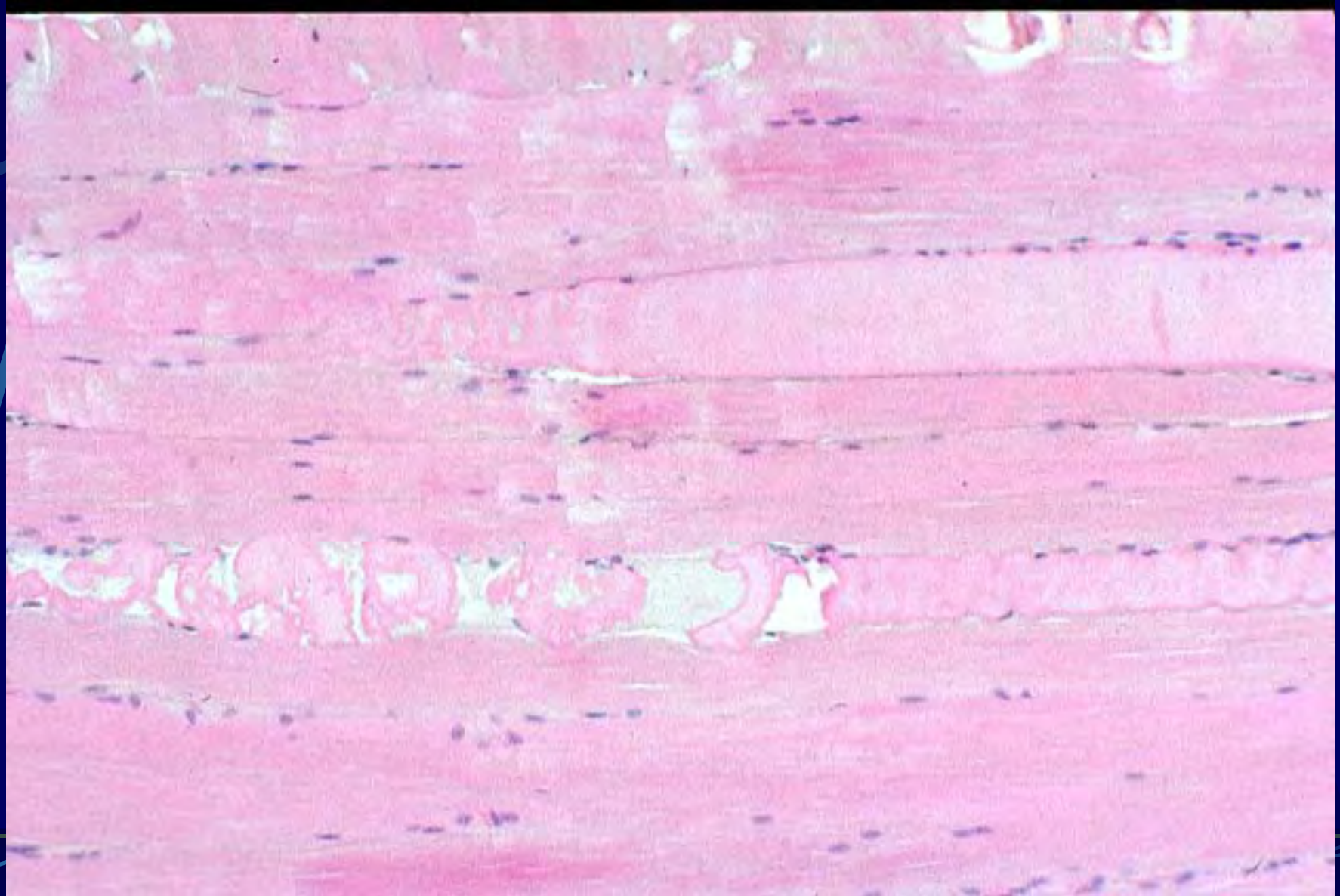
# Gross Lesion

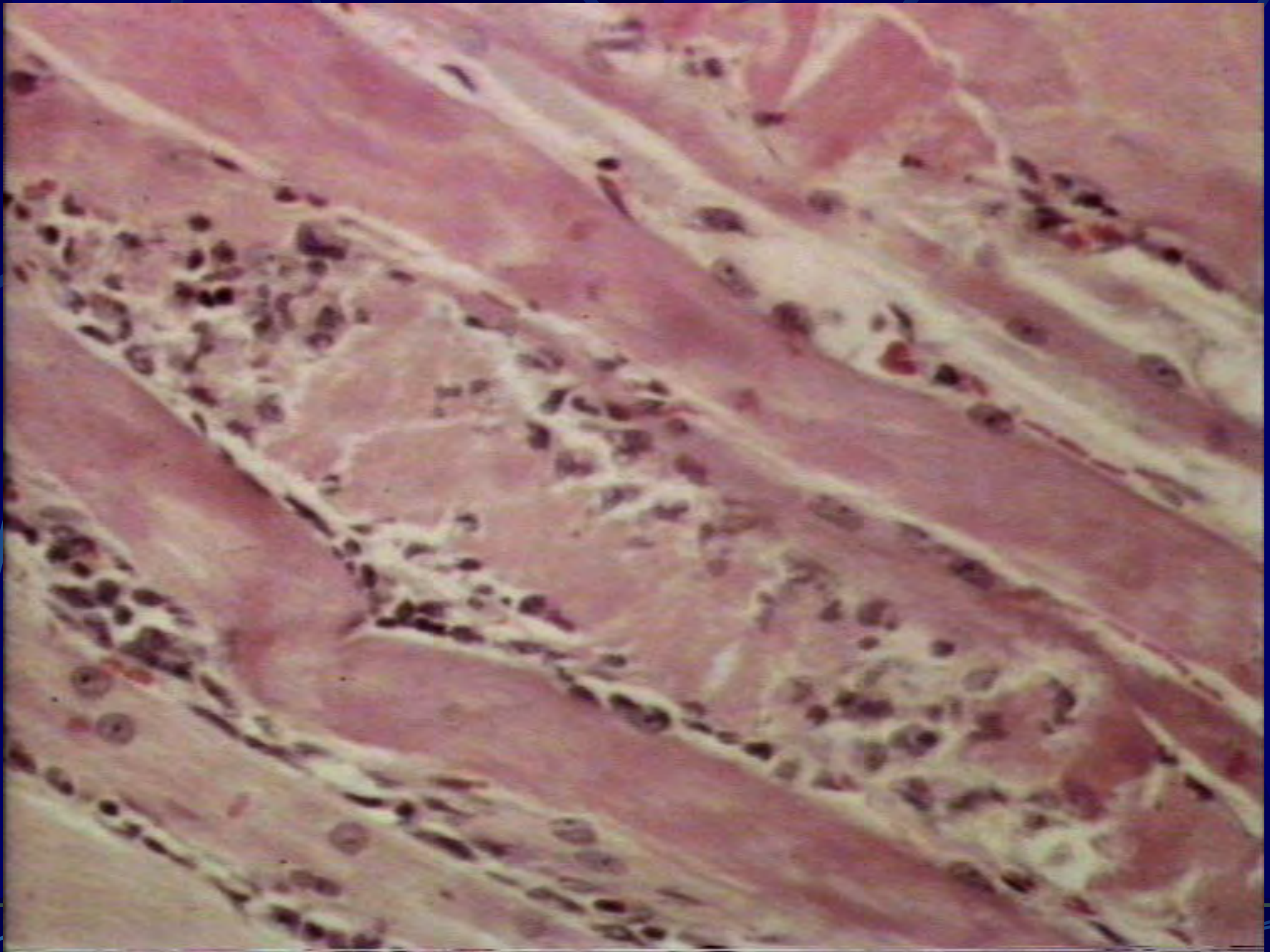
- Hard swollen muscles
- Pale streaking in muscle
- Secondary changes
  - Disuse atrophy
  - Congestive heart failure
  - Nephrosis
  - Hepatic lipidosis

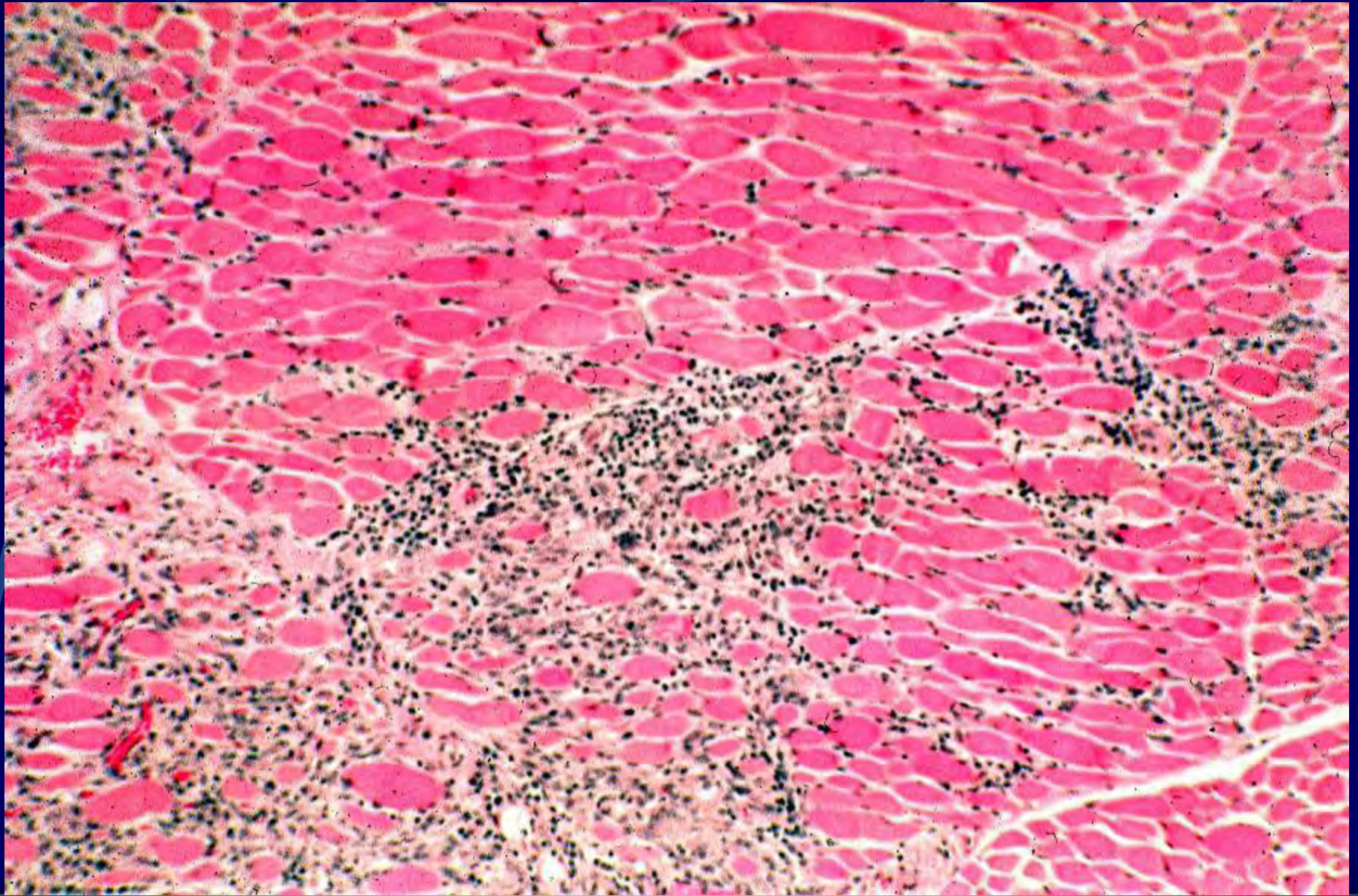




# Histologic Lesions







# “Tremetol”-containing plants

- Rayless Goldenrod  
(*Isocoma wrightii*)



- White Snakeroot  
(*Eupatorium rugosum*)



# Introduction

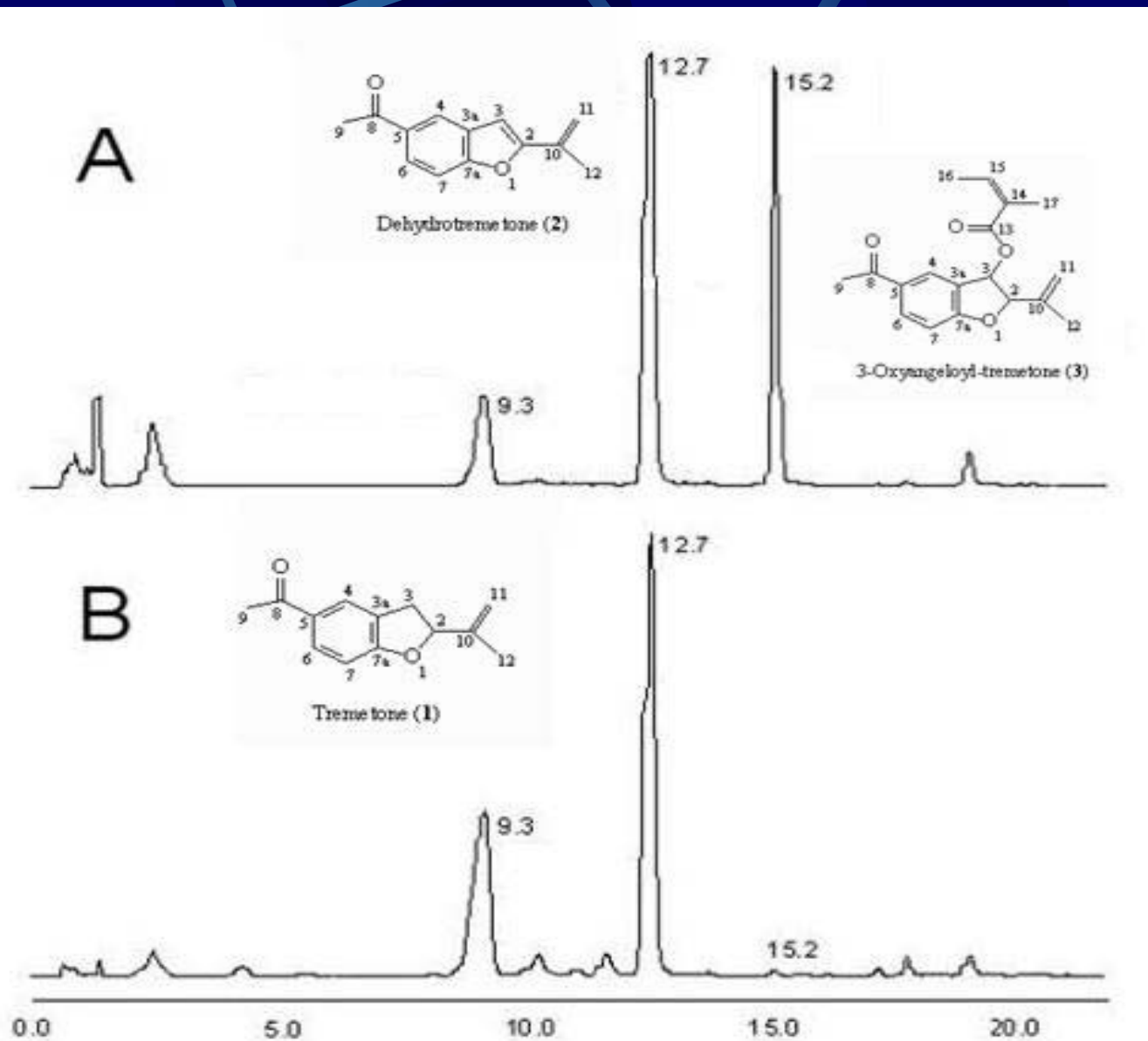
- Caused “trembles” and “milk sickness” in humans since the early 1800s (death of Abraham Lincoln’s mother)
- In 1930 the toxin was identified as tremetol
- In 1960s tremetol was determined to be a mixture of alcohols and ketones
- Comprised of 4 major benzofuran ketone compounds (tremetone, dehydrotremetone, 3-hydroxytremetone, and 3-oxyangeloyl-tremetone)
- Symptoms include depression, muscle weakness, reluctance to stand, and trembles especially following exercise
- Toxicity is sporadic



# White Snakeroot



# HPLC Chromatogram of Benzofuran compounds

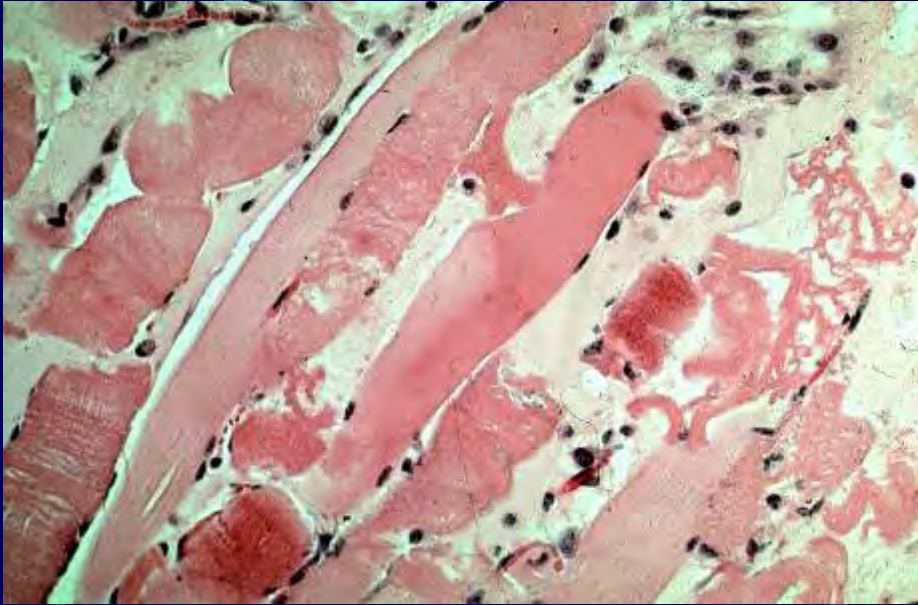


Compounds Concentration (µg/mg)											
Collection Site	Structure Numbers										
	1	2	3	4	5	6	7	8	9	10	11
<b>Illinois Sites</b>											
Stidham Woods	2.6	6.3	0.53								
Hart Woods	1.3	2.0	0.94								
Brownfield Woods	0.61		0.89								
Rutan Woods	0.86	5.7	0.99								
Larimore Property	4.7	2.7	0.53								
Interstate	2.0	0.079	0.43								
VRO	1.3	7.6	0.56								
Tonica	0.56	0.082	0.88								
Allerton Park	0.25	0.094	0.059				0.076				0.027
Trelease Woods	0.12	0.062	0.036	1.0		0.61					
<b>Missouri Sites</b>											
Davies County	0.20		0.075				1.4	0.090			1.1
Shooting Star Trail	0.21	0.32	0.052	0.010	0.17	0.039	1.3	0.047			0.69
Karst Trailhead	0.28	0.59	0.30	0.058	0.23	0.16	2.2				0.47
VMDL	0.19	0.34	0.066		0.33	0.079	0.58	0.040	0.27		0.55
Evans Place	0.22	0.35	0.094	0.14	2.1	0.11	0.77				0.87
Pierpont Meadows	0.16	0.16	0.056	0.050	2.4	0.10	0.59				0.44
<b>Indiana Site</b>											
Wabash River			0.021							9.9	
<b>Ohio Site</b>											
Cincinnati Zoo	0.053									1.7	

- Tremetol (mixture of tremetone, dehydroytremetone, dihydrotremetone and hydroxytremetone)
- Cytochrome P450 activated and quickly detoxified
- Green, dry and frosted plant are toxic
- Lipid soluble results in relay of secondary toxicity
- Stiffness, depression, ataxia, sternal recumbency, anorexia, tremors, coma, death
- Horses develop CHF



# Disease in Livestock



- 0.5-1.5% BW disease in 7-11 days
- 6 month old hay toxic
- Lactating cows protected
- Histology
  - Myonecrosis
  - Hepatic lipidosis
  - Hemorrhages and congestion
  - Gastroenteritis

*Jimmy Weed, Rayless Goldenrod, Burrow Weed*  
*Isocoma pluraflora (Isocoma wrightii),*  
*(Haplopappus heterophyllus)*

- An erect, sparsely branched, woody perennial growing to 1 meter high
- Sticky leaves are linear and alternate
- Yellow numerous flowers form small, terminal flat topped heads of 7 to 15 flowers







PPRL 2010



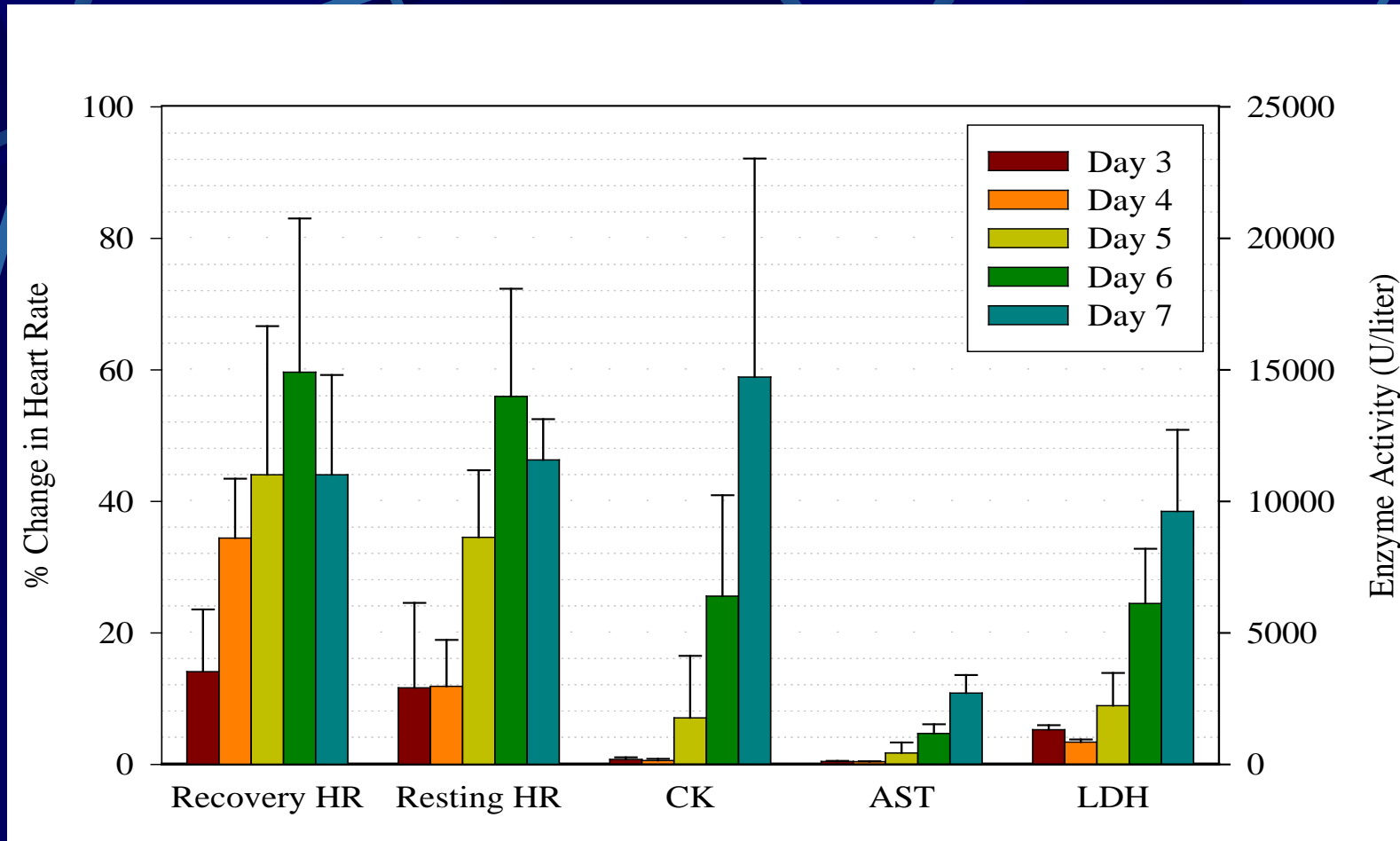
- Alkaline soils of drier rangeland, river valleys, drainage areas, and irrigation canals
- TX, NM, AZ, and CO
- Horses, cattle, sheep and goats
- 1.5% bw toxic in cattle





- 20 goats dosed via oral gavage for 7 days
- Treadmill evaluation of physical strength and endurance
- Electrocardiograms
- Hematology and serum biochemistry
- All animals were euthanized and the lesions (muscle necrosis) were evaluated via light and electron microscopy, histochemistry and immunohistochemistry

# Serum enzyme and heart rate changes of affected goats



## Muscles of affected goats



# *Senna or Cassia spp.* - coffee weed or coffee sena

- Troublesome weeds southeastern United States, Hawaii, Mexico. Opportunist annuals that grow in waste areas, roadsides, fence lines. Common as weeds of corn and soybean fields.
- Green and dry plants are toxic
- Poison horses, cattle, sheep and goats.

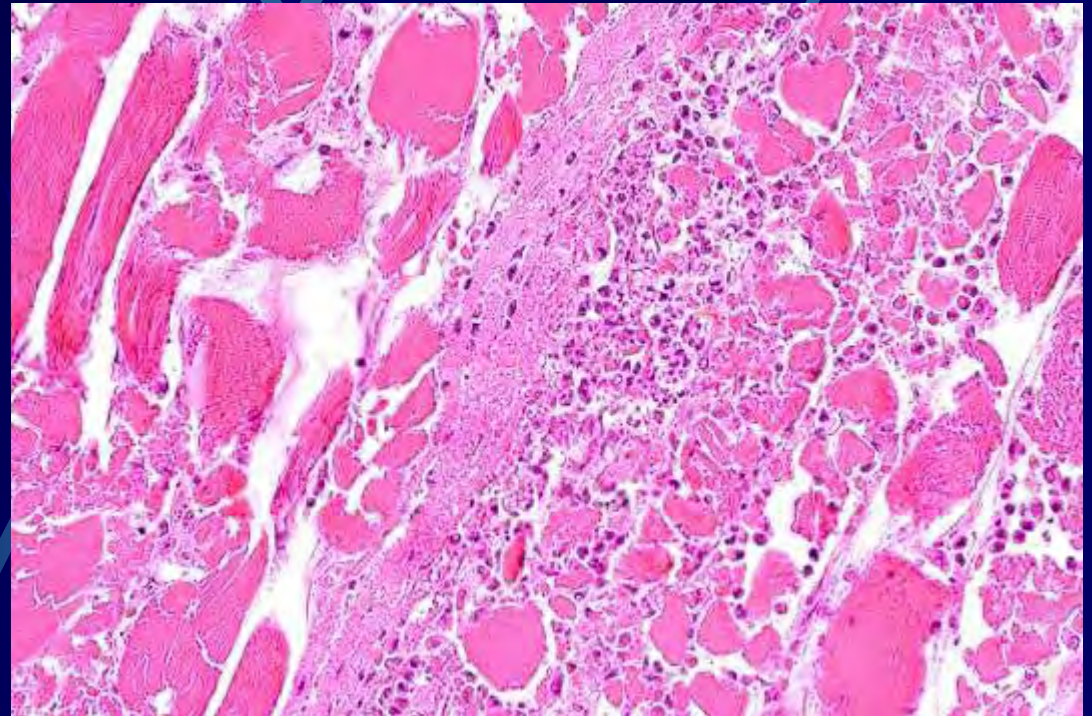


# *Cassia obtusifolia*



- Woody, erect, lightly branched annual, 2-3 m tall
- Alternate pinnate leaves with 4-5 pairs of leaflets spaced on common stalk
- Flowers are yellow in loose clusters on leaf axils
- Curved seed pods (20 cm) are thick, dark brown and slightly flattened with with pale longitudinal stripes and brown seeds

- Most poisoning in cattle occurs in Nov. and Dec. after frosts. Calves are more susceptible
- Horses may have liver disease sooner than the myonecrosis.
- Toxin is unknown but speculated to be substituted quinones- some evidence it uncouples oxidative phosphorylation.
- 0.4-12% BW toxic
- Skeletal and cardiac toxicity
- Recovery depends on the severity. Rarely does an animal recover once it has become recumbent.



## *C. roemeriana*, twin-leaf senna



- 30 to 70 cm tall principally on limestone soils in central and western Texas (yellow flower in spring and fall)
- Toxin is unknown but likely a quinone type compound
- Calves- hepatopathic poisoning, little-to- no skeletal muscle damage
- Goats- mild-to-severe skeletal muscle damage, and mild hepatocellular injury



# *Thermopsis montana* of *T. rhombifolia*- Golden Banner, Mountain Thermopsis, False Lupine, Yellow Pea

- A perennial pea like plant with a rhizomatous root system and erect, branching stems that reach a height of 30 to 46 cm.
- Alternate with three leaflets (lupine has 5+).
- Bright yellow flowers in dense racemes from the leaf axils
- Densely haired, erect seed pods that are straight (*T. montana*) or curved (*T. rhombifolia*).





- MO ID OR WA NE UT CO
- Quinolizidine alkaloids:
  - n-methylcytisine
  - cytisine
  - 5,6 dehydrolupamine
  - thermopsine
  - Anagyrine
- 1 g/kg BW for 2 to 4 days



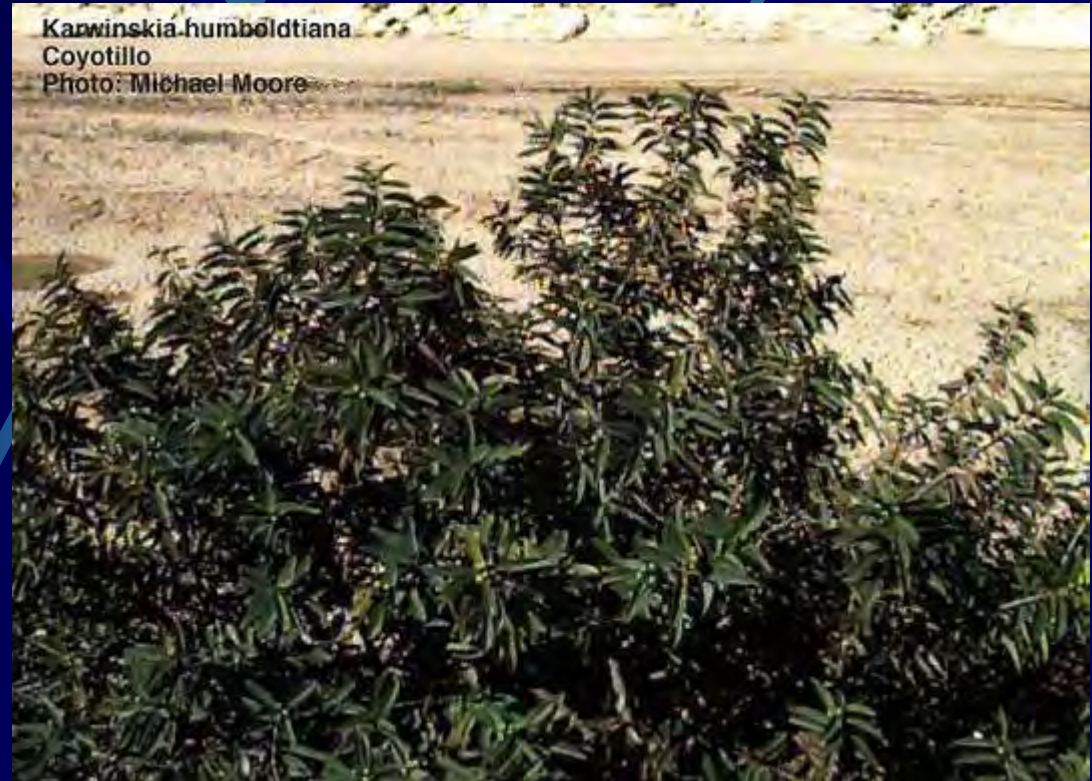
# Signs and Lesions



- Depression, weakness, trembling, recumbency and death
- Edema, arched back, swollen eyelids
- Increased serum enzymes
- Muscle degeneration and necrosis

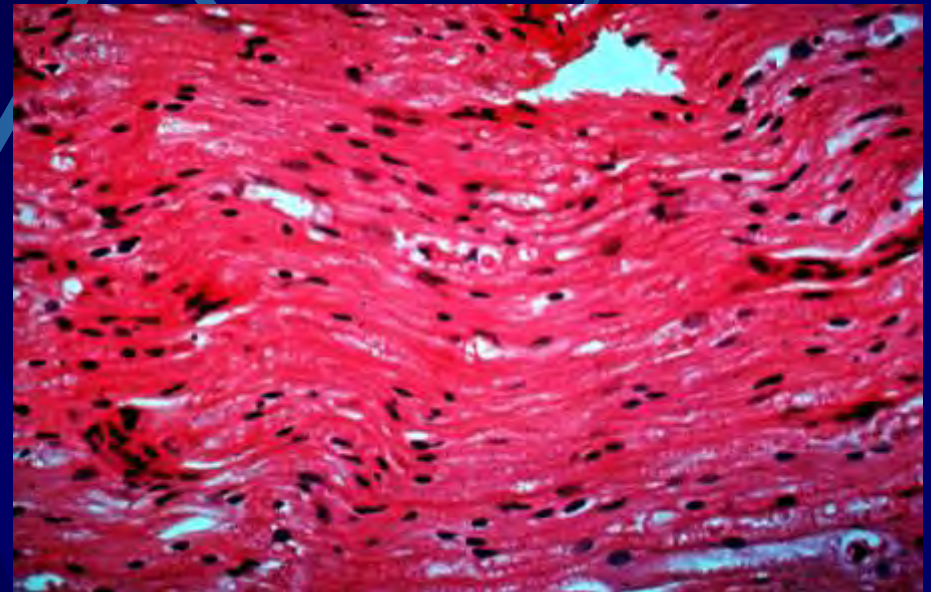
# *Karwinskia humboldtiana*

- Coyotillo, buckthorn, tanglefoot, tullidora
- Woody shrub or small tree
- TX, Mexico and SW States
- Gravelly hills, canyons, and along arroyos
- Polyneuropathy with ascending paralysis
- Anthracenones (T496, T514, T516, T544) usually called tullidinol and possibly other neurotoxins
- Interfere with neuronal synthesis and axonal transport
- Large, long axons most severely affected



# *Karwinskia humboldtiana*

- Cattle most sensitive but poisoning reported in goats, sheep, hogs, fowl, horses and man
- Signs
- Lesions: Demyelinating neuropathy, lymphadenopathy, epicardial hemorrhage, skeletal and myocardial degeneration and necrosis, nephrosis and lipidosis
- Axoplasmal dysruption, wallerian degeneration, myelin degeneration



# Gossypol

- *Gossypium* spp. (cotton plants)
- Polyphenolic binaphthalene found in the seed
- Monogastrics and young ruminants most susceptible
- Lesions
  - CSM for several weeks
  - Inappetence, weight loss, weakness, ascites, hydrothorax, CHF, skeletal and cardiac muscle degeneration and necrosis, regeneration



# *Lathyrus* spp.

- Europe, Africa, Russia and India
- People eat *Lathyrus* seeds
- *L. hirsutus*, *L. incanus*, *L. pusillus*, *L. sylvestris*, *L. odoratus* used in US
- Horses may be more susceptible
- Beta-(gamma-L-glutamyl)-aminopropionitrile
- Metabolized to aminopropionitrile that is thought to inhibit collagen cross linking (inhibits lysyl oxidase)
- Results in osteolathyrism and angiopathy- spinal cord and nerve degeneration, vascular aneurysms



- Cattle- stilted gait, weak, shift weight often
- Horses- severe weakness, laryngeal hemiplegia (roaring disease), lameness, sudden death





## *Vicia villosa*

- Hairy vetch
- OK and midwest
- Myotoxin plus hepatotoxin, and neurotoxin
- Granulomatous inflammation in heart, skeletal muscle, adrenal glands, kidney, thryroid, brain and lungs (hypersensitivity ?)



# *Cestrum diurnum*

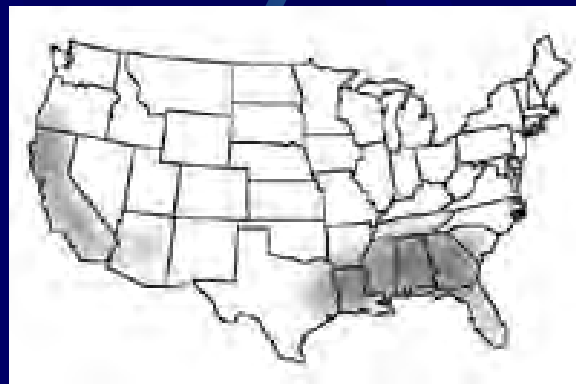
- 1,25-dihydroxycholecalciferol
- Increases Ca absorption from GI, increases Ca mobilization from bone, decreases renal Ca excretion
- Hypercalcemia and hyperphosphatemia-  $>60$  product=soft tissue mineralization
- Cardiac, pulmonary, renal, and gastrointestinal mineralization
- Dystrophic calcification



# US *Solanum* spp.



- *S. verbascifolium*,  
*S. torvum*,  
*Nierembergia*  
*veitchii*, *Cestrum*  
*diurnum*  
(jessamine, wild  
jasmine, day  
cestrum, king of the  
day, Chinese  
inkberry) FL



# Enzootic Calcification

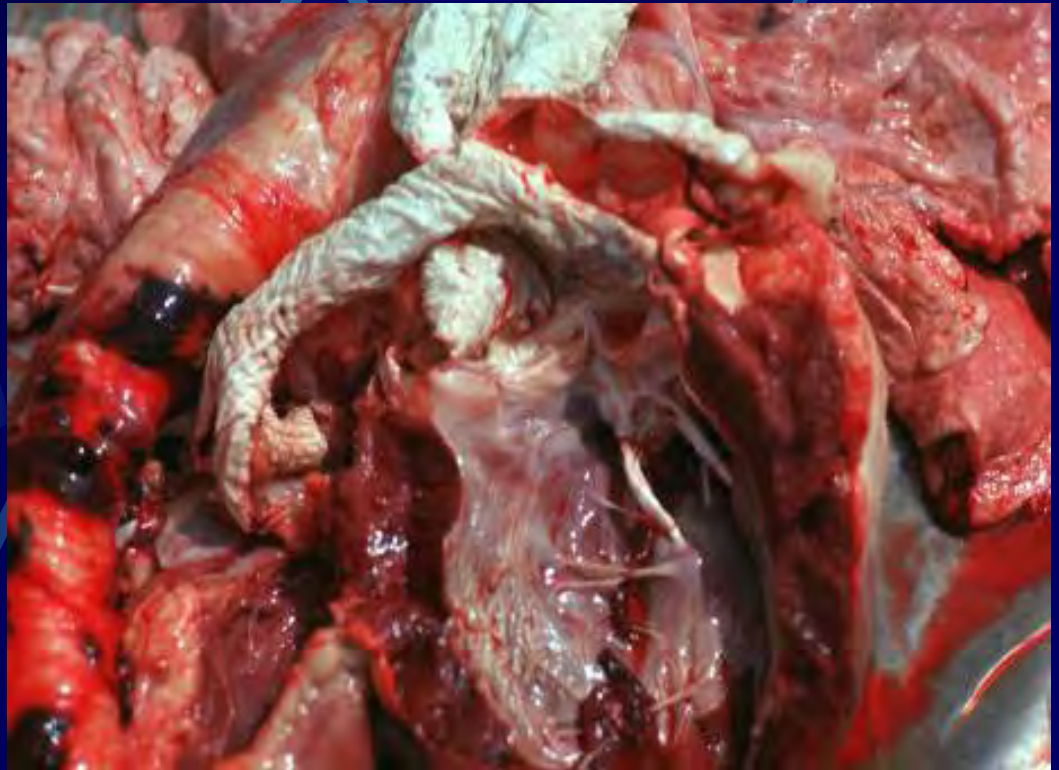
## Signs/Lesions:

- Chronic weight loss despite normal appetite
- Stiffness » lameness » recumbency
- Pain in the ligaments and tendons
- Heart murmurs » failure
- Calcification of tendons, ligaments, and elastic arteries » calcinosis of aorta, pulmonary arteries, heart valves, and endocardium



# Prognosis

- Recovery is rare if poisoning is chronic
- Less severely poisoned animals will probably recover if they are denied further access to the plant and are given a balanced ration.



# Cardiac Glycoside Containing Plants

- Digitalis (model compound)
- 100-200 mg/kg lethal
- 8% use results in toxicity
- Blocks Na/K ATPase causing increased intracellular Na and lowering the membrane potential
- Resulting increased Ca causes a positive inotropic effect
- High doses interfere with the cardiac conduction system especially the SA and AV nodes
- Asystole

# Lesions (Cardiac Glycosides)

- Arrhythmias (tachycardia), cold extremities, dilated pupils, blue mucous membranes, sweating, colic, anorexia, vomiting, diarrhea, bradycardia, heart block, asystole, and death.
- Minimal myocardial hemorrhage, myofiber vacuolation with minimal inflammation.

# *Digitalis purpurea*

- Foxglove
- Biennial herb from Europe, common on west coast
- Digtoxin, digoxin, gitoxin
- Toxic green or when dry





# *Nerium oleander*

- Ornamental throughout North America
- Evergreen shrub
- Nerioside, oleandroside, oleandrin, digitoxigenin, neriin, folinerin, oleandromycin, rosagenin, and odoroside that are similar to digitoxin
- Toxic green and dry
- Most poisonings from clippings



# *Convallaria majalis* and *C. montana*

- Lilly of the valley
- Ornamental throughout North America
- *C. montana* native to eastern US
- Convallarin, convallamarin, convallatoxin (cardiac glycosides)
- All parts, green and dry are toxic
- Signs persist for 3 weeks including dermatitis and gastroenteritis



## *Apocynum* spp.

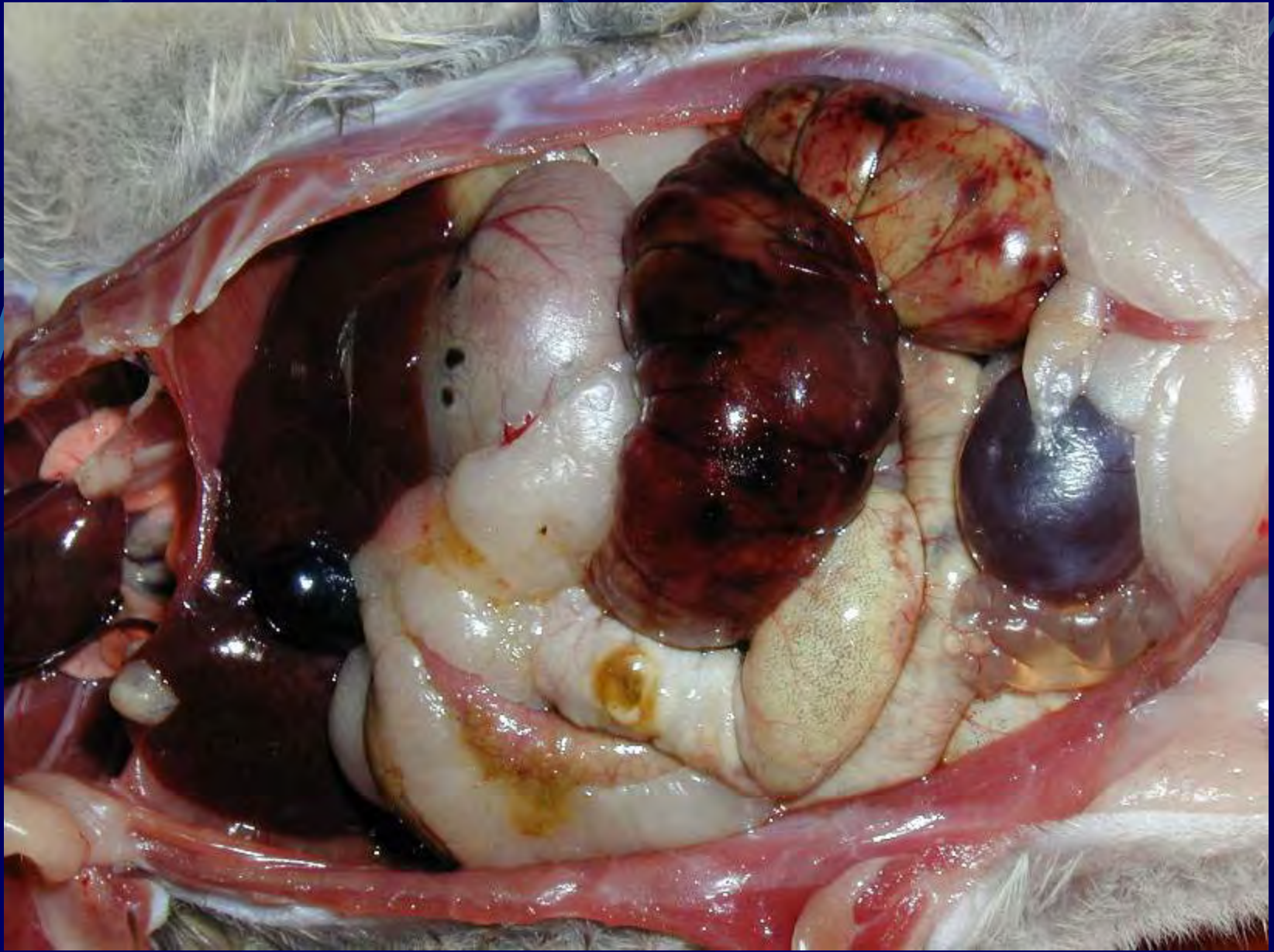
- Dogbane, Indiana hemp
- Perennial erect plant of North America
- Green and dry plant are toxic
- Root used therapeutically

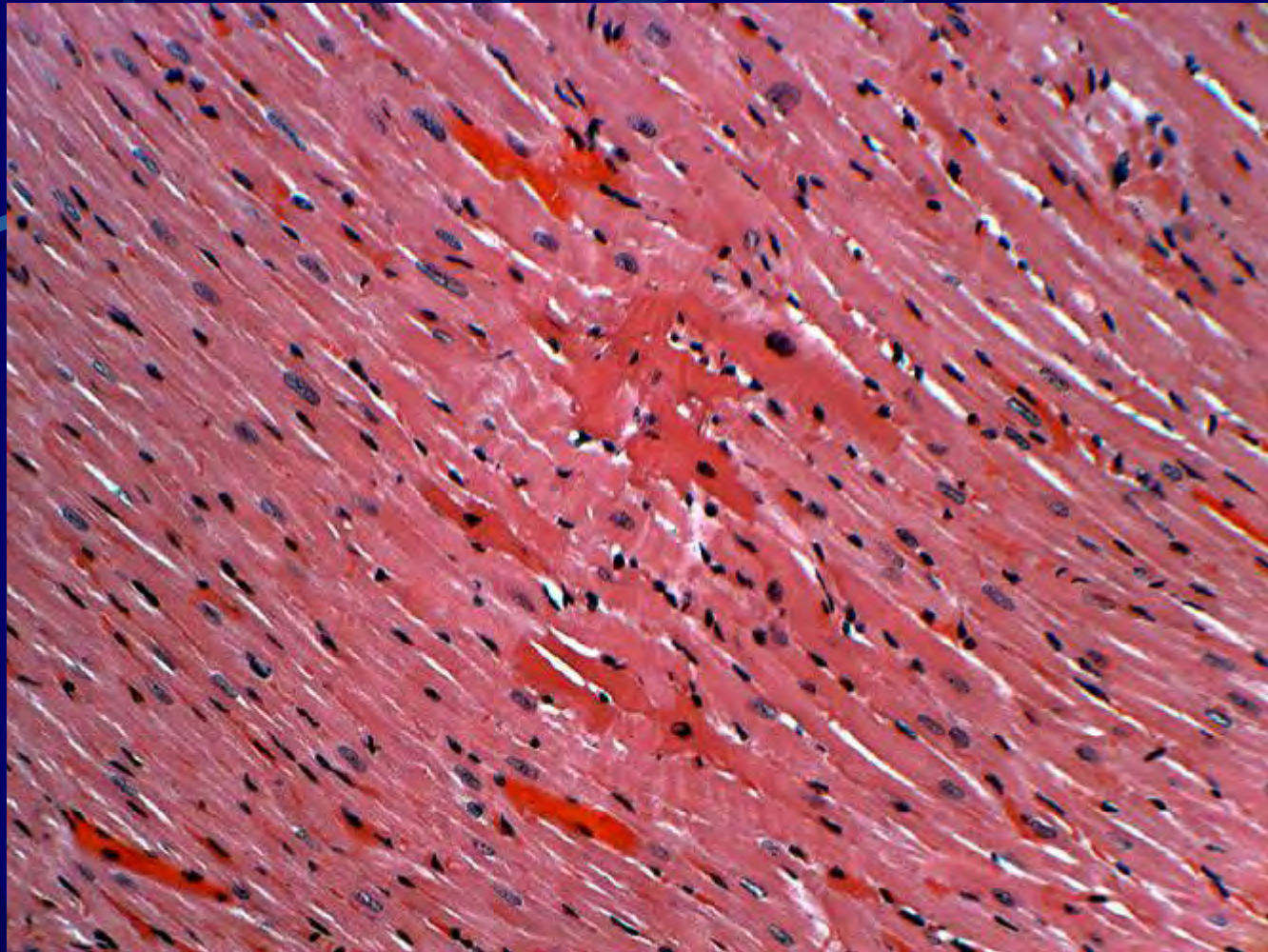


## *Adonis aestivalis* (Pheasant's Eye)

- Less toxic or more toxic?







# *Rhododendron* spp.

- Rhododendron
- Deciduous shrub found throughout North America
- Andromedotoxin, grayanotoxin (Alters Na channels)
- Cattle, sheep, goats, rarely horses and people have been poisoned
- All parts both green and dry are toxic
- Gastroenteritis, colic, salivation, epiphora, anorexia, depression, nausea, vomiting, defecation, weakness, incoordination, paralysis, absent pupillary reflexes, coma, nephrosis, liver degeneration, aspiration pneumonia



## *Kalmia* spp.

- Laurels
- Evergreen shrub
- grayanotoxin





# *Pieris japonica* and *P. foribunda*

- Japanese Pieris
- Woody shrub
- Grayanotoxin



## Other potentially myotoxic plants

- *Macadamia* nuts- transient muscular weakness in dogs
- Hops (*Humulus lupulus*)- malignant hyperthermia syndrome in dogs
- *Ixiolaena brevicompta*- Australian plant causing tiring syndrome in sheep
- *Helichrysum argyrophaeum*- South Africa
- *Geigeria ornativa*- South Africa
- *Cytisus scoparius*- Scotch broom, leguminous shrub



Disease of neglect

# *Centaurea* spp.

*Centaurea repens* or *Acroptilon repens*  
(Russian knapweed)





- Creeping perennial with black horizontal roots
- Erect, rather stiff, and branched plant up to 1 meter high
- Stems are covered with soft gray hair or nap
- Lower leaves are linear, alternate with toothed margins
- Lavender-white thistle-like flowers have papery spineless bracts
- The grayish seeds are 1-2 mm with bristles at one

# *Centauria solstitialis* (yellowstar thistle, Barnaby's thistle)



- Annual herbaceous weed, branching from the base up to 30 cm tall
- Winged ascending branches with cottony hair covered, basal, lobed leaves
- Yellow disc flowers tipped with characteristic stiff yellow spines (1 to 2 cm) long



- Aspartic and glutamic acids
- Sesquiterpene lactones, solstitialin A 13-acetate and cynaropicrin
- Dopaminergic neurotoxin, 2,3 dihydro-3, 5 dihydroxy-6-methyl-4 (H) pyran-4-1



- Weeks to months of exposure
- Green yellow star thistle equal to 86 to 200 percent of their body weight before clinical signs develop





# Chewing Disease

- Dysfunction of facial, mouth, and throat muscles (chewing disease)
- Facial paralysis that causes “smiling”, tongue lolling, protruding tongue, and head tossing
- Depression, loss of interest in food, dehydration and malnutrition, difficult breathing, incoordination, muscle tremors



# Negropallidal encephalomalacia

- Necrosis of the substantia nigra and globus pallidus (negropallidal encephalomalacia)
- As there is no treatment and the disease is irreversible, it is best to avoid exposure.

