PRELIMINARY STUDIES OF THE TOXICITY OF LOCOWEED EXTRACTS[1]

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Locoism, a chronic poisoning of domestic stock (horses, cattle, sheep, and goats) is produced by continued eating of most growths of the species of

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Astragalus and *Oxytropis* (Leguminosae). Seven of these plants known to produce locoism are listed by Marsh *et al.* (6, 7). A study of the disease in horses, cattle, sheep, and goats was carried out by Mathews (8). The toxic dose as dry weed approximates the body weight of the animal, and the time required for first symptoms to appear is about 60 days. Although various animals react differently, the typical complex consists of head tremor, progressive weakness, lack of coordination, aberrant behavior, and finally anorexia, cachexia, and death. Morphological changes are occasional intestinal ulcerations, polyhydramnion, and edema of cerebral nerve cell bodies.

Couch (2) found cats susceptible to loco poisoning when fed extracts of the weed, but was unable to produce the disease in goldfish, rats, and chicks. Mathews (8) warns that the handling of dry locoweed produces a severe inflammation of the moist membranes and painful hyperesthesia of the skin of man. The complete toxicity for man is unknown but one instance of locoweed poisoning, as reported by Crawford (3), occurred in Mexico in the early part of the century when symptoms similar to those of locoism in animals resulted from the drinking of beer made from the fermented weed.

The present paper reports pilot tests made in an attempt to determine the mode of action, and to seek other animals susceptible to the toxin.

Extracts of dry locoweed used were either prepared by the ion-exchange method of Chervenka and Wender (1) or were contributed by that group. Since the composition of the toxic principle is unknown and since no assay unit has been established, the dosage was based on the weight of dry weed from which the extract was made.

Three adult cats were locoed by feeding each the extract of one to two kilograms of the weed divided into daily doses for 40 to 60 days. The symptoms produced (head tremor, weakness, lack of coordination, "staring eyes", anorexia, and cachexia) were substantially the same as those reported by Couch (2), Fraps and Carlyle (4), and Fraps and Wender (5). In addition, we observed initial hyperesthesia of the feet, intermittent bouts of diarrhea, and intermittent abdominal distention. At the onset the limb weakness was hypotonic, but later the legs became moderately spastic. Two of the cats were removed from the diet containing locoweed extract and have evidently recovered completely after several months of gradual improvement. Anorexia disappeared first and the spastic lack of coordination disappeared last. The similarity of the symptoms of locoism to those of thiamin deficiency led to feeding one of these cats 50 milligrams of thiamine per day for 76 days following its removal from the diet containing locoweed extract. Its recovery was not appreciably different from that of the other cat that received only the basic diet of canned dog meat, canned fish, and milk after withdrawal of the extract.

Physostigmine salicylate increased the spasticity moderately when given subcutaneously in physiologically active doses to a cat that exhibited all the symptoms of locoism. Epinephrine had no effect on the symptoms.

One locoed cat was killed by severing the cervical cord. Although it was so severely locoed that it could scarcely stand or walk, the agonal trunk and limb movements that followed the severance of the cord seemed as strong as those of a normal angry restrained cat. This would seem to indicate that the primary lesion in this specimen was not in the cord or peripheral neuromotor system; it would further indicate that in locoism the brain exerts an inhibitory effect on lower structures.

The absorption spectra of the extracts used initially (1) were similar to those exhibited by niacin analogs. Consequently, 3.5 grams of trigonelline, 3.7 grams of N-1 methyl nicotinamide, and 3.1 grams of 3 acetyl pyridine were fed to cats in divided daily doses over a period of 62 to 70 days without visible effect.

Two mice were fed locoweed extract in addition to their regular diet for six months and four hamsters were fed extract for four months without effect. Four weanling hamsters were fed extract until their growth curves indicated maturity and were compared with control litter mates. The extract had no effect. One hamster was given subcutaneous injections of extract daily for fifty days without effect. In each case the total dry weed equivalent was many times the body weight of the animal.

The scant data at hand suggest that the primary effect of the toxin is one the cranial central nervous system, probably the cerebrum. There is thus far no clue regarding the biochemical mechanism involved or the basis of the specificity of the toxin for certain species.

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