Sweet Clover Disease

The hemorrhage inducing substance of improperly cured hay or silage isolated and synthesized

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THE DISEASE in cattle known in veterinary practice as "sweet clover disease" is caused by the eating of improperly cured hay or silage made from the common sweet clovers, *Melilotus alba* and *Melilotus officinalis*. Its occurrence was originally described by Schofield[7,8] in Canada (1921) and at about the same time Roderick[5,6] recorded the etiology and pathology of the disease in a study made at the North Dakota Agricultural Experiment Station.

When cows, sheep or rabbits are fed spoiled sweet clover hay made from any of the common *Melilotus* varieties, the disease causes a progressive diminution in the clotting power of the blood and the resultant hemorrhages usually prove to be fatal. Horses, sheep, and rabbits do not ordinarily contract the disease under natural conditions but have shown themselves equally susceptible in feeding experiments.

In cattle the age of onset is chiefly below three years, although Roderich[5,6] reported that mature and aged cattle will ultimately present the evidence of hemorrhage if the feeding with toxic hay is continued.

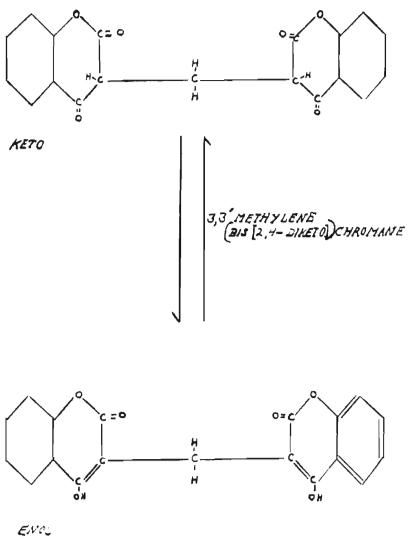
Roderick[5,6] observed that hemorrhage may occur in almost any part of the body but most frequently in the subcutaneous and intramuscular fascia. No visible alteration was found in the blood vessels to explain the internal hemorrhage, but external hemorrhage may readily be induced by any accidental or operative wound, as from dehorning or castration. At the time of parturition there is danger of death from hemorrhage to both the dam and the calf, for substances causing hemorrhage gain entrance to the fetal circulation.

The causative agent in the spoiled hay apparently survives the digestive process, enters the blood stream and by some mechanism, at present unknown, either prevents the formation of prothrombin in the liver or effects an inactivation of formed prothrombin. This same observation has recently been confirmed by Quick[4].

In 1934, Link *et al*[3] of the Wisconsin Agricultural Experiment Station began biochemical studies in an effort to extract the causative agent from hay known to induce the hemorrhagic condition characteristic of the disease. The spoiled sweet clover hay used in this work was produced experimentally from *Melilotus alba* by the procedure developed by Smith and Brink[9] of Wisconsin. In its color and tobacco-like, suffocating odor the artificially spoiled hay corresponded to the spoiled hays that are encountered in agricultural practice and, as Roderick[5,6] showed, are usually fatal to cattle. By use of an extraction and fractionation scheme they have succeeded in separating the hemorrhage inducing substance quantitatively from the spoiled hay. They are now able to produce consistently an active concentrate with a potency approximately 200 times greater than the original spoiled hay. This concentrate is essentially free from fats, waxes, certain

pigments, sugars, glucosides, water-soluble proteins and water-soluble decomposition products of chlorophyll.

When 0.6 Gm. of this concentrate is fed to standarized susceptible rabbits, the plasma prothrombin is reduced to 10 percent of the normal in 40 to 48 hours. This is equivalent to a two hundred fold concentration (minimum) of the hemorrhagic agent. C. P. Link (Wisconsin) in a recent lecture at Iowa State College, stated that the Wisconsin workers had been able to synthesize the factor responsible for the toxicity of spoiled sweet clover hay, the structural formula of which is as follows:



Because of the reduction in prothrombin it has been suggested that there might be some relationship between vitamin K and sweet clover disease. However, Link pointed out in his lecture that to date vitamin K therapy had been found to be of no value in the treatment of sweet clover disease.

This series of investigations by C. P. Link *et al*[3] on hemorrhagic sweet clover disease was undertaken at the suggestion of Dr. R. A. Brink of the Wisconsin Genetics Department, who, in 1933, initiated the first trials to select a non-bitter strain of sweet clover.

Schofield[7,8] early recognized that the disease could be controlled in cattle by the withdrawal of the spoiled hay from the diet and by the injection of blood serum freshly drawn from normal cattle.

A transfusion of 2cc. per kilo of body weight of fresh defribinated bovine blood which, when filtered through sterilized linen, has been successful in saving life when other measures have failed. Citrated blood also is curative in the proportion of 0.5 - 1.0 percent sodium citrate in a liter of blood. The coaguability of the blood returns in from 15 to 30 minutes after the transfusion through the restoration of the prothrombin activity. Recovery is complete in from a week to ten days.

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