RELATION OF BITTERNESS TO THE TOXIC PRINCIPLE IN SWEETCLOVER[1]

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INTRODUCTION

During the last three decades, sweetclover in North America has risen from the status of a roadside weed to a place of importance as a forage crop. This rapid adoption as a cultivated crop has taken place in spite of several undesirable characteristics. One of the factors at present limiting its usefulness is its rather bitter taste. Although livestock, at first reluctant to eat it, become accustomed to the taste, the bitterness may be a disadvantage when sweetclover is used for pasture in mixtures with grasses and other clovers. Another limiting factor is that unless sweetclover hay is thoroughly cured, certain changes may take place during storage in the stack or mow which render the hay toxic when fed to livestock. The resulting disease has been referred to as "sweetclover disease." Some studies on the relation between the two undesirable characteristics—bitterness and toxicity—are described in this paper.

THE SWEETCLOVER DISEASE

In 1922 Schofield (*9*)[3] called attention to a disease in cattle characterized by low clotting power of the blood and the development of extensive hemorrhages which were usually fatal. He showed the causal relation of the feeding of spoiled sweetclover hay or silage. Since that date, numerous reports of the occurrence of the disease have appeared. A careful series of studies on the pathology and therapy in cattle was made by Roderick and Schalk (*8*) with observations on the malady in other livestock. Roderick (*7*), working on cattle, has shown that in this disease the low clotting power of the blood is the result of a deficiency of prothrombin—one of the constituents of the blood essential for clotting. This finding has recently been confirmed by Quick (*5*) on rabbits by the use of the technique of Quick, Stanley-Brown, and Bancroft (*6*) for prothrombin determination.

Cannon and Greenwood (*4*) observed in rabbits a lowering of the calcium content of the blood on a diet of well-cured sweetclover hay and suggested that hemorrhage in sweetclover disease may be linked

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[3] Italic numbers in parentheses refer to Literature Cited, p. 153.

with the decline in serum calcium. In testing this point with cattle, Brown, Savage, and Robinson (*3*) found that variations in blood calcium and phosphorus were not significant either when the animals were fed well-cured sweetclover hay or when the clotting power of the blood was low following a feeding period on a known toxic sweetclover hay.

MATERIALS AND METHODS

In the present studies rabbits were used exclusively. The rabbit consumes a small amount of feed, and as was first noted by Schofield (*10*), gives a prompter response than cattle. The progress of the disease has been followed by recording the clotting time of small samples of blood taken at intervals during the feeding period. Approximately one-half cc of blood is allowed to drop from a freely bleeding incision in the marginal vein of the ear into a 50-mm watch glass. Another watch glass of the same size is inverted over the first and the time required for clot formation is determined by tilting the watch glasses at 30-second intervals at a laboratory temperature of 23° to 24° C. In a normal rabbit a firm clot forms in 5 to 7 minutes. Young rabbits, 8 weeks old, are much more susceptible than mature animals, but among rabbits of the same age a marked difference in reaction to the toxic principle has been observed.[4] Some show a prolonged clotting time with a small amount of toxic hay, while others show no symptoms even on an exclusive diet of toxic hay over a prolonged period. Further, as Roderick (*7*) found to be the case with cattle, there is no indication in rabbits of an acquired resistance to the toxic principle. One can induce the symptoms of the disease in a susceptible rabbit, allow it to recover on a nontoxic diet, and in subsequent feeding of the same amount of toxic hay the reaction will be very similar, allowance being made for advancing age. For comparisons of the relative toxicity of spoiled hays, a group of rabbits is subjected to a preliminary feeding test on a known toxic hay in amounts proportional to the body weight (45 g per 1,000 g of body weight daily) and those showing symptoms promptly in the blood clotting test are transferred to nontoxic feed in an early stage of the disease. After an interval of several days, they may be used in comparative trials.

Toxic hay can be prepared by drying to 40 or 50 percent moisture freshly cut common sweetclover, stacking it, and covering the piles as described below for individual tests. In the experiments of Roderick and Schalk (*8*), the hay was allowed to remain in small piles for 60 days or more. The writers have found, however, that the hay may become toxic in a much shorter period. In one test, 290 pounds (green weight) of Hubam, an annual form of *Melilotus alba* Desr., cut when in midflower, was dried in the sun to 49 percent moisture, put in a pile in a basement laboratory, and covered to a depth of about 6 inches with slightly wilted third-cutting alfalfa. After 8 days the pile was opened and a feeding test begun with two mature susceptible rabbits. After 7 days of feeding, one animal showed a clotting time of 30 minutes as compared with 5 minutes at the beginning of the test, while the other showed 26½ minutes as compared with 6 minutes, indicating a fairly toxic sample of hay. Another larger pile (400 pounds green weight) was found to be highly toxic in a feeding test beginning 9 days after stacking. No contin-

[4] SMITH, W. K. THE ALLEGED PROTECTIVE ACTION OF ALFALFA AGAINST THE HEMORRHAGIC SWEETCLOVER DISEASE. Unpublished.

uous temperature records have been taken in piles of sweetclover spoiled under the conditions described above, but observations indicate that after 5 to 7 days a maximum temperature is reached. The pile then begins to cool. These observations suggest the relation of the heating period to the development of toxicity.

EXPERIMENTAL DATA

TESTS TO DETERMINE TOXICITY OF SPOILED MELILOTUS DENTATA AND HUBAM SWEETCLOVER

The bitter taste characteristic of common sweetclover seems not to have been reported in any other cultivated forage crop of importance. Likewise, the disease induced by the feeding of spoiled sweetclover has not been associated with the eating of any other feed. There arises therefore the possibility of some relationship between the bitter principle of common sweetclover and the development of the toxic principle in spoiled sweetclover hay. An annual form of the typically biennial *Melilotus dentata* (W. and K.) Pers., found to be nonbitter in 1933 (*1*), seemed to offer favorable material to test the existence of such a relationship. Comparisons have been made of the toxicity of spoiled hay of the annual *M. dentata* and Hubam.

A preliminary test made in 1934 was inconclusive because of the small amount of hay available and the moldy and resulting unpalatable nature of the nonbitter hay. In this trial, however, the Hubam was found to be toxic and the nonbitter to be nontoxic.

TABLE 1.—*Reaction of susceptible rabbits when fed spoiled Melilotus dentata and Hubam sweetclover hays prepared in 1935*

Kind of spoiled hay fed	Rabbit No.	Period on diet	Weight	Period on diet	Blood-coagulation time
		Days	*Grams*	*Days*	*Minutes*
Hubam	[1] 34–R–4	0	2,170	0	5
				4	12
Do	[2] 27–A–3	0	1,910	0	5
		7	1,859	4	15½
				6	34
M. dentata	17–A–5	0	2,235	0	5
		7	2,211	4	5
		14	2,235	7	6
		21	2,213	14	6
				21	5½
Do	40–R–4	0	2,262	0	5½
		7	2,192	4	6½
		14	2,125	7	5
		21	1,819	14	5
				21	6
Hubam	[3] [4] 17–A–5	0	2,213	0	5½
		5	2,203	5	13½
Hubam plus 30 g mixed grain daily	[3] [5] 40–R–4	----------	----------	0	4
				6	7
				10	18

[1] Dead on morning of the sixth day from a typical ear hemorrhage.
[2] Died on the seventh day with severe hemorrhage into the lung cavity.
[3] 17–A–5 and 40–R–4 on Hubam after a 21-day period on *M. dentata*.
[4] Died on the seventh day with severe intestinal hemorrhage.
[5] On tenth day transferred to nontoxic feed.

In the 1935 season 400 pounds (green weight) of Hubam in full bloom and a similar amount of the nonbitter annual in early bloom were cut and allowed to dry in the field until the moisture content was 52 percent for the Hubam and 47 percent for *Melilotus dentata*.

A pile of each was made in a basement laboratory. Both stacks were covered with paper, burlap, and canvas and in both vigorous heating took place. When opened for feeding after 9 days, both hays were brown with only limited amounts of mold growth. The hays were then fed ad libitum to four rabbits (two for each pile), with the results shown in table 1.

It is apparent from the data in table 1 that the Hubam sweetclover was highly toxic, inducing a significant increase in the time of blood clotting on the fourth day and killing the two rabbits (34–R–4 and 27–A–3) on the sixth and seventh day, respectively. In contrast, the blood of rabbits on the nonbitter sweetclover (*Melilotus dentata*) remained normal over a feeding period of 21 days. At the conclusion of the initial feeding period the two surviving rabbits were transferred from *M. dentata* hay to Hubam to verify their susceptibility. Of the two rabbits, 17–A–5 consumed daily during the 21-day period amounts of *M. dentata* hay comparable to that eaten by the rabbits on Hubam and maintained its weight throughout; a blood-clotting time of 15½ minutes on the fifth day of the Hubam diet and the death of this rabbit on the seventh day (table 1) demonstrate its susceptibility. On the other hand, 40–R–4 ate somewhat less *M. dentata* than the rabbits on Hubam and lost some weight during the feeding period. To compensate for this smaller consumption of nonbitter hay, when spoiled Hubam was fed, 40–R–4 received daily 30 g of mixed grain and it was estimated that by this means the amount of Hubam ingested daily was less than the daily amount of the nonbitter hay. Nevertheless, 40–R–4 showed a clotting time of 18 minutes after 10 days of feeding, indicating its susceptibility to the toxic principle.

A quantity of hay from an additional larger stack of *Melilotus dentata* sweetclover (800 pounds dry weight) which had undergone a satisfactory spoilage was fed to two additional susceptible rabbits over a 48-day period with no indication of any change in the clotting power of the blood.

In each test, the common bitter sweetclover, when spoiled, became toxic while the spoiled *Melilotus dentata* showed no indication of toxicity. Even a low level of toxicity would have been revealed since the clotting time of the blood was determined at intervals during the feeding period. There is therefore substantial evidence that the nonbitter *M. dentata* does not become toxic when the hay is stacked with a relatively high moisture content. This finding adds weight to the suggestion that the bitter principle of common sweetclover is causally related to the development of toxicity in spoiled hay.

THE RELATION OF COUMARIN TO TOXICITY

Coumarin is responsible, in part at least, for the bitter taste of common sweetclover. It has recently been shown by Brink and Roberts (*2*) that the nonbitter species, *Melilotus dentata*, does not contain this compound in measurable amount in the vegetative tissues, although small amounts were found in the seeds. Because of the absence of measurable amounts of coumarin in *M. dentata* hay and the nontoxicity of the spoiled hay, a relationship is suggested between the presence of coumarin and the production of the toxic principle in spoiled common sweetclover hay.

Coumarin apparently does not induce the sweetclover disease. Roderick and Schalk (*8*) administered coumarin in capsules to rabbits and none of the animals showed the typical symptoms of the disease. Furthermore, large numbers of cattle and other susceptible livestock when on sweetclover pasture or on well-cured sweetclover hay ingest daily considerable quantities of coumarin with apparently no effect on the clotting power of the blood. Likewise considerable quantities of spoiled alfalfa are eaten annually by cattle with no clear evidence of the occurrence of this disease. As described in detail below, coumarin was added to alfalfa, the mixture was allowed to spoil, and the resulting product was fed to rabbits.

On October 19, 1935, a lot of 500 pounds (green weight) of freshly mown third-cutting alfalfa was spread out in a greenhouse and with frequent turning was allowed to dry to approximately 50 percent moisture. It was then put through a silage cutter, and when taken to a basement laboratory was divided into two equal portions, one of which was piled up without further treatment. The other was spread out and 1 pound of coumarin ground in a ball mill was added by sifting through an 80-mesh screen; this amount gave a concentration of coumarin of 1.4 percent on the dry-weight basis—a percentage comparable to that found in sweetclover tissue. The alfalfa was turned frequently while the coumarin was being added. It was then piled up and both lots were covered with paper, burlap, and canvas. Strong heating developed rapidly in the control pile and in 3 days vigorous mold growth was apparent. The covering was removed from this material after 8 days. The alfalfa to which coumarin had been added heated more slowly, and even after 7 days no mold growth was apparent microscopically. Because of the writers' early experience of the low palatability of moldy sweetclover, the heavily molded alfalfa was not saved for feeding. In the control pile the mold infestation was so severe that the amount of mold-free hay was insufficient for a critical test of toxicity, but in the alfalfa treated with coumarin only small amounts of moldy hay were noted towards the outside of the pile. Two susceptible rabbits, fed for 10 days on the spoiled coumarin-treated alfalfa (table 2), showed clear-cut symptoms of the disease, indicating that coumarin plays a rôle in the development of toxicity.

TABLE 2.—*Reaction of two susceptible rabbits fed spoiled coumarin-treated alfalfa prepared in 1935*

Kind of hay fed	Rabbit no.	Period on diet	Blood-coagulation time
		Days	*Minutes*
Spoiled coumarin-treated alfalfa	29–A–2	0	6
		9	17½
		10	47
Do	16–A–4	0	6
		9	41
		10	60+
Well-cured alfalfa	27–A–2	0	7
		9	6
		10	7

FEEDING OF MELILOTIC ACID AND COUMARIC ACID

It has been pointed out above that coumarin does not induce the sweetclover disease but alfalfa treated with coumarin and allowed to spoil does become toxic. There is the possibility, therefore, that during spoilage coumarin is converted into a closely related compound. Two such compounds, melilotic acid and coumaric acid, which are present in relatively small amounts in sweetclover, were prepared and each was fed in capsules to two susceptible rabbits over a period of 33 days. A mixed grain and alfalfa hay were fed ad libitum. During the first 3 days each of the four rabbits received 0.1 g of compound. The amount was increased every 3 days until on the fifteenth day each received 0.75 g and by the thirtieth day, 1.5 g. The blood of the four rabbits, which was tested at intervals of a few days during this period, remained normal throughout. If all the coumarin in sweetclover tissue were converted during spoilage into melilotic acid or coumaric acid, the amount of each would rarely exceed 1 percent of the dry tissue. An animal consuming 75 g of hay daily would not absorb an amount of each compound greater than 0.75 g daily. Further, clear-cut symptoms of the disease can be detected after 5 days of feeding on a sample of sweetclover hay of moderate toxicity. One can conclude, therefore, that the amounts of melilotic acid and coumaric acid are adequate and that neither compound is directly responsible for the symptoms of sweetclover disease.

A difference was observed between the effect of coumaric and of melilotic acid on the animals. The two rabbits receiving coumaric acid had a normal appetite during the feeding period and maintained their weight, one of the rabbits at the end of the 33-day period weighing only 34 g less than at the beginning of the period, while the other weighed 17 g more. In contrast, the animals receiving melilotic acid showed signs of digestive disturbance by the fifteenth day, consuming decreasing amounts of grain ration. Alfalfa was being fed ad libitum and no weighings were made. It was apparent, however, towards the end of the feeding period, that both animals ate only the stems and refused the leafy part of the forage. One rabbit with an initial weight of 2,665 g lost 739 g in 33 days and the other with an initial weight of 2,324 g lost 452 g.

ADDITION OF MELILOTIC ACID LACTONE TO ALFALFA BEFORE SPOILAGE

The toxicity of alfalfa treated with coumarin before spoilage has already been mentioned. Since melilotic acid occurs in sweetclover in appreciable amounts and coumarin is fairly readily converted into melilotic acid in vitro, an attempt was made to determine whether melilotic acid plays a rôle in the development of the substance or substances responsible for the diminution of the prothrombin in the blood of animals afflicted with sweetclover disease. For an adequate test an amount of acid in excess of 1 pound was required. Since the lactone form can be prepared in quantity more readily than the free acid, the former was used in this experiment.

A quantity of third-cutting alfalfa was mowed on October 6 and dried down in the field to 48 percent moisture. It was then chopped in a silage cutter, taken to a basement laboratory, and put in three equal lots, each lot containing 210 pounds of partially cured hay. The first lot was left untreated; the second received 646 g of coumarin

as described in the earlier experiment; the third was treated with 655 g of melilotic acid lactone applied to the hay as a fine spray while the hay was being turned. All lots were piled and covered as earlier described. The temperature rose in the control pile more rapidly than in the other two. The control pile was likewise the first to begin cooling off. Although no temperatures were recorded during the heating period, it was estimated that all three piles heated to a similar degree. After 14 days all piles were opened and the temperature towards the center of the pile recorded; in the alfalfa plus coumarin lot, it was 42.25° C., in the alfalfa plus melilotic acid lactone 47.5°, and in the control pile 37.5°. The portions of hay having a heavy mold infestation, which was most abundant on the control pile, less on the plus lactone pile, and slight on the plus coumarin, were discarded; the remainder—with the exception of the bottom of each pile—was spread out to dry at room temperature with circulating air. When fed to susceptible rabbits, each rabbit received hay in amounts proportional to body weight. The results of the feeding tests are shown in table 3.

The absence of toxicity on the untreated but spoiled alfalfa in table 3 is in agreement with the results of farming practice wherein annually considerable quantities of brown or moldy alfalfa are fed to cattle with no indication of the symptoms of sweetclover disease. The increase in the clotting time of the blood of the two rabbits fed alfalfa treated with coumarin confirms the results of the experiment of 1935. The association of coumarin with the alfalfa tissue during spoilage in some way leads to the development of the toxic principle. There was no indication of any toxicity in the alfalfa treated with melilotic acid lactone. Although one test cannot be considered conclusive, the fact that the hay treated with lactone was part of the same lot of chopped hay used for the test with coumarin, and after treatment was kept under conditions as nearly as possible the same as the toxic coumarin-treated material, suggests that melilotic acid lactone is not a factor in the development of toxicity.

TABLE 3.—*Reaction of susceptible rabbits fed alfalfa treated with coumarin and with melilotic acid lactone prior to spoilage*

Kind of spoiled hay fed	Rabbit no.	Period on diet	Blood-coagulation time	Kind of spoiled hay fed	Rabbit no.	Period on diet	Blood-coagulation time
		Days	*Minutes*			*Days*	*Minutes*
Alfalfa alone	53–F–5	0	7½	Alfalfa plus coumarin	S–50	0	6½
		5	6½			5	16
		7	6			7	15
Do	54–F–1	0	6	Alfalfa plus melilotic acid lactone	50–S–3	0	6½
		5	6			5	6
		7	6½			7	6
Alfalfa plus coumarin	53–F–6	0	6	Do	S–48	0	6
		5	13			5	6
		7	12			7	5

DISCUSSION AND CONCLUSIONS

The widely accepted view that the characteristic bitterness of the common sweetclovers is basically attributable to coumarin has been strengthened by the discovery of a nonbitter *Melilotus* species of

which the vegetative parts are coumarin-free. It is now shown that the presence of coumarin in sweetclover has an even wider significance. Not only does the substance contribute to unpalatibility but it also gives rise to the toxic condition in spoiled hays associated with the so-called sweetclover disease in livestock.

Two lines of evidence are brought forward showing that the disease-inducing property of certain sweetclover hays results from the coumarin present in the fresh material. Recognition of *Melilotus dentata* as a sweetclover whose vegetative parts are free of coumarin provided the basis for one approach to the toxicity problem. Supplementing the evidence from this source are the results of experiments involving the addition of coumarin to partially cured alfalfa hay.

The toxicity of the various diets employed was measured by the change in time required for blood clotting in rabbits shown to be susceptible by a preliminary test.

Using hays prepared in two different years under conditions favorable to vigorous heating, direct comparisons were made between the disease-inducing capacity of an annual form of common white sweetclover and annual *Melilotus dentata*. The evidence shows that only the common sweetclover becomes toxic, the spoiled *M. dentata* hay failing to alter the blood-clotting time even with prolonged feeding. There is thus established within the genus *Melilotus* itself a parallel between the presence of coumarin and the capacity to become toxic. It would appear from these results that the absence of coumarin in the vegetative parts of *M. dentata* is the explanation both for the nonbitterness of the species and the nontoxicity of its spoiled hays.

Confirmation of this view is found in the results of further feeding experiments in which alfalfa was treated with coumarin. Roderick and Schalk (*8*) have already shown by feeding trials with rabbits that coumarin as such is not toxic, a finding which is in accord with the general observation that cattle ingesting considerable amounts of the substance on sweetclover pastures do not develop the disease. Nor is the feeding of spoiled alfalfa hay known to affect the clotting power of the blood. In the present experiments a markedly toxic preparation was obtained, however, by adding coumarin to alfalfa dried to approximately 50 percent moisture and allowing the mixture to heat. The time required for the blood to clot increased from 6 minutes to 47 and 60+ minutes, respectively, with the two rabbits fed for 10 days on this material. This result establishes a direct relationship between the presence of coumarin and the development of toxicity in a spoiling hay.

The factor immediately responsible for sweetclover disease remains to be worked out. It is shown in the present investigations that the toxicity may arise within 7 days in a vigorously heating sample of common sweetclover hay. The inference is that some change involving coumarin occurs during the fermentation period which gives rise to a substance in the hay having a destructive effect on prothrombin in the animal. Melilotic acid and coumaric acid are found to be nontoxic so that a transformation of coumarin into either of these closely related compounds during the heating period would not explain the disease-producing property of the spoiled hay. It was likewise found that the addition of melilotic acid lactone to alfalfa preceding spoilage failed to render the hay toxic. As a working hypothesis

it may be suggested that coumarin interacting with another constituent or constituents of the plant tissue common to both sweetclover and alfalfa, under moisture and temperature conditions favorable for spoilage, gives rise to a specific toxic substance.

These findings are of significance in the improvement of sweetclover as a forage plant. The evidence clearly points to the conclusion that bitterness and toxicity have a common basis in coumarin. Reduction of coumarin content by breeding or the discovery of coumarin-free forms offers the possibility not only of improving palatability but also of removing the hazard associated with the feeding of spoiled sweetclover hays.

SUMMARY

Melilotus alba, a bitter sweetclover, on being stacked at about 50 percent moisture and allowed to heat, gives a hay which, when fed to rabbits, induces a condition characteristic of the so-called sweetclover disease in cattle by markedly lowering the clotting power of the blood.

Parallel tests with *Melilotus dentata*, a sweetclover which has recently been recognized as being nonbitter, show that this species does not become toxic on being similarly spoiled.

Neither spoiled alfalfa hay nor coumarin appears to modify the clotting power of the blood. If, however, coumarin is mixed with partially cured alfalfa hay containing about 50 percent moisture, the mixture on being allowed to heat becomes distinctly toxic.

Melilotic acid and coumaric acid, compounds closely related to coumarin, are like the latter substance in that they do not induce sweetclover disease on being fed to rabbits.

In one test melilotic acid lactone added to alfalfa before spoilage, contrary to the behavior of coumarin, did not induce toxicity.

It is tentatively suggested that coumarin interacting with another constituent or constituents of the plant tissue, under conditions favorable for spoilage, gives rise to a specific toxic substance which is responsible for the sweetclover disease in animals.

Since coumarin appears to be a basic factor in both bitterness and toxicity, the development of nonbitter forms of sweetclover gives promise not only of improving the palatability of this plant but also of eliminating the hazard associated with the feeding of improperly cured hay.

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