REVIEW ARTICLE

ARTICLE DE REVUE

Alsike clover poisoning: A review

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Abstract

Trifolium hybridum (alsike clover) has been implicated as the cause of two diseases of the horse. One of these is photosensitivity, of which alsike clover is only one of a number of presumed causal agents. The other is a fatal syndrome which is known as "alsike clover poisoning" and which is manifest by progressive loss of condition, signs of hepatic failure, and varying degrees of neurological impairment. The underlying lesion of alsike clover poisoning is fibrosis and proliferation of the biliary tree. The experimental evidence implicating alsike clover as the cause of this syndrome comes entirely from a series of feeding trials performed by Dr. Frank Schofield between 1928 and 1933.

This review surveys the literature on the association of alsike clover with both photosensitivity and biliary fibrosis in horses, and summarizes the clinical and pathological features of "alsike clover poisoning". The experimental evidence that has been used to implicate *Trifolium hybridum* as the cause of alsike clover poisoning is critically examined. It is concluded that the existing experimental evidence is insufficient to prove that *Trifolium hybridum* is the cause of alsike clover poisoning.

Résumé

Intoxication par le trèfle alsike : une revue

Deux maladies furent reliées à l'ingestion de *Trifolium hybridum* (trèfle alsike) chez le cheval. La première est la photosensibilité bien qu'il y ait beaucoup d'autres agents présumément impliqués dans son développement. La seconde, l'intoxication par le trèfle alsike, est un syndrome fatal qui se caractérise par une perte de condition progressive, des signes d'insuffisance hépatique et des désordres neurologiques variables. La lésion hépatique sous-jacente dans l'intoxication par le trèfle alsike se manifeste par de la fibrose et une prolifération des canaux biliaires. L'évidence expérimentale impliquant le trèfle alsike dans ce syndrome provient exclusivement de travaux effectués par le Dr Frank Schofield entre 1928 et 1933.

Une revue de la littérature sur l'association du trèfle alsike avec le développement de photosensibilité et de la fibrose biliaire chez les chevaux ainsi qu'un résumé des observations cliniques et pathologiques de l'intoxication par le trèfle alsike sont présentés. L'évidence expérimentale témoignant de l'implication de *Trifolium hybridum* dans cette intoxication est évaluée. Cependant, cette dernière est insuffisante pour conclure définitivement que *Trifolium hybridum* est la cause directe de l'intoxication par le trèfle alsike.

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Introduction

In the late 1920's, Dr. Frank Schofield of the Ontario Veterinary College became interested in a syndrome of biliary fibrosis and associated clinical signs which was recognized in horses in northern Ontario. After conducting a series of field and experimental investigations during the late 1920's and early 1930's, he became convinced that a legume, *Trifolium hybridum* (alsike clover), was responsible. Consequently, the term "alsike clover poisoning" was adopted by veterinarians and horsemen in reference to this syndrome.

Alsike clover poisoning is a disease that is still regularly diagnosed in horses in various parts of Canada. It has been neglected by veterinary researchers and experimental studies have not been published since Schofield's time.

My intent in this paper is to critically review the available literature on alsike clover poisoning for the benefit of equine practitioners and diagnostic pathologists, and to highlight those questions about the syndrome that require further research. For the purposes of this review, the term "alsike clover poisoning" will refer to a specific clinicopathological syndrome associated with the pattern of biliary proliferation and fibrosis described below. The classical hepatic lobule will be used as the basis for the pathological description because most of the literature was written before the concept of the acinus was developed.

Clinical aspects

Trifolium hybridum is a common forage crop in northern regions of Canada. Believed to have been first cultivated in the area of the village of Syke in central Sweden (1), it was introduced into Canada around 1839 (2). Clinical disease has been associated with alsike clover in horses both on pasture and in hay and falls into two distinct categories (3). One of these is

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photosensitivity (4) and is reversible. The other, known as "alsike clover poisoning", is an irreversible syndrome characterized by progressive loss of condition and accompanied by varying degrees of neurological disturbance (5) caused by progressive hyperplasia and fibrosis of the biliary tree (6,7).

a. Photosensitivity: Photosensitivity is a condition that occurs in a number of species. Trifoliosis is the name given to photosensitivity that occurs in horses pastured on alsike clover and cattle pastured on legumes (4,8). Trifoliosis associated with *T. hybridum* has been described from the late 19th century in England (9), from 1905 in the United States (1), and from 1911 in Australia (5). It is accepted by most authors to be a photosensitization of sporadic, transient occurrence and of uncertain etiology (4,10). A good account of trifoliosis in horses is provided by Fincher and Fuller (11).

Morrill (8) claims that alsike-associated photosensitivity is due to a pigment derived from chlorophyll. If this is indeed the case, then trifoliosis would fall into Clare's definition of type III (hepatogenous) photosensitization (4). In type III photosensitization, hepatic damage prevents products of chlorophyll metabolism (usually phylloerythrin) from being excreted by the liver, resulting in photosensitization and allowing the expression of photosensitivity when the animal is exposed to light (4). The literature is uncertain as to whether there is actually hepatic damage in alsike-associated photosensitization. Kingsbury (9) claims that, in the majority of cases of alsike clover-induced photosensitization in the horse, signs of hepatic dysfunction have not been recorded. This is supported by Fincher and Fuller (11). However, Schofield (12) documents second-hand reports of "alsike rash" and notes it occurs in conjunction with jaundice (12,13). The mechanism of the photosensitization caused by *Trifolium hybridum* in horses has not been documented.

Alsike clover-induced photosensitivity is reversible upon removal of affected horses from alsike pasture (1,9,14). Photosensitivity in general has been covered in a number of excellent reviews such as that of Clare (4) and will not be discussed further here.

b. Alsike clover poisoning: The horse is the only species known to be affected by "alsike clover poisoning" (7) as the syndrome is widely known in North America. Thought to have been occurring in northern Ontario since the 1880's (6), synonyms include "liver disease" (13,15), "hypertrophic cirrhosis" (6,13,15), "big liver" (13), and "endemic cirrhosis" (6).

Most clinical descriptions of alsike clover poisoning were provided by Schofield and based upon both field and experimental observations. Other than those of Schofield, the only English language description of the clinical signs of alsike clover poisoning in a specific animal is that given by Traub *et al* (3). Morgan and Jacob (1) and Dodd (5) both mention lesions in advanced cases of trifoliosis that are consistent with alsike clover poisoning. Morgan and Jacob (1) state that if lesions are external (i.e. photosensitivity) the animal will recover, but if vital organs are affected (i.e. alsike clover poisoning), death ensues. Tennant *et al* (16) in reporting a series of cases of hepatic disease in 66 horses over an eight-year period at the Veterinary Medical Teaching Hospital at the University of California, Davis, list two cases of primary biliary cirrhosis which from the clinicopathological description might be cases of alsike clover poisoning, although nutritional information is not included in the case reports.

One of the factors that might influence the development of alsike clover poisoning is whether a horse is exposed to the clover on pasture or as hay during the stabled period. Schofield noted in his 1932 experiments that some horses on pasture appeared to find alsike unpalatable, palatability varying with the individual (17). This would affect development of the disease on pasture (17) and might explain why the disease is sporadic even in the same herd. He suggests that horses eat other vegetation in preference to alsike wherever possible, and notes that this might explain remission of jaundice in horses on pasture in one experiment (17). Such an explanation would also account for the observation that most cases of alsike clover poisoning occur after continuous feeding of hay when there is no opportunity for selection of food (17). In contrast, Morgan and Jacob (1) state that "all classes of livestock relish the hay". This statement was made at a time when alsike was being promoted in Tennessee as an alternative to red clover and should be read with this in mind.

Alsike clover poisoning takes time to develop. Horses must be exposed to alsike on pasture or as hay for a year or more before signs of hepatic insufficiency develop (18). Imported horses rarely develop the disease before a residence of a year or more in endemic areas (6). Native horses are rarely affected before maturity in these areas (6). Signs include discoloration and congestion of mucous membranes (6,12), neurological disturbances (6,12), anorexia, slight elevation of temperature and pulse (6), or high fever (12). Dark urine referred to as "black water" has been reported (13).

Schofield divided the clinical syndrome of alsike clover poisoning into two forms: acute or cerebral, and chronic or cachectic. The cerebral form begins with anorexia. There are periods of alternating depression and excitement followed by intermittent or constant head-pressing (12). Animals on pasture may exhibit persistent purposeless walking (13). There may also be incoordination (7), spasmodic contractions of the neck muscles, and yawning and grinding of the teeth. Rapid progression to paralysis and death in a coma is usually seen. Occasionally, spontaneous recoveries may occur, but such animals usually have relapses which are eventually fatal (15).

Horses suffering from the cachectic form show a variable appetite with progressive loss of condition, weakness and sluggishness (6,7,12). They have a dry, harsh hair coat and dirty yellow conjunctivae with marked jaundice (7,18). There will be passage of dark urine and periods of constipation alternating with diarrhea with little change in temperature or pulse. Ultrasound examination reveals enlargement of the liver (3). Originally exhibiting an unsteady gait, such animals wander aimlessly and are apparently blind (3,12,18). Head-pressing and yawning have also been reported

(18). Most cases terminate suddenly and fatally (7) after a period of marked excitement, but there may be several periods of excitement (12) interspersed with long periods of dullness (18). Occasionally there is mania prior to death (13).

Photosensitivity is not a constant feature of alsike clover poisoning, but may affect nonpigmented areas of the face (3,18). As with trifoliosis, the mechanism is not known, but it may be due to hepatogenous photosensitivity. There are two possible ways in which this might occur: by biliary obstruction or by metabolic dysfunction of the liver (4). The anatomic pattern of the lesions (see below) suggests that biliary tree obstruction is the most likely cause and that varying degrees of interference with biliary drainage in different animals would explain the inconsistency of photosensitization. If the primary effect of the causative agent was to reduce hepatic metabolism of photosensitizing agents of plant origin, then photosensitivity should be observed consistently.

There is no known cure for alsike clover poisoning (3,15), and treatments have not been reported. Schofield made recommendations for prevention based upon his conviction that alsike clover is the cause of the condition (15). These included: feeding alsike-containing hay sparingly; adding grain and bran to the ration; feeding straw in the place of hay; and preventing the grazing of horses on pasture where alsike is growing heavily.

Pathology

Descriptions of the lesions of alsike clover poisoning are all very similar. The liver is greatly enlarged (6,12) with rounded borders and fibrous bands on the surface. It is grey-brown (6) or green-yellow (3,6). The parenchyma is firm (3) having the consistency of dense rubber (6). The capsular surface is either rough or smooth (3,6). The weight in advanced cases may be much greater than normal (3,6,7). Weights of as much as 22.7–27.3 kg have been reported (6,7) in comparison to a 5.45–6.82 kg weight for a normal equine liver (7).

The microscopic findings in naturally occurring cases are those of marked bile duct proliferation and perilobular fibrosis (6). The proliferating bile ducts are well-formed (3,6,18) and in the early stages they are more prominent than is fibrosis. Later, the relative proportions are reversed (18). Fibrosis begins in the periportal region, moving outwards to link periportal regions and outline individual lobules. The proliferating fibrous tissue spares the sinusoids, but gradually constricts the parenchyma (18). In advanced cases, severe perilobular fibrosis develops (6) and the liver looks macroscopically like a pig's liver (13).

Characteristically, there is no inflammation and no parenchymal damage (18). Degenerative parenchymal changes are rare and minimal (18). They are confined to the regions of the lobule compressed by proliferating fibrous tissue and consist of atrophy (6,18), vacuolation (3), fatty degeneration (18), and necrosis with pyknotic nuclei (6,18). Regeneration of hepatocytes is seen in some cases. Hepatocellular swelling is apparently not a feature, being specifically mentioned in only one report (3).

In one case, Schofield (6) reported hepatic fibrosis in a two-day-old foal whose dam was suffering from an incipient form of the disease.

Etiology

Numerous associations have been made between environmental factors and alsike clover poisoning. These include the time of year (7,13), cold nights in rainy seasons followed by warm days with plenty of sunshine (8), hay feeding (7), wet seasons (7,12), and heavy clay soil (12,19). The most common association however, is the feeding of alsike hay or pasturing on alsike. A case can be made that the above associations incriminate alsike clover, since all correlate with the feeding of alsike hay or with conditions that favor the growth of alsike, and have not been associated with the syndrome in the absence of alsike clover.

One of the first veterinarians to publicly associate the heavy feeding of alsike clover with the syndrome was Dr. H.E. Batt of the Ontario Veterinary College in 1918 (6). Based upon Dr. Batt's observation and his own summary of the existing information about the disease (6) as well as his field observations (7), Schofield initiated a series of investigations in 1930. He attempted to correlate various factors with alsike clover poisoning in order to determine the etiology of the condition (7). Initially, he doubted that alsike was the cause of alsike clover poisoning, stating "there is no direct evidence that would incriminate the plant, however strong the circumstantial evidence may be" (6), and again, "In fact, the evidence incriminating alsike clover decreases as our knowledge increases" (7). Despite these statements, as a result of his experimental investigations during the years 1928–32, Schofield felt in 1932 that sufficient evidence had accumulated to "definitely incriminate this plant as the cause of "big liver' " (17). He named the condition equine hypertrophic cirrhosis (15), but it has been referred to commonly as "alsike clover poisoning" since that time. The reports of Schofield's studies (13,15,17,19) remain the only published experimental observations attempting to demonstrate an etiology for alsike clover poisoning.

Is the conclusion reached by Schofield in 1932 justified? His feeding experiments, including a total of 15 horses, were reported in the annual reports of the Ontario Veterinary College for 1931 (19), 1932 (13,17) and 1933 (15). These are summarized in Table 1. To evaluate these data, the criteria by which a case will be judged as alsike clover poisoning are as follows: clinical signs of hepatic disease with postmortem findings of proliferation and fibrosis of the biliary tree. If ingestion of alsike clover by horses can be demonstrated to produce these changes, then alsike clover can be considered to cause alsike clover poisoning.

Schofield was never able to obtain pure alsike clover hay and proceeded with his *first set of experiments in 1931* with hay of less than 50% alsike content (19). Hay was fed free choice to three horses, with alsike clover seed added in each case for part of the experiment (19). From his discussion of this experiment it is difficult to determine whether he reached a conclusion regarding the role of alsike clover. He states that none

TABLE 1
Summary of experimental alsike clover poisoning

Animal	Sex	Age (yrs)	Wt (lbs)	Photo sensitivity	Jaundice	Died/ Euth	Gross hepatic enlargement	Gross hepatic fibrosis	Bile duct proliferation	Perilobular fibrosis	Comments
Schofield 1931 experiment (Schofield 1931a)											
Black	M(C)	13	1600	–	–	yes	–	–	×	×	delete: inadequate lesions
Sorrel	M(C)	3	900	–	–	yes	–	–	×	×	delete: inadequate lesions
Roan	M(C)	15	900	–	–	yes	–	+	×	×	delete: inadequate lesions
Schofield Brigden experiment (Schofield 1932a)											
Chestnut	F	aged	1150	+	+	yes	+	+	+	+	alsike clover poisoning
Gray	F	16	1000	–	+	yes	+	+	–	+	delete: heaves?
Bay	M(C)	3	1000	–	+	yes	–	–	–	S	delete: heaves?
Royal	?	aged	1100	–	+	no	–	–	–	–	delete: no necropsy
Bay	F	aged	?	–	–	yes	–	+/–	+	+	control alsike clover poisoning
Black	F	18	950	–	+	yes	+/–	+	–	+	alsike clover poisoning
Schofield New Liskeard experiment (Schofield 1932b)											
Bay	F			–	–	no	–	–	–	–	delete: no necropsy
Bay	F	14	890	–	–	no	–	–	–	–	delete: no necropsy
Bay	M(C)	aged	1000	–	+	no	–	–	–	–	delete: no necropsy
Bay	F	16	1127	–	+	yes	+	+	–	+	delete: heaves
Bay	M	aged	?	–	–	yes	+	+	+	+	alsike clover poisoning
Roan	M	3	1175	–	–	yes	–	–	–	–	delete: died/no lesions

Gross hepatic enlargement and gross hepatic fibrosis: – : negative/not examined
Fibrosis/bile duct proliferation: –: not seen/not mentioned/not examined
+: marked/extensive
S : slight
×: Schofield states that the histological changes, though present were not sufficient to designate this as alsike clover poisoning

of the changes in his experimental animals were sufficient to call them "typical hypertrophic cirrhosis" (19). However, his description of the histopathological changes in each case suggests that the disease might have been developing, and he leaves the impression that these were possibly early cases of alsike clover poisoning. He states that the lesions in all three horses indicate the possibility that alsike clover poisoning would develop with a longer period of feeding of alsike clover hay of greater concentration. Nevertheless, as the experimenter was unwilling to diagnose "hypertrophic cirrhosis", we should deduct them from the total of experimental cases. There were no control animals in these feeding trials.

In a 1932 report Schofield (13) alludes to a case of alsike clover poisoning produced during feeding experiments in 1929, but there is no published record of the trial. Apparently, some of Schofield's experiments may remain unreported.

His second set of experiments, conducted at Brigden, Ontario in 1932 (13) involved six horses, and are referred to as *the Brigden experiments*. In his discussion of this trial, Schofield claims that the results "allow for little doubt as to the toxicity of alsike clover for the equine liver at least when fed under the conditions here described" (13). Critical examination of data calls this conclusion into serious doubt. The trial essentially consisted of feeding alsike hay to horses in the winter of 1931–32, putting them on alsike pasture during the summer of 1932, and feeding them alsike hay in the fall of 1932. One animal of the six was a control, yet Schofield's histological description is of "widespread proliferation of the fibrous tissue and biliary epithelium", i.e. a description of the lesions of alsike clover poisoning. This particular animal was indicated by Schofield as being "at pasture all summer with the other horses", the other horses being on alsike pasture. Therefore, there is some doubt as to whether the bay mare was truly a control. If we accept Schofield's statement and assume that this is a true control animal, then the presence in the control of lesions consistent with alsike clover poisoning does not allow the conclusion drawn by Schofield from the experiment.

Difficulties exist in interpreting the experimental data for three of the remaining five horses. One showed clinical evidence of liver disease but was not killed. Two others were killed following the feeding trial and both had varying degrees of centrilobular fibrosis, but there is no mention of bile duct proliferation. This, in conjunction with the comment in the discussion, that "In our experimental horses the most acute cases have been in animals suffering from passive congestion of the liver due to pulmonary emphysema" throws considerable doubt as to whether the lesions in these two horses are related to alsike clover. It seems that in Schofield's time, as now, research money was hard to obtain, and Schofield might have tried to stretch his research dollars by purchasing animals with pulmonary emphysema. This suggestion is supported by Schofield's identification of one horse in the third feeding trial (see below) as suffering from pulmonary emphysema. These three horses do not qualify as cases of alsike clover poisoning according to the criteria selected and should be deleted from further consideration. Thus,

in Schofield's second feeding trial, only three animals were confirmed to have hepatic lesions consistent with alsike clover poisoning, one of them being the control.

The third feeding trial took place in New Liskeard, Ontario in 1932 and is referred to as *the New Liskeard trial*. There were some difficulties growing adequate alsike in 1932, nevertheless, the trial proceeded with six animals. One was being used for contact dermatitis studies and did not ingest alsike hay throughout the study. The animal died of undetermined causes during the experiment and did not show evidence of alsike clover poisoning. A second animal had pulmonary emphysema (see above), and upon necropsy was found to have hepatic fibrosis associated with chronic passive congestion. This animal also should be removed from further consideration.

Of the remaining four horses, two did not develop signs of hepatic disease during the experiment and were not killed. A third showed signs of hepatic disease but was not subjected to postmortem examination. The fourth did not show signs but at necropsy had fibrosis and (probably) bile duct proliferation.

None of these six animals meets the criteria of alsike clover poisoning. If we relax the criteria to allow postmortem lesions in the absence of clinical signs, one animal can be considered to have the disease. This brings the number of experimental cases in all feeding trials to four. The entire experimental evidence that has been used to incriminate alsike clover as the cause of alsike clover poisoning is therefore based upon four animals that developed signs and/or lesions consistent with the disease, and one of these is a control animal. This is not sufficient to sustain Schofield's conclusion that "results.....point conclusively to alsike clover as the cause of 'big liver' or hypertrophic cirrhosis in the horse" (17).

Two horses with alsike clover poisoning are discussed in Schofield's 1933 paper, but these two are from the Brigden and New Liskeard experiments (13,17).

Thus, Schofield's conclusion that alsike clover is responsible for the condition described as alsike clover poisoning was premature. However, the experimental evidence does not indicate that alsike clover is *not* the cause of alsike clover poisoning, it simply fails to confirm it. There remains a strong body of observation and association that links alsike clover with the syndrome that bears its name.

Unanswered questions

Schofield's work raises a number of interesting avenues for further investigation. Both alsike hay and alsike pasture have been incriminated, but Schofield's descriptions imply that signs may be exacerbated by hay and resolve somewhat on pasture (7,17). If this is found to be correct, then it begs the question of whether it is the alsike hay itself, or something that happens in curing that is the culprit. It is conceivable that there is a breakdown product of the plant that forms during curing, or perhaps a mycotoxin that is formed on moist or spoilt alsike hay.

Also unanswered is the question of whether there is greater toxicity associated with any particular part of the plant. Schofield cites observations suggesting that the blossom is the most toxic part of the plant but he was unable to obtain sufficient blossoms to test this hypothesis (13).

The enlargement of the liver in alsike clover poisoning is said to be caused by diffuse hepatic fibrosis (13). However, when there is fibrosis, the liver is usually shrunken. It is questionable whether the degree of proliferation of bile ducts can account for the increased size, and there is not significant proliferation of hepatic parenchyma. It could be that a net increase of fibrous tissue and bile ducts together account for the increased size and weight of the liver.

Schofield (13) also observes that there may be some effects of alsike on humans. Humans suffer "marked nausea, chills, and a general feeling of malaise when exposed to alsike dust at the time of threshing" (13). This is not mentioned by any other author, but is a point worth future investigation.

Conclusions

Alsike clover has been associated with two diseases in horses; photosensitization, referred to as "trifoliosis", and biliary proliferation with fibrosis, referred to as "alsike clover poisoning". Alsike clover poisoning has been studied experimentally by only one investigator, Schofield, in the early 1930's. His experiments do not prove a causal association between the ingestion of alsike clover by horses and the syndrome of alsike clover poisoning. Therefore, the agent responsible for alsike clover poisoning remains unknown.

Until such time as the true etiology of alsike clover poisoning is discovered, the name "alsike clover poisoning" should be retained. The name is associated closely with the disease syndrome in the minds of veterinarians and horsemen, and to rename the disease given present knowledge would be premature and might potentially further confuse the syndrome.

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Abstract

Nephrotoxicity of amphotericin B in dogs: A comparison of two methods of administration

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Two methods of administration of amphotericin B were compared for their ability to produce nephrotoxicity in 12 dogs. Six dogs received six alternate day doses of amphotericin B: 1 mg/kg administered as a rapid bolus in 25 mL 5% dextroxe in water. Another six dogs received alternate day treatments of the same dose of amphotericin B in 1 L 5% dextroxe in water over 5 h. Renal lesions characteristic of amphotericin B administration were observed in all dogs tested. The dog which received amphotericin B as a rapid bolus had a significantly greater number of tubular lesions than the slow infusion group. Systemic side effects, such as vomiting, diarrhea and weight loss, were observed in both treatment groups but were most severe in the rapid bolus group. This study demonstrates that the administration of amphotericin B by slow infusion with supplemental fluids causes less functional impairment, less severe systemic signs, and less renal damage than rapid bolus administration without supplemental fluids. On the basis of these experimental findings, we recommended that for the treatment of systemic fungal infections, AMB be administered slowly in 1 L of D5W over a minimum period of 5 h.

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