# Thyroid function in mature horses ingesting endophyte-infected fescue seed

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EQUINE

**Objective**—To determine whether ingestion of fescue seed infected with the endophyte *Neotyphodium coenophialum* would alter thyroid function in adult horses.

**Design**—Original study.

**Animals**—4 adult mares that were not pregnant and 6 adult geldings.

**Procedure**—Thyrotropin releasing hormone stimulation tests were performed while horses received a standard diet and after infected seed (2.3 kg/d [5 lb/d]) had been fed for 1 and 2 months. Serum prolactin concentrations were measured to verify endophyte absorption.

**Results**—Serum prolactin concentrations indicated that at least 8 of 10 horses absorbed the endophyte. Baseline concentrations of thyroid stimulating hormone, total and free triiodothyronine, and total and free thyroxine and the change in hormone concentrations in response to administration of thyrotropin releasing hormone (1 mg, IV) were not altered by ingestion of endophyte-infected fescue seed.

**Conclusions and Clinical Relevance**—Results suggest that ingestion of fescue seed infected with the endophytic fungus *N coenophialum* for 2 months has little effect on thyroid function in adult horses that are not pregnant. (*J Am Vet Med Assoc* 2003;223:340–345)

Tall fescue (*Festuca arundinaceae*) is a cool-season, seed-propagated perennial grass that is commonly grown in the southeastern part of the United States. It is relatively easy to establish, has a long growing season with good growth during the winter, and has good disease and drought resistances, which allow it to survive the hot, humid summers of the region. It has been estimated that approximately 688,000 horses in the United States graze fescue pastures.[1] However, a variety of reproductive problems in mares grazing tall fescue have been reported since the 1980s, including increased duration of gestation, dystocia, agalactia, thickened placentas, and decreased fertility. Foals born to mares fed fescue grass have poor vigor and viability, clinical signs suggestive of hypothyroidism, low serum **triiodothyronine ($T_3$)** concentrations, and histologically abnormal thyroid glands containing distended, colloid-filled follicles.[2] It is now known that many, if not all, of the reproductive problems of horses consuming fescue are caused by an endophytic fungus, *Neotyphodium coenophialum*, that lives symbiotically on fescue plants.[3,4] The endophyte makes the fescue more resistant to overgrazing, insect damage, and drought stress[5] and is transmitted with the seed. Although strains of fescue have been developed that are endophyte free, these strains have not been as vigorous as endophyte-infected strains.

Although endophyte-associated periparturient problems of mares and their foals have been studied extensively, the effects of endophyte ingestion in adult horses that are not pregnant have received little attention. Decreased fertility in mares and laminitis have been associated with ingestion of endophyte-infected fescue,[3,6,7] and hypothyroidism has been associated with decreased fertility and laminitis.[4,8,9] However, in 3 studies in which hypothyroidism was induced by surgical removal of the thyroid glands[10,11] or administration of propylthiouracil,[12] laminitis did not occur. Also, in a study[13] of clinically normal broodmares, no relationship was found between serum **thyroxine ($T_4$)** concentration and pregnancy rate 15 to 16 days after ovulation or between thyroid supplementation and pregnancy rate.

Although thyroid function of adult horses fed endophyte-infected fescue has not been studied, it is reasonable to predict that thyroid function may be altered. Alkaloids produced by the endophyte have been shown to act at dopamine receptors to inhibit prolactin release from the pituitary gland[14,15] and to inhibit corticotrophin releasing hormone stimulation of adenylate cyclase activity in rat pars intermedia cells in vitro.[16] Because release of **thyroid stimulating hormone (TSH)** from the pituitary gland is also inhibited by dopamine,[17] a similar mechanism could inhibit stimulation of thyrotrophs in the pituitary gland by **thyrotropin releasing hormone (TRH)**, resulting in decreased release of TSH. Messer et al[18] recently suggested that ingestion of endophyte-infected fescue by mares on a farm in central Kentucky may have contributed to lower serum concentrations of TSH in mares and foals on that farm, compared with concentrations in mares and foals on a nearby farm grazing pastures that were mainly free of endophyte-infected fescue. The purpose of the study reported here was to determine whether ingestion of tall fescue seed infected with *N coenophialum* would alter thyroid function in adult horses by decreasing serum TSH concentration and blunting the TSH response to TRH administration.

## Materials and Methods

**Horses**—Four mares (2 Quarter Horses and 2 Thoroughbreds) between 7 and 17 years old and 6 geldings (2 Quarter Horses and 4 Thoroughbreds) between 6 and 12

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years old were used in the study. The first 2 geldings were studied between February and April to ensure that they would eat the seed and that there would be no adverse effects of seed ingestion. The remaining 8 horses were studied between July and September. Horses were cared for according to principles outlined in the National Institute of Health's *Guide for the Care and Use of Laboratory Animals*. Horses were considered to be clinically normal on the basis of results of physical examinations prior to the study, and none of the horses had received any medications for at least 4 weeks prior to the beginning of the study.

**Experimental protocol**—Horses were maintained on Bermuda grass pasture (free from fescue contamination) and timothy hay throughout the study; water was available ad libitum. In addition, prior to the study, horses were provided with supplemental 12% protein pellets mixed with a small amount of sweet feed. Supplemental pellets were fed at 8:00 AM and 4:30 PM in an amount sufficient to maintain body weight. Beginning on day 0 of the study, endophyte-infected fescue seed was substituted for the protein pellets, and horses were fed 2.3 kg (5 lb) of the endophyte-infected seed daily for the next 2 months. Horses were confined to individual pens in the pasture while they ate the concentrate portion of the diet. Nutritional analysis[a] of the 2 concentrates was performed (**Table 1**). Further analysis of the fescue seed revealed it to be 72% infected with endophyte.[19,b] Ergovaline concentration was 2,200 µg/kg (ppb).[20,c] Evidence of ergot (*Claviceps purpurea*) contamination was not seen, and ergopeptine alkaloids associated with *C purpurea* (ie, ergosine, ergotamine, ergocornine, ergocryptine, and ergocristine) were not detected at the 50 ppb detection limit.[21,c]

Horses were observed daily throughout the study. A complete physical examination (including assignment of a body condition score[22]; evaluation of rectal temperature, heart rate, respiratory rate, mucous membrane color, capillary refill time, pulse quality, digital pulse strength, gastrointestinal tract motility, and manure quality; and manual palpation of the neck to detect possible thyroid gland enlargement) and a TRH stimulation test were performed on day 0 and after the endophyte-infected seed had been fed for 1 and 2 months.

**TRH stimulation test**—On days the TRH stimulation test was to be performed, horses were brought into stalls and fed their morning ration at 8:00 AM. Hay and water were available throughout the day. A catheter[d] was placed aseptically in a jugular vein, and a blood sample was collected. One milligram of TRH[e] was administered IV between 9:30 and 10 AM. Additional blood samples were collected 15, 30, 45, 60, 120, 240, and 360 minutes after administration of TRH. Blood was allowed to clot at room temperature for 30 to 60 minutes, and serum was removed and stored at –70°C until assayed.

Table 1—Nutritional analysis (dry matter basis) of the 2 concentrates fed to horses in a study of the effect of feeding endophyte-infected fescue seed on thyroid function in adult horses

| Variable | Pelleted feed | Fescue seed |
|---|---|---|
| Adjusted crude protein (%) | 12.0 | 14.3 |
| Acid detergent fiber (%) | 20.8 | 15.3 |
| Neutral detergent fiber (%) | 31.1 | 29.1 |
| Nonfibrous carbohydrate (%) | NA | 51.7 |
| Nonstructured carbohydrate (%) | 41.6 | 47.2 |
| Starch (%) | 32.0 | 42.1 |
| Sugar (%) | 9.6 | 5.1 |
| Crude fat (%) | 5.3 | 2.7 |
| Total digestible nutrients (%) | 66 | 73 |
| Digestible energy (Mcal/lb) | 1.33 | 1.47 |

NA = Not applicable.

**Measurement of hormone concentrations**—Serum TSH concentration was measured in all serum samples. Serum total $T_3$, free $T_3$, total $T_4$, and free $T_4$ concentrations were measured in samples obtained before and 60, 120, 240, and 360 minutes after TRH administration. Serum prolactin concentration was measured in samples obtained before TRH administration. All hormone concentrations were measured by use of radioimmunoassays as described.[12,23,24]

**Statistical analyses**—Serum concentrations of TSH, total $T_3$, free $T_3$, total $T_4$, and free $T_4$ in samples obtained prior to TRH administration (ie, baseline concentrations) were analyzed by use of blocked ANOVA[25,f] to determine effects of feeding endophyte-infected seed for 1 and 2 months on baseline values. Changes in thyroid hormone and TSH concentrations in response to TRH administration before and after 1 and 2 months of endophyte-infected fescue seed ingestion were compared by blocked ANOVA for repeated measures over time.[25,f] Post hoc tests were performed with the Bonferroni adjustment.[25,f] Values of $P < 0.05$ were considered significant. Except as indicated, data were expressed as mean ± SD.

## Results

There were no adverse reactions to switching horses from the pelleted ration to the fescue seed ration, although 1 horse failed to eat the entire ration for the first few days. Within 2 to 3 days, however, all horses were consuming all the fescue seed offered to them. Body condition score, heart rate, respiratory rate, rectal temperature, manure consistency, and digital pulse strength remained within reference limits throughout the study.

In 7 of the 10 horses, serum prolactin concentrations were substantially lower after the fescue seed had been fed for 1 month, compared with concentrations at the beginning of the study. In the remaining 3 horses (horses 3, 7, and 10; **Table 2**), serum prolactin concentrations after the fescue seed had been fed for 1 month were unchanged or had increased. However, in 1 of these 3 (horse 7), serum prolactin concentration at the beginning of the study was so low that it would have been difficult to identify any decrease. Therefore, data for this horse were included in statistical analyses, and data for the 2 other horses in which serum prolactin concentration was not altered (horses 3 and 10) were excluded. Exclusion of data from these 2 horses did not alter results of statistical analyses of thyroid hormone and TSH data.

Table 2—Serum prolactin concentrations (ng/mL) in 10 horses fed a control diet and subsequently fed endophyte-infected fescue seed (2.3 kg/d [5 lb/d]) for 1 and 2 months

| | | Fescue seed | |
|---|---|---|---|
| Horse No. | Control diet | 1 month | 2 months |
| 1 | 3.4 | 0.5 | 2.5 |
| 2 | 1.3 | 0.4 | 1.5 |
| 3 | 12.4 | 21.8 | 3.4 |
| 4 | 9.9 | 2.2 | 1.6 |
| 5 | 9.5 | 2.9 | 1.3 |
| 6 | 11.4 | 3.1 | 1.2 |
| 7 | 0.7 | 1.0 | 0.5 |
| 8 | 6.6 | 1.1 | 0.7 |
| 9 | 3.0 | 1.3 | 0.3 |
| 10 | 2.5 | 2.4 | 1.2 |

Horses 1 and 2 were studied between February and April; horses 3 through 10 were studied between July and September.

Baseline serum total $T_4$ concentrations at the beginning of the study and after endophyte-infected fescue seed had been fed for 1 and 2 months were 19.4 ± 7.3, 23.3 ± 12.2, and 19.1 ± 8.3 nmol/L, respectively (**Fig 1**). These values were not significantly different from each other. Baseline serum free $T_4$ concentrations at the beginning of the study and after endophyte-infected fescue seed had been fed for 1 and 2 months were 11.9 ± 0.6, 12.5 ± 0.9, and 12.6 ± 2.0 pmol/L, respectively (**Fig 2**); again, these values were not significantly different from each other. There was no significant effect of diet on the change in serum total or free $T_4$ concentration in response to TRH administration. However, there was a significant block effect by horse for total and free $T_4$ concentrations, indicating that the variation in total and free $T_4$ concentrations among horses was greater than the variation in total and free $T_4$ concentrations on different days within the same horse.

Baseline serum total $T_3$ concentrations at the beginning of the study and after endophyte-infected fescue seed had been fed for 1 and 2 months were 1.31 ± 0.44, 1.18 ± 0.40, and 0.96 ± 0.43 nmol/L, respectively (**Fig 3**). These values were not significantly different from each other. Baseline serum free $T_3$ concentrations at the beginning of the study and after endophyte-infected fescue seed had been fed for 1 and 2 months were 3.19 ± 0.99, 2.94 ± 1.27, and 3.66 ± 1.40 pmol/L, respectively (**Fig 4**); again, these values were not significantly different from each other. There was no significant effect of diet on the change in serum total or free $T_3$ concentration in response to TRH administration. However, there was a significant block effect by horse for total and free $T_3$ concentrations.

Baseline serum TSH concentrations at the beginning of the study and after endophyte-infected fescue seed had been fed for 1 and 2 months were 0.25 ± 0.14, 0.22 ± 0.20, and 0.29 ± 0.22 ng/mL, respectively (**Fig 5**). These values were not significantly different from each other. There was no significant effect of diet on the change in serum TSH concentration in response to TRH administration. However, there was a significant block effect by horse.

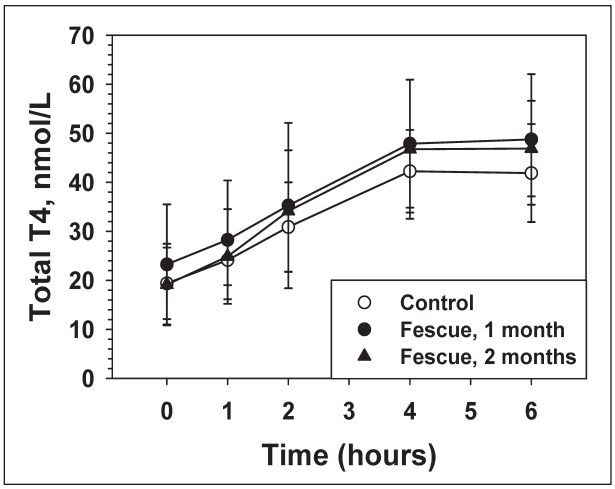


Figure 1—Serum total thyroxine ($T_4$) concentrations in 8 horses in response to administration of thyrotropin releasing hormone (TRH; 1 mg, IV) before (control) and after ingestion of endophyte-infected fescue seed for 1 and 2 months. Error bars represent SD.

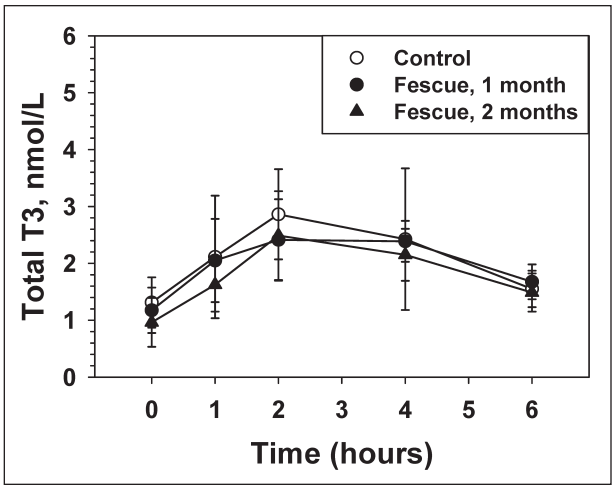


Figure 3—Serum total triiodothyronine ($T_3$) concentrations in 8 horses in response to administration of TRH before and after ingestion of endophyte-infected fescue seed for 1 and 2 months. Error bars represent SD.

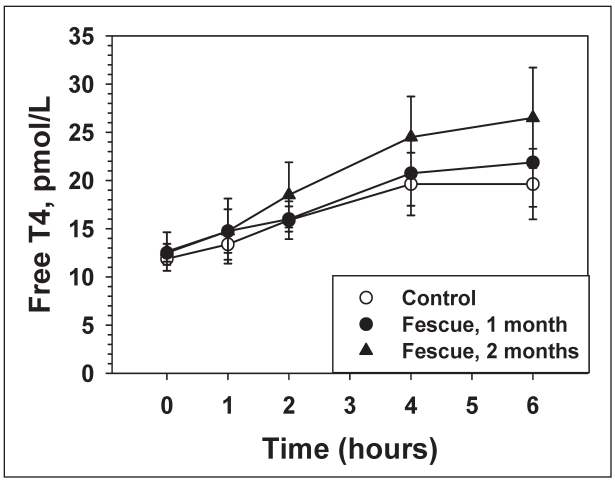


Figure 2—Serum free $T_4$ concentrations in 8 horses in response to administration of TRH before and after ingestion of endophyte-infected fescue seed for 1 and 2 months. Error bars represent SD.

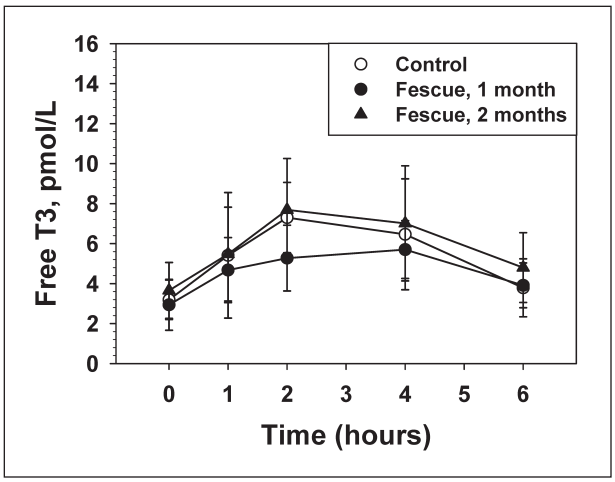


Figure 4—Serum free $T_3$ concentrations in 8 horses in response to administration of TRH before and after ingestion of endophyte-infected fescue seed for 1 and 2 months. Error bars represent SD.

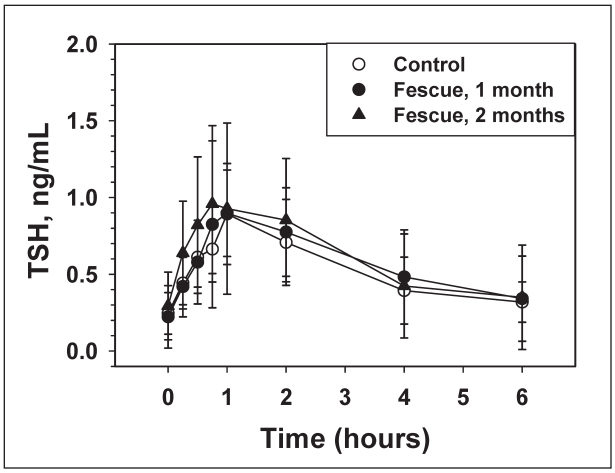


Figure 5—Serum thyroid stimulating hormone (TSH) concentrations in 8 horses in response to administration of TRH before and after ingestion of endophyte-infected fescue seed for 1 and 2 months. Error bars represent SD.

## Discussion

Although alkaloids produced by the endophyte *N coenophialum* act as dopamine agonists,[14,15] and TSH secretion from the pituitary is inhibited by dopamine,[17] baseline serum TSH concentrations were not decreased by feeding horses endophyte-infected fescue seed in the present study, nor was the change in TSH concentration in response to TRH administration decreased. It is unlikely that small sample size masked a significant effect of endophyte-infected fescue seed on TSH concentration, because the change in TSH concentration in response to TRH administration appeared subjectively to be increased after ingestion of infected seed for 2 months, rather than decreased. Similar to results of the present study, consumption of endophyte-infected fescue has been shown to not alter TSH, $T_4$, and $T_3$ concentrations in cattle and sheep.[26,27] However, it has been hypothesized that ruminants are less susceptible to the effects of the alkaloids produced by the endophyte, because such alkaloids are metabolized in the rumen and are not absorbed to the same extent that they would be in monogastric species, such as horses.[28,29]

While some studies have shown that changes in dietary energy and protein concentrations can alter thyroid function in horses,[23,30] particularly weanling horses,[31-33] other studies[34-36] failed to detect changes in serum $T_4$ or $T_3$ concentrations despite profound alterations in energy content or the ratio of roughage to concentrate. Transient alterations in serum thyroid hormone concentrations in weanlings fed various diets were observed in response to feeding after food was withheld for 24 hours, but these alterations were no longer seen 2 to 4 hours after eating,[31,32] and similar alterations were not observed in the same horses when they were 12 to 14 months old. Horses in the present study were adults, food was not withheld prior to TRH stimulation tests, and thyroid hormone concentrations were measured beginning 2 hours after horses were fed their morning meals. The change from pelleted feed to fescue seed likely resulted in changes in protein and energy concentration of the overall diet that were too small to alter thyroid hormone concentrations. Although there is no way to know how much grass any individual horse eats at pasture, if one were to assume that horses typically eat 2% of their body weight per day and that horses in this study weighed approximately 450 kg (1,000 lb), then one could calculate that horses in this study consumed approximately 9 kg (20 lb) of feed per day, of which 2.3 kg (5 lb), or approximately 25%, consisted of pellets or fescue seed. Thus, at most, changing from pellets to fescue seed resulted in a 4.8% increase in protein concentration and a 2.6% increase in the overall energy consumed. If the horses ate less grass to compensate for the higher energy level of the fescue seed, compared with the pellets, these differences would be less.

Our inability to detect a significant effect on thyroid function in the present study was unlikely to have been a result of feeding fescue seed, rather than fescue hay or grass. Administration of endophyte as endophyte-infected fescue seed has been used successfully in studies[37,38] involving cattle and a previous study[39] of the effects of endophyte ingestion on reproductive problems and foal health in pony mares. The amount of fescue seed (on a kilogram of seed per kilogram of body weight basis) fed to horses in the present study was similar to the second highest amount fed to the ponies in the previous study.[39] The advantage of feeding seed is that it allows investigators to be certain that a known amount of alkaloid is actually ingested, since it is difficult to determine how much grass a horse eats when allowed free access to pasture, and hay is often trampled and not completely eaten. Furthermore, the concentration of ergovaline in fescue seed is usually 1,000 to 3,000 ppb, while the concentration in fescue grass is typically only 100 to 600 ppb,[20] and the concentration in fescue hay is usually less than the concentration in fresh grass because of degradation of the alkaloid.[g] Ergovaline is fairly stable in fescue seeds.[g]

Although serum prolactin concentration was measured in the present study in an attempt to verify digestion and absorption of endophyte with the fescue seed, the somewhat erratic serum prolactin concentrations among horses in the study makes interpretation of the data difficult. An absence of any change in serum prolactin concentration while ingesting endophyte-infected fescue seed does not necessarily mean that endophyte was not absorbed, because other physiologic influences on serum prolactin concentrations (eg, season and stress) may overwhelm any effects of endophyte. Inconsistent changes in serum prolactin concentration in response to ingestion of endophyte-infected fescue pasture (as opposed to seed) have been reported previously.[40] In that study, serum prolactin concentrations were not significantly different between pregnant mares grazing endophyte-infected fescue pasture and mares grazing endophyte-free fescue pasture during 1 of 3 years of the study. The authors suggested that seasonal alterations in serum prolactin concentrations or physiologic alterations related to gestation may have taken precedence over the effects of endophyte and may have been responsible for the lack of effect of fescue ingestion on serum prolactin concentrations in that year.

Despite potential problems with interpretation of the serum prolactin concentration data, it appears that in at least 8 of the 10 horses in the study, a sufficient amount of

seed was fed, and a sufficient amount of the alkaloid was absorbed to affect serum prolactin concentration. The first 2 horses in the present study were evaluated between February and April, a time of year when serum prolactin concentrations are typically increasing.[41] Despite this, serum prolactin concentrations were lower after the first month of fescue seed ingestion than they had been at the beginning of the study. Increases in serum prolactin concentrations in these 2 horses the following month most likely reflected the seasonal increase in serum prolactin concentration, rather than a sudden change in fescue seed digestibility.[41] The remaining 8 horses in this study were evaluated between July and September. Baseline serum prolactin concentration in 1 gelding (horse 3) was high and did not decrease during the first month of fescue seed ingestion. This may indicate that the horse was stressed at the time blood samples were collected but may also indicate that this horse did not adequately digest the fescue seed during the first month or that the amount of endophyte absorbed was not enough to alter the horse's serum prolactin concentration. For these reasons, thyroid hormone and TSH data for this horse and another horse (horse 10) in which serum prolactin concentration did not decrease were not included in statistical analyses. Serum prolactin concentrations in the remaining 6 horses after ingestion of endophyte-ingested fescue seed for 1 and 2 months were lower than one would expect on the basis of season or photoperiod alone.[41]

Serum prolactin concentration data might have been easier to interpret if a crossover study design had been used. This was not done, because it was impossible to predict prior to the study how long it might take for any possible effects of fescue ingestion on thyroid function to wear off. Performing the study concurrently in an additional 10 horses without changing their diets would have provided a time control and, in hindsight, would have facilitated interpretation of any seasonal influences on serum prolactin concentrations. However, it also would have doubled the cost of the study, and the usefulness of this was not anticipated in advance. Except for the first 2 horses, the study was conducted between July and September, and there was no reason to expect thyroid function to vary over that time period. If the present study had demonstrated a change in thyroid function, a crossover design or use of control horses might have been necessary to prove that the change in thyroid function was indeed related to the change in diet and not to some other factor, such as time or season. However, because there was no change in thyroid function, and because thyroid hormone concentrations and responses to TRH administration in these horses were within reference limits for healthy horses,[12] the necessity of control horses is minimized.

Our inability to detect an effect on thyroid function in this study was probably not related to inadequate duration of endophyte-infected fescue seed ingestion. Serum prolactin and progesterone concentrations decreased in pregnant mares within 2 days after introduction to pastures containing endophyte-infected tall fescue and returned to reference limits within 5 to 10 days after cessation of endophyte ingestion.[40] In an earlier study,[42] mares grazing endophyte-infected pastures were switched with mares grazing endophyte-free pastures after 305 days of gestation. Even with < 60 days of exposure to the endophyte, mares switched from endophyte-free pastures to endophyte-infected pastures had more difficult deliveries, less udder development, and weaker foals than the mares switched from endophyte-infected pastures to endophyte-free pastures. In another study,[2] serum $T_3$ concentration was low in foals born to mares grazing endophyte-infected pasture for < 60 days (from day 300 of gestation to parturition).

An effort was made in this study to use fescue seed that contained only those alkaloids produced by the endophyte *N coenophialum*. Eight lots of fescue seed were tested prior to the start of this study before 1 was found that was adequately infected with endophyte and did not contain ergot alkaloids. The presence of ergot alkaloids was either not measured or not mentioned in many previous studies of the physiologic or reproductive effects of fescue ingestion. It remains unknown whether the absence of ergot alkaloids in the seed fed in the present study contributed to the results.

Because fescue pasture is very common in the southeastern part of the United States, one might expect to see more cases of hypothyroidism among horses in this region if fescue ingestion did indeed make horses hypothyroid. That this is not the case may be due to the fact that dopamine appears to act more as an acute modulator of TSH secretion, rather than as the primary control. In humans, while short-term dopamine blockade results in increases in TSH secretion and serum concentrations of thyroid hormones, long-term administration does not cause long-term alterations in thyroid hormone status.[17] It has been proposed that compensatory mechanisms maintain TSH secretion and euthyroidism.[17] A similar situation likely exists in horses.

Dopaminergic inhibition of TSH release also varies according to sex, thyroid status, time of day, and prolactin secretory status.[17] In humans, dopaminergic inhibition of TSH release is greater in women than men and in patients with mild or subclinical hypothyroidism than euthyroid patients.[17] In the study reported here, the change in TSH concentration in response to TRH administration did appear to be lower in geldings ingesting endophyte-infected fescue seed, compared with mares, but this difference was not significant (data not shown). While the lack of significance may have been a result of the small number of horses used (4 geldings and 4 mares), any potential difference between geldings and mares observed in this study was in the opposite direction of that reported for humans. It remains possible that ingestion of endophyte-infected fescue may have more substantial effects on thyroid function in horses that have subclinical thyroid abnormalities.

In conclusion, ingestion of fescue seed infected with the endophytic fungus *N coenophialum* for 2 months did not alter serum concentrations of TSH or the change in TSH concentration in response to TRH administration in adult horses. Baseline concentrations of total and free $T_4$ and $T_3$ and responses of these thyroid hormones to TRH administration also were unchanged. Ingestion of the endophytic fungus *N coenophialum* appears to have little effect on thyroid function in adult horses that are not pregnant.

[a]Forage Testing Laboratory, Dairy One Inc, Ithaca, NY.
[b]North Carolina Department of Agriculture and Consumer Services, Tall Fescue Endophyte Testing Service, Seed Pathology Laboratory, Raleigh, NC.
[c]Veterinary Medical Diagnostic Laboratory, University of Missouri, Columbia, Mo.
[d]Angiocath, The Deseret Co, Sandy, Utah.
[e]pGLU-HIS-PRO amide, Sigma Chemical Co, St Louis, Mo.
[f]SYSTAT, Evanston, Ill.
[g]Rottinghaus GE, Veterinary Medical Diagnostic Laboratory, College of Veterinary Medicine, University of Missouri, Columbia, Mo: Personal communication, 2000.

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