JULY 10-15 AND THEREABOUTS E-MAILS SETTING FORTH THE FIRST ITERATIONS OF THE SEPTIC PENETRATING SETAL EMBOLI (SPSE) HYPOTHESIS OF MRLS

The June 10, 2004, cover e-mail was directed to a Gluck Center colleague, Dr. Barry Fitzgerald, copying him on some e-mails presenting the first two iterations of the SPSE hypothesis, e-mails sent to him after a June 10, 2004, discussion of the SPSE hypothesis of MRLS and the time-line of the initial conception of this hypothesis.

In the early morning hours of July 10, 2002, I became aware of the critical mechanistic implications for MRLS of having the actual setal fragments themselves distribute hematogenously. When I got to work that morning I drafted the first outline describing the significance of this possibility and shared it in draft form (8:25 AM) with two pathologist colleagues and later with a Gluck Center Administrator (12:06 PM). The response from one of the pathologists is the final document in this set, dated July 10, 12:39 PM. The responses were not enthusiastic.

I carefully re-drafted and re-worked the Septic Penetrating Setal Emboli hypothesis over the next few days including Sunday July 14, and sent the redrafted concept in a much more detailed format to an off-campus colleague and to a UK administrator. The second iteration makes clear (Point 2, page 3 of 10) the stastical/probabilistic nature of the proposed mechanism and also specifically notes in closing (Point 7, page 7 of 10), *"Other Caterpillars: If this simple hypothesis is correct then similar exposure to mechanically equivalent setae from other species should also have the potential to produce MRLS."*

All of these communications were marked confidential and the second iteration, the first to leave the Department of Veterinary Science, was also marked copyrighted.

Thomas Tobin, Monday, February 24, 2014

Thomas Tobin

From: "Thomas Tobin" <ttobin@ukv.edu>
To: "Barry P. Fitzgerald"
Sent: Thursday, June 10, 2004 11:09 AM
Subject: Fw:

Barry,

Found this right after you left the office.

Tom T

---- Original Message ----
From: Thomas Tobin
To: [redacted]
Sent: Wednesday, July 10, 2002 12:06 PM
Subject: Fw:

[redacted]

See attached hypothesis. I have sent this to [redacted] and [redacted] and [redacted] for review.

It has not gone across campus.

I understand that [redacted] has given you some of the EM shots of the setae.

Your thoughts and input would be appreciated.

Tom T

----- Original Message -----
From: Thomas Tobin
To:
Cc:
Sent: Wednesday, July 10, 2002 8:25 AM

[redacted]

Review this draft and comment.

Tom T

Pathogenesis of MRLS and Experimental Demonstration of Same

Wednesday, July 10, 2002

7/10/02 8:12:32 AM

Confidential Draft for Review

MEMORANDUM

To: [redacted]

From Tom Tobin

Re: Pathogenesis of MRLS and Experimental Demonstration of Same

1/ Based on the two most recent experiments, our previous experience and our discussions yesterday, the following is highly likely to be the mechanism of MRLS.

2/The primary and only significant pathogen(s) involved are the barbed setal fragments of the ETC "hairs".

3/ Introduction of these barbed setal fragments with microbiological hitchhikers into the circulatory system by any route results in microscopic loss of structural integrity in those areas of the body in which they lodge.

4/ Modest local disruption of cellular/structural integrity, with associated introduction of bacterial pathogens ***generally*** does not cause significant long-term pathology, except in pregnant animals. Exceptions would be the few uveitis and pericarditis cases observed with MRLS.

5/ In pregnant mares, loss of structural integrity in the placenta due to placental lodgement of setal fragment(s) immediately exposes the fetus to bacterial proliferation. The fetus is unprotected against such exposure. Bacterial proliferation follows, then death of the fetus, as seen in our the LFL model.

6/ The bacteria proliferating may depend on the bacteria circulating in the maternal system, or may be actually seeded by the setal fragments themselves.

7/ It should also be considered that the setal fragments may carry different bacterial passengers, depending on their route of entry into the body. This presumably accounts for the different bacterial patterns found between natural (oral exposure to setae) and intestinal (tubing exposure to setae).

8/ If this hypothesis is correct, then introduction of setal fragments directly into the blood stream of horses should rapidly reproduce EFL and or LFL.

9/ THIS HYPOTHESIS IS THEREFORE EASILY AND RAPIDLY TESTABLE

10/ An unknown factor in this approach is the role of damage to intestinal integrity and the concomitant increase in blood borne pathogens caused by the large oral doses of caterpillars (setae) used in the very dramatic oral dosing experiments.

11/ This hypothesis is a modification and simplification of the hypothesis that drove our mouse setae experiment, which assumed that the setae were introducing a protein toxin that was the primary pathogen. This new and simpler hypothesis assumes that hematogenously borne setal fragments, plus possible bacterial hitchhikers, are the primary and only significant pathogen(s) in MRLS.

12/ I now propose that we perform this setal test ASAP with the remaining control LFL mares from our recent LFL model.

13/ If this experiment works, we will have established the pathogenesis of MRLS, and can confidently tackle the matter of control measures.

[redacted]

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For information on TIP publications http://windpub.org/lasix.htm

Thomas Tobin

From: "Thomas Tobin" <ttobin@uky.edu>
To: [redacted]
Sent: Thursday, June 10, 2004 1:55 PM
Subject: Fw: separation

Barry,

Thought some more about it and cleaned it up over the weekend and shared it with [redacted] and [redacted] in a much cleaner form on July 15th, 2002

Also added copyright symbol

Tom T

----- Original Message -----
From: "Thomas Tobin" <ttobin@uky.edu>
To: [redacted]
Cc: [redacted]
Sent: Monday, July 15, 2002 12:10 AM
Subject: Re: separation

> CONFIDENTIAL COMMUNICATION
>
>
> Sunday, July 14, 2002
>
>
> MEMORANDUM
>
> To: [redacted]
>
> From: Tom Tobin
>
> Re: Attached Hypothesis
>
> 1/ I have been out of town for about ten days on urgent family matters in
> Ireland.
>
> 2/ Attached is a hypothesis which I believe explains many of the major
> characteristics of MRLS and which best fits the data obtained to date, and
> the data developing as we speak.
>
> 3/ It is an extremely simple hypothesis, requiring no toxins, viruses,
duck

> poop or other magical factors, etc
>
> 4/ Have a look over this draft and give me your thoughts.
>
> 5/To help your evaluation this hypothesis along, I have just been told
that
> the ongoing Rood and Riddle experiments on the inside Vs the outside of
> caterpillar experiments have produce their first EFL, apparently due to
> caterpillar outsides.
>
> 6/ If this hypothesis is correct, the next experiment is obviously shaved
> caterpillars (no setae) Vs the shavings (setae).
>
> 7/ This new hypothesis is a simplification of the hypothesis that drove
our
> mouse setae experiment, which assumed that the setae were introducing a
> protein toxin that was the primary pathogen. This new and simpler
hypothesis
> assumes that hematogenously borne setal fragments, plus bacterial
> hitchhikers, are the primary and only pathogen(s) in MRLS.
>
> 8/ Unless I am mistaken, I think the MRLS end game, at least as far as its
> etiology is concerned, is right now in progress.
>
>
> C:
>
>
>
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>
> CONFIDENTIAL COMMUNICATION
>
> DRAFT IN PROGRESS
>
> © Thomas Tobin, July10th, 2002.
>
> A New Working Hypothesis of the Mare Reproductive Loss Syndrome (MRLS):
> Eastern Tent Caterpillar (ETC) Exposure and "Septic Penetrating Setal
> Emboli" (SPSE).
>
> BACKGROUND:
>
> We should carefully consider the possibility that simple hematogenous
> spread of barbed ETC setal fragments, with associated bacterial
hitchhikers,
> is the fundamental underlying pathophysiological mechanism of each of the
> four recognized MRLS syndromes, Early Fetal Loss (EFL) Late Fetal Loss
> (LFL), Uveitis and Pericarditis.
>
> The pivotal assumption in this hypothesis is that we have incorrectly

> evaluated and/or underestimated the combined effect in pregnant horses of
> two key factors already in evidence.
>
> Factor 1 is the well established ability of caterpillar setae to migrate
in
> tissues.
>
> Factor 2 is the enormous relative sensitivity of the pregnant mare to
> exposure to ETC setae, as compared with the non-pregnant horse and also,
> apparently, most other animals, including humans.
>
> 1/ ETC Setae and Setal Migration:
>
> ETC setae are barbed, designed to penetrate tissues and well recognized to
> do so. As such, setae may enter the body by any route, including the
> intestinal route. Once lodged in a tissue, setal fragments migrate, the
rate
> of migration depending only on rate/frequency of movement in the host
> tissue. These movements serve to "ratchet" the barbed seta along in an
> entirely random manner through the host tissue.
>
> 2/ Septic Penetrating Setal Emboli:
>
> We propose that setal fragments that penetrate blood vessels create
"Septic
> Penetrating Setal Emboli", which may move rapidly to new and more distant
> locations in the body. All setal movements are passive, secondary to
tissue
> movement and/or blood flow, and all events are statistical. These events
> presumably occur at some level in all species, apparently with only
> occasional substantial adverse health consequences.
>
> However, the Pregnant Mare, and especially the Late Pregnant Mare is
highly
> susceptible to fetal loss from septic penetrating setal emboli.
>
> 3/ Generating Septic Penetrating Setal Emboli: The Role of the Intestinal
> Tract:
>
> For the purposes of this hypothesis, and MRLS in general, we may view the
> equine intestinal tract, with its ongoing peristaltic movements, as an
ideal
> organ to propel setal fragments through its tissues and, with its network
of
> absorptive blood vessels, as a body system highly likely to yield septic
> penetrating setal emboli following ETC exposure.
>
> (NB: The apparently protective efficacy of muzzling mares may suggest
> considerable importance for the oral route of exposure).
>
> 4/ Unusual Susceptibility to SPSE of the Pregnant Mare, and Especially the

> Late Pregnant Mare:
>
> 4.1/ The Role of Myometrial and General Activity:
>
> Septic setal emboli lodged in the uterine blood vessels of pregnant mares
> will again begin their "through tissue" migration. In uterine tissues,
> myometrial movement, either due to the musculature of the myometrium itself
> or, especially in LFL, the physical activity of both the mare and the fetus,
> again drives migration of the septic setal fragments. Sooner or later, the
> septic fragment will penetrate a fetal membrane.
>
> 4.2/ The Role of Fetal Membrane Penetration:
>
> Penetration of the fetal membranes alone may be sufficient to cause fetal
> death. Experience with amniocentesis suggests that limited aseptic trauma
> to fetal membranes will rapidly produce placental separation and fetal death
> (Dr. Jim Bowen, personal communication).
>
> Well established clinical experience suggests that very modest bacterial
> contamination of amniotic fluid can result in rapid bacterial overgrowth,
> followed by death and expulsion of the fetus within a day or days. Based on
> these data, penetration of the fetal membranes by a single septic setal
> fragment should be sufficient to produce ELFL or LFL (Dr. Jim Bowen,
> personal communication).
>
> Review of our recently acquired LFL experimental data suggests that
> bacterial proliferation was a primary event in LFL, occurring prior to signs
> of fetal distress and fetal death.
>
> (On the other hand, toxicological hypotheses assume that toxic damage to
> the fetal membranes or the fetus is the primary event, followed by secondary
> bacterial invasion, a proposed sequence of events apparently inconsistent
> with the data from the recent LFL experimental model).
>
> 4.3/ The Role of Fetal Size and Movement:
>
> Because the Late Fetus presents a relatively much larger "capture" area for
> randomly distributing setae, any Late Fetus is statistically more likely to
> be "hit" than the much smaller Early Fetus. Additionally, myometrial
> movement is presumably relatively greater in the Late Fetus, driving the
> tissue migration of setae lodged in uterine tissue, and ensuring their
> relatively rapid migration through a fetal membrane. Together, these

> factors immediately explain the much more rapid onset of LFL than EFL in the
> recent ETC oral administration experimental models.
>
> (NB: The role of movement in onset of LFL could easily be tested with
> tocolytic agents. Such agents might also conceivably be protective against
> EFL and LFL).
>
> 4.4/ Role of the Mares Placentation Pattern:
>
> It should also be noted that the fact that the fetal/maternal placentation
> interface of the mare covers virtually the entire surface of the placenta.
> This placental arrangements renders the mare relatively much more
> susceptible to this kind of attack than, for example, the bovine, with its
> very compact and localized cotyledonary placentation.
>
> Given the simple nature of the model, it is unclear why we have been unable
> to reproduce EFL and LFL with oral gavage of caterpillars in mice. However,
> Rolands has pointed to the remarkable reproductive inefficiency of
> perissodactyls, and notes that members of this family have suffered
> extinction at a rate greater than that of any other placentated mammal. It
> may well be that the relatively unsophisticated placenta of the horse
> renders it much more susceptible to this form of attack than the more
> evolved placental structures of other mammals. Beyond this, other mechanisms
> by which mice may be protected also suggest themselves.
>
> 4.5/ Role of Delayed Fetal Membrane Penetration:
>
> This mechanism also readily explains cases of EFL or LFL occurring at some
> time after exposure to caterpillars has ceased. Inopportune myometrial
> location of a septic setal fragment, and or location in a less mobile area
> of the myometrium would delay onset of puncture of the fetal membranes,
> yielding classic EFL or LFL at some time after exposure to living ETC had
> ceased.
>
> 4.6/ Lack of Positive Blood Cultures:
>
> This model is consistent with the lack of positive blood cultures from LFL
> horses. This is because the blood borne bacterial contamination is carried
> in discrete packets on individual setal fragments.
>
>
>
> 5/ The Uveitis and Pericarditis Cases:
>
> This hypothesis requires that not just mares, but all central Kentucky
> horses exposed to the ETC caterpillars suffer exactly the same episodes of
> septic setal spread. We propose that the uveitis and pericarditis cases,

> which occurred across central Kentucky in horses of all ages and genders,
> are clear evidence of this process at work in a systemic penetrating fashion
> at some level in the entire at risk population of horses when MRLS occurred.
>
> 5.1/ The Uveitis Cases:
>
> The cases of uveitis presumably represent hematogenous delivery of a septic
> setal fragment to the eye. The very low incidence of uveitis observed is
> presumably related to the relatively low target size/fraction of cardiac
> output that is required to supply an individual eye.
>
> (I also seem to recall that the eye is an immunologically privileged area;
> as such, the eye may be particularly susceptible to damage by penetrating
> septic fragments such as septic setae. Our ability to observe eye pathology
> associated with MRLS is most likely due to the relative ease of observation
> of the eye, the highly significant consequences of eye damage compared with
> limited local damage in other areas of the body and the possible
> immunological difficulty of controlling a septic focus that has penetrated
> the eye.)
>
> 5.2/ The Pericarditis Cases:
>
> The pericarditis cases presumably represent setae that entered the coronary
> blood supply, lodged in the blood vessels and then proceeded to migrate
> through the cardiac muscle. Of all muscles in the body, the heart is the one
> through which one might expect barbed setae to migrate fastest.
> Additionally, for every seta that migrated "out" and appeared at the
> epicardial surface, at least one migrated in the opposite (or other)
> directions. Presumably a much larger number of subclinical epicarditis
> cases occurred associated with the MRLS episodes, and resolved
> spontaneously, as presumably do most incidents of systemic septic setal
> spread.
>
> 6/ Intellectual Economy of the Hypothesis:
>
> This hypothesis does not require or assume the presence with or in the
> caterpillars of any extra toxins, venoms, viruses, unusual weather patterns,
> other plant toxins, fungal overgrowth, duck poop, etc.(Which,
> unfortunately, severely limits its intellectual property
> potential/applications).
>
> We must also be note that a clear characteristic of MRLS has been that no

> traces, associations or evidence of toxins, viruses, mycotoxins, etc, have
> thus far been identified with this syndrome, despite very extensive searches
> for the same.
>
> This hypothesis also explains why no significant hormonal patterns or other
> clinical chemistry changes have yet been identified in the aborting mares.
> MRLS, both ELF and LFL, is dependent on the direct seeding of small amounts
> of bacterial contaminants directly into the fetus. The bacterial
> proliferation occurs directly in the fetal membranes, followed by bacterial
> invasion of the fetus, which is then rapidly "slipped".
>
> This hypothesis is grounded in the well-established physics and mechanics of
> the movement of barbed fragments through motile soft tissues, and the
> likelihood of bacterial contamination of such barbed fragments. We propose
> that it can account for all of the major characteristics of the four
> simultaneously occurring MRLS syndromes.
>
> This hypothesis is a modification and simplification of the hypothesis that
> drove our first mouse setae experiment, which assumed that the setae were
> introducing a protein toxin that was the primary pathogen. Further
> reflection suggested that a setal toxin is not required, and the speed of
> onset of LFL also does not support a toxic mechanism.
>
> 7/ Other Caterpillars???
>
> If this simple hypothesis is correct, then similar exposure to mechanically
> equivalent setae from any other species should also have the potential to
> produce MRLS.
>
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> 7/10/02 12:31 PM
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> Confidential Draft #2 for Review
>
>
> MEMORANDUM
>

> To:
>
> From Tom Tobin
>
> Re: Pathogenesis of MRLS and Experimental Demonstration of Same. A
> Mechanical Hypothesis
>
> Based on the two most recent experiments, our previous experience and our
> discussions yesterday, the following is highly likely to be the mechanism
of
> MRLS.
>
> 1/The primary and only significant pathogen(s) involved in MRLS are the
> BARBED setal fragments of the ETC "hairs". (See attached electron
> micrograph).
>
> 2/ Introduction of these barbed setal fragments, with associated
> microbiological hitchhikers, into the circulatory system by any route
> results in microscopic loss of structural integrity in those areas of the
> body in which these barbed setae lodge/penetrate.
>
> 3/ Modest local disruption of cellular/structural integrity, with
associated
> introduction of bacterial pathogens generally does not cause significant
> long-term pathology, except in pregnant animals. Exceptions to this rule
> would be the very few uveitis and pericarditis cases observed.
>
> 4/ In pregnant mares, penetration of a barbed setal fragment through the
> placenta membranes results in loss of structural integrity in the
placenta.
> The fetal membranes are seeded by setal contaminants and bacterial
> proliferation commences. The fetus/fetal membranes are immunologically
> unprotected against such exposure. Bacterial proliferation follows,
> followed by death of the fetus, as seen in the LFL model.
>
> 5/ The specific bacteria seeded into the fetal membranes may depend on the
> bacteria circulating in the maternal system, or may more likely be seeded
by
> the barbed setal fragments themselves.
>
> 6/ It should also be considered that the setal fragments may carry
different
> bacterial passengers, depending on their route of entry into the body.
This
> presumably accounts for the different bacterial patterns found between
> natural (oral exposure to setae) and intestinal (tubing exposure to
setae).
>
> 7/ A setal "hit" on the placenta or anywhere else is a random statistical
> event. Given the larger uterus in LFL cases, and the larger proportion of

> cardiac output to the LFL uterus, it is not surprising that LFL developed
> much more rapidly than EFL.
>
> 8/ If this hypothesis is correct, then introduction of barbed setal
> fragments directly into the blood stream of horses should rapidly
reproduce
> LFL, and less rapidly and reliably, EFL.
>
> 9/ THIS HYPOTHESIS IS EASILY AND RAPIDLY TESTABLE
>
> 10/ Caveat: An unknown factor in this approach is the role of damage to
> intestinal integrity and the concomitant increase in blood borne pathogens
> caused by the large doses of caterpillars (setae) used in the very
dramatic
> oral dosing/LFL experiments.
>
> 11/ This hypothesis is a modification and simplification of the hypothesis
> that drove our mouse setae experiment, which assumed that the setae were
> introducing a protein toxin that was the primary pathogen. This new and
> simpler hypothesis assumes that hematogenously borne setal fragments, plus
> bacterial hitchhikers, are the primary and only pathogen(s) in MRLS.
>
> 12/ I propose that we perform this setal test ASAP with the remaining
> control LFL mares from our recent LFL model.
>
> 12/ If this experiment works, we will have established the pathogenesis of
> MRLS, and can confidently tackle the matter of control measures.
>
>[redacted]
>[redacted]
>[redacted]
> Thomas Tobin, Professor, Dept. of Vet. Science & Graduate Center for
> Toxicology
> Room 331, Maxwell H. Gluck Equine Research Center, University of Kentucky,
> Lexington, KY 40546-0099
> Ph 859 257 3739 Fax 859 257 5169, Home Phone/Fax 859 269 3192,
> E-mail ttobin@uky.edu or Thomastob@aol.com.
> For general information, check www.thomastobin.com
> For information on TIP publications http://windpub.org/lasix.htm
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> copy or deliver this mail to anyone, and you should destroy this message
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>
>
> ----- Original Message -----

> From: [redacted]
> To: "Thomas Tobin" <ttobin@uky.edu>
> Sent: Friday, June 28, 2002 2:13 PM
> Subject: separation
>
>
> > Tom - FYI - I made the following recommendation to Bill Bernard about a
> > possible "next step".... Terry
> >
> >
> > Something that has the potential to take things one step further along:
> > feeding one group of mares the integuments of caterpillars and the other
> > the internal organs (guts). I experimented a bit with separating the
> > two and found that the following procedure works well and is fast.
> > After removing the head of a frozen caterpillars with a razor blade and
> > letting the body thaw, use a "rolling pin" (wooden pencil) to roll out
> > the guts from the center of body forward then roll from the center
> > backward. The guts will exit both the head end and the anus and leave
> > behind a virtually clean integument. The will be a few seta with the
> > guts and some small residue of gut with integument but this should be of
> > minor concern. The attached photo shows what the two piles look like
> > after doing two caterpillars (heads go in the with the integument
> > pile!). If you used the same number of caterpillars that gave you
> > results the first time (50 or so) and adminster them the same way then I
> > would expect that one of the two treatments would produce abortions, or
> > at least one would be markedly more effective than the other. It is
> > possible that fetal losses would occur sooner with more caterpillars
> > ingested so perhaps 100 per treatment would be better. I would estimate
> > that it would take an hour or less per day to prepare the caterpillars
> > in this manner for all the mares involved.
> >
> > The integument treatment tests the potential of the setae, cuticular
> > steriods, and other cuticular chemicals. The other treatment has the
gut
> > contents, the malphigian tubules, hemolymph, fat body, etc. If it
> > could be established that one treatment is more effective, this would
> > narrow the search significantly
> >
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Thomas Tobin

From: [redacted]
To: "Thomas Tobin" <ttobin@uky.edu>
Cc: [redacted]
Sent: Wednesday, July 10, 2002 12:39 PM
Subject: Re:

[redacted]

Review this draft and comment.
Pathogenesis of MRLS and Experimental Demonstration of Same

1/ Based on the two most recent experiments, our previous experience and our discussions yesterday, the following is highly likely to be the mechanism of MRLS.
*I have neither heard nor seen anything to suggest problems due to setae. The eye problems would be the most likely manifestation and examination of several eyes have not supported this. I feel the natural disease and especially the rapid abortions following experimental administration support a toxic principal.
2/The primary and only significant pathogen(s) involved are the barbed setal fragments of the ETC "hairs".
*I don't know how we can make this statement.
3/ Introduction of these barbed setal fragments with microbiological hitchhikers into the circulatory system by any route results in microscopic loss of structural integrity in those areas of the body in which they lodge.
*I doubt that ingested setae would find the vascular system. This would endow them with the properties of a migrating parasite which would actively seek the vascular compartment. Rather, I feel ingested setae would either pass through the alimentary tract or if random penetration of the mucosa occurred, that a local inflammatory response would ensue with enzymatic destruction of the setae (a granulomatous reaction typical of the response to any foreign material).
4/ Modest local disruption of cellular/structural integrity, with associated introduction of bacterial pathogens ***generally*** does not cause significant long-term pathology, except in pregnant animals. Exceptions would be the few uveitis and pericarditis cases observed with MRLS.
*No comment.
5/ In pregnant mares, loss of structural integrity in the placenta due to placental lodgement of setae fragment(s) immediately exposes the fetus to bacterial proliferation. The fetus is unprotected against such exposure. Bacterial proliferation follows, then death of the fetus, as seen in our the LFL model.
*If setae were able to enter the circulation, they would lodge in capillary beds, presumably. In the pregnant mare the site would be the endometrium, not the placenta. They would have to migrate through 3-4 tissue layers to reach the placenta. In examination of 100's of placentas we saw virtually no placental changes to suggest penetration by foreign material. Also, why would there not be problems in other vascular locations in the mare: glomerular capillaries, lung alveolar capillaries, or meningeal vessels as examples? These are sites where vascular problems tend to manifest. Why not a generalized vasculitis? Once the endothelium is breached a powerful inflammatory cascade is initiated with definite systemic manifestations.
6/ The bacteria proliferating may depend on the bacteria circulating in the maternal system, or may be actually seeded by the setal fragments themselves.
*Once again in my opinion of the unlikely event of vascular entry, if septic material is in circulation, there would be no reason to think that bacteria would just hang out on the setae, but rather would be proliferating maximally. The foreign protein and bacteria would cause the immune system would be

activated (the reticluoendothelial system) with phagocytosis by fixed macrophages resident in spleen, liver, lung, and lymphnodes. Once again I would expect a sizable immune reaction with dumping of acute phase reactants by the macrophages.

7/ It should also be considered that the setal fragments may carry different bacterial passengers, depending on their route of entry into the body. This presumably accounts for the different bacterial patterns found between natural (oral exposure to setae) and intestinal (tubing exposure to setae).

*No comment

8/ If this hypothesis is correct, then introduction of setal fragments directly into the blood stream of horses should rapidly reproduce EFL and or LFL.

* Or anaphylaxis or nothing.

9/ THIS HYPOTHESIS IS THEREFORE EASILY AND RAPIDLY TESTABLE

*True.

10/ An unknown factor in this approach is the role of damage to intestinal integrity and the concomitant increase in blood borne pathogens caused by the large oral doses of caterpillars (setae) used in the very dramatic oral dosing experiments.

11/ This hypothesis is a modification and simplification of the hypothesis that drove our mouse setae experiment, which assumed that the setae were introducing a protein toxin that was the primary pathogen. This new and simpler hypothesis assumes that hematogenously borne setal fragments, plus possible bacterial hitchhikers, are the primary and only significant pathogen(s) in MRLS.

*Do we conclusively know that ETC setae have the harmful effects documented with other caterpillars?

12/ I now propose that we perform this setal test ASAP with the remaining control LFL mares from our recent LFL model.

13/ If this experiment works, we will have established the pathogenesis of MRLS, and can confidently tackle the matter of control measures.

For your consideration,

[redacted]