Is it time to re-evaluate transition period energy and mineral dogmas

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Nutritionists are Often Incorrectly Blamed for:

- High NEFA
- Hyperketonemia
  - Clinical and subclinical ketosis
- Subclinical hypocalcemia

- These are due to 1 of 2 things:
  - High productivity in healthy cows (profitable dairy producer)
    - The nutritionist deserves a raise
  - Metabolic reflection of immune activation
    - Likely stemming from metritis, mastitis, pneumonia or GIT inflammation
      - These are mostly management issues and not caused by nutrition

Everything in today's talk is thoroughly covered in our recent review

Horst et al., 2021, JDS 14:8380-8410

J. Dairy Sci. 104:8380–8410
https://doi.org/10.3168/jds.2021-20330

Invited review: The influence of immune activation on transition cow health and performance—A critical evaluation of traditional dogmas

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ABSTRACT

The progression from gestation into lactation represents the transition period, and it is accompanied by marked physiological, metabolic, and inflammatory adjustments. The entire lactation and a cow's opportunity to have an additional lactation are heavily dependent on how successfully she adapts during the periparturient period. Additionally, a disproportionate amount of health care and culling occurs early following parturition. Thus, lactation maladaptation has been a heavily researched area of dairy science for more than 50 yr. It

feed intake and causes hypocalcemia. Our tenet is that immune system utilization of glucose and its induction of hypophagia are responsible for the extensive increase in NEFA and ketones, and this explains why they (and the severity of hypocalcemia) are correlated with poor health, production, and reproduction outcomes. In this review, we argue that changes in circulating NEFA, ketones, and calcium are simply reflective of either (1) normal homeorhetic adjustments that healthy, high-producing cows use to prioritize milk synthesis or (2) the consequence of immune activation and its sequelae.
Key words: inflammation, hypocalcemia, ketosis,

Guiding Concepts and Principles

- The best indicators of “health” are feed intake and milk yield.
- Everyone agrees that “stress” reduces productivity……..
  then high productivity CANNOT be stressful
- We have over complicated animal health
  - Cows that are eating and producing large quantities of milk ARE healthy
- The Progressive dairy industry is ahead of academia
  - With regards to transition cow management
    - Large successful dairy farms are already doing everything I’m talking about
- Inconsistent and unreproducible data should create doubt
  - When scientific papers do not agree we should be skeptical

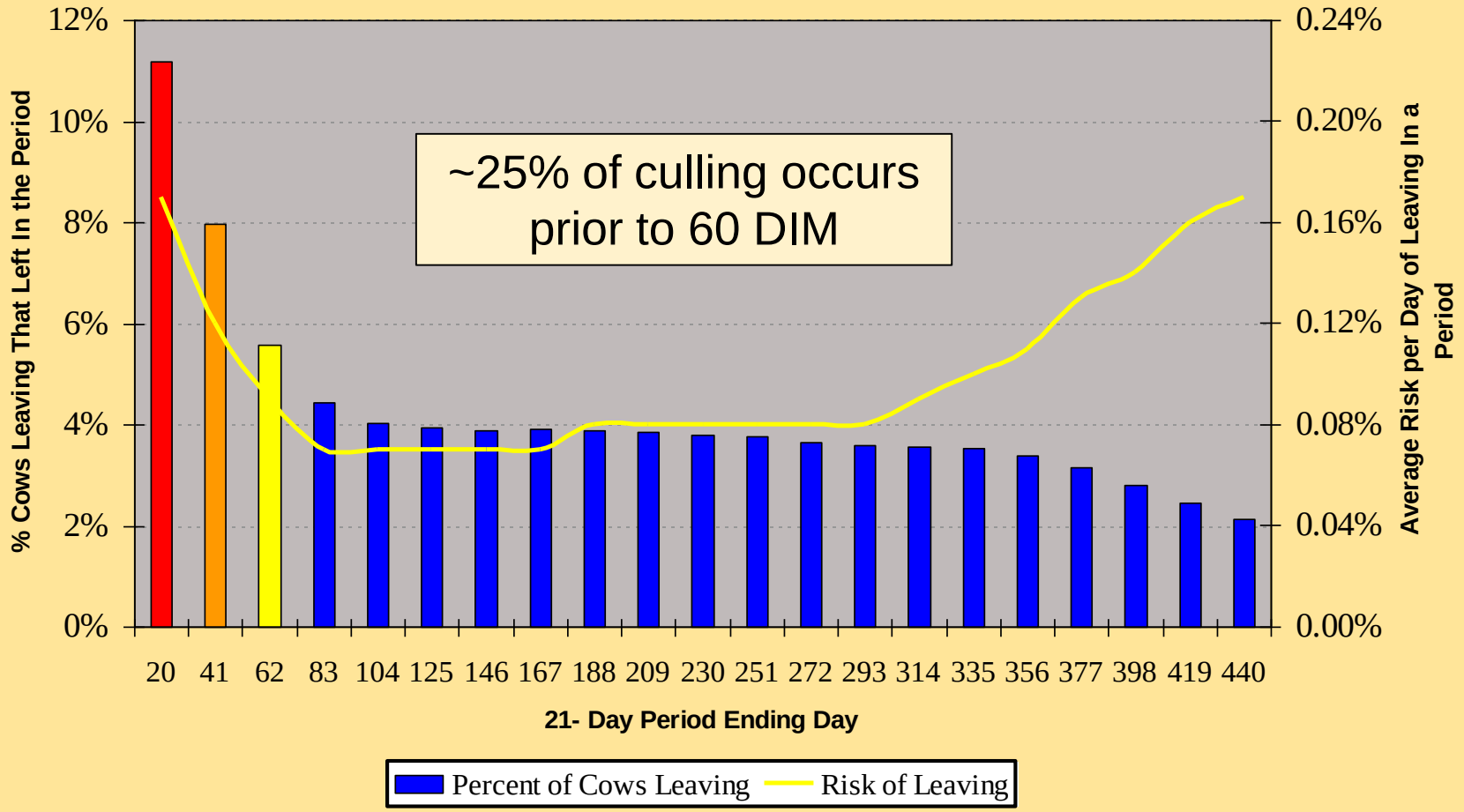
Transition Period Morbidity

Disorders affects 50%:

- Dystocia
- Milk fever
- Retained placenta
- Metritis
- Ketosis
- DA
- Fatty liver
- Lameness
- Death

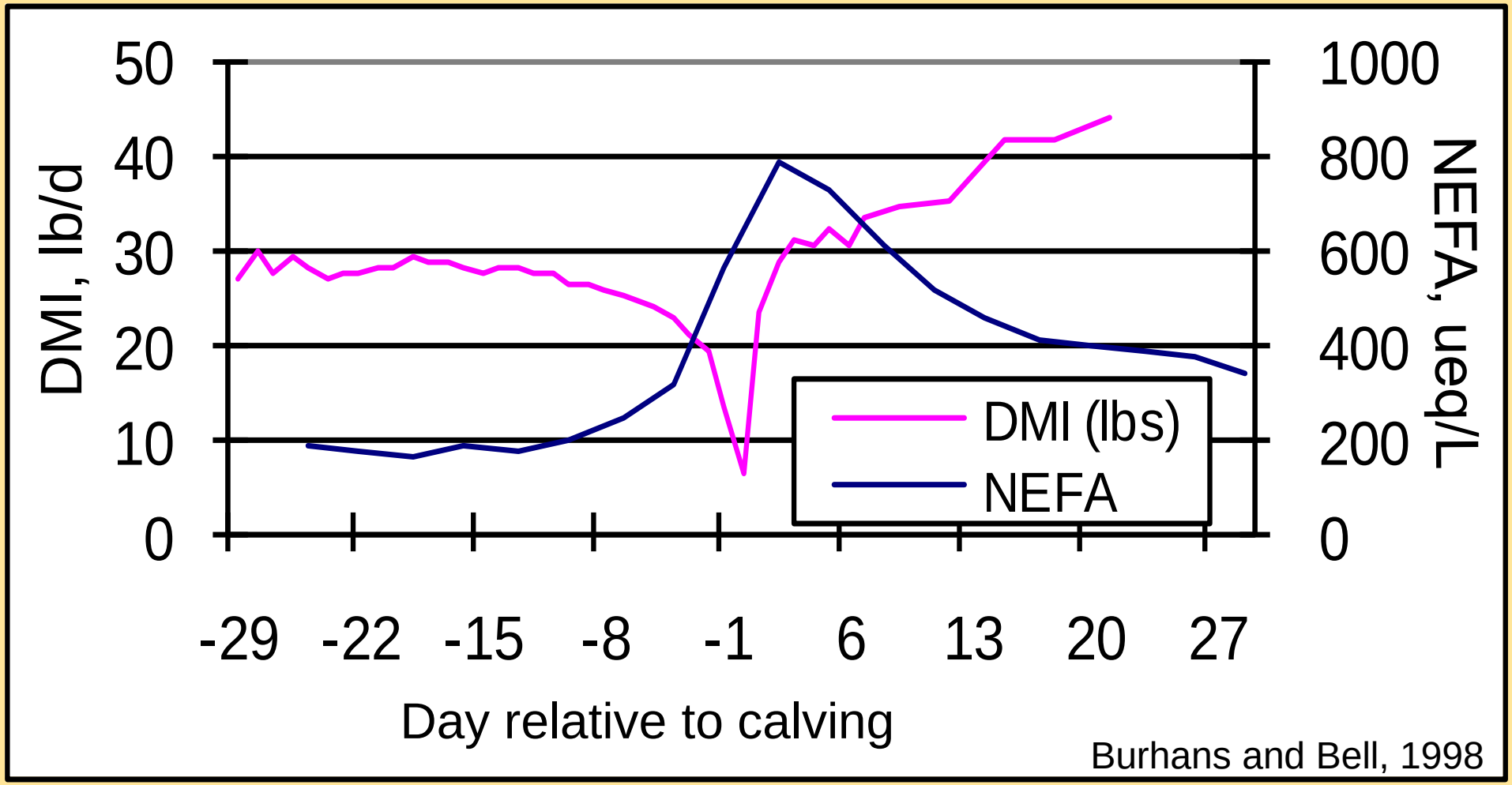
Drackley, 1999

When cows leave the herd

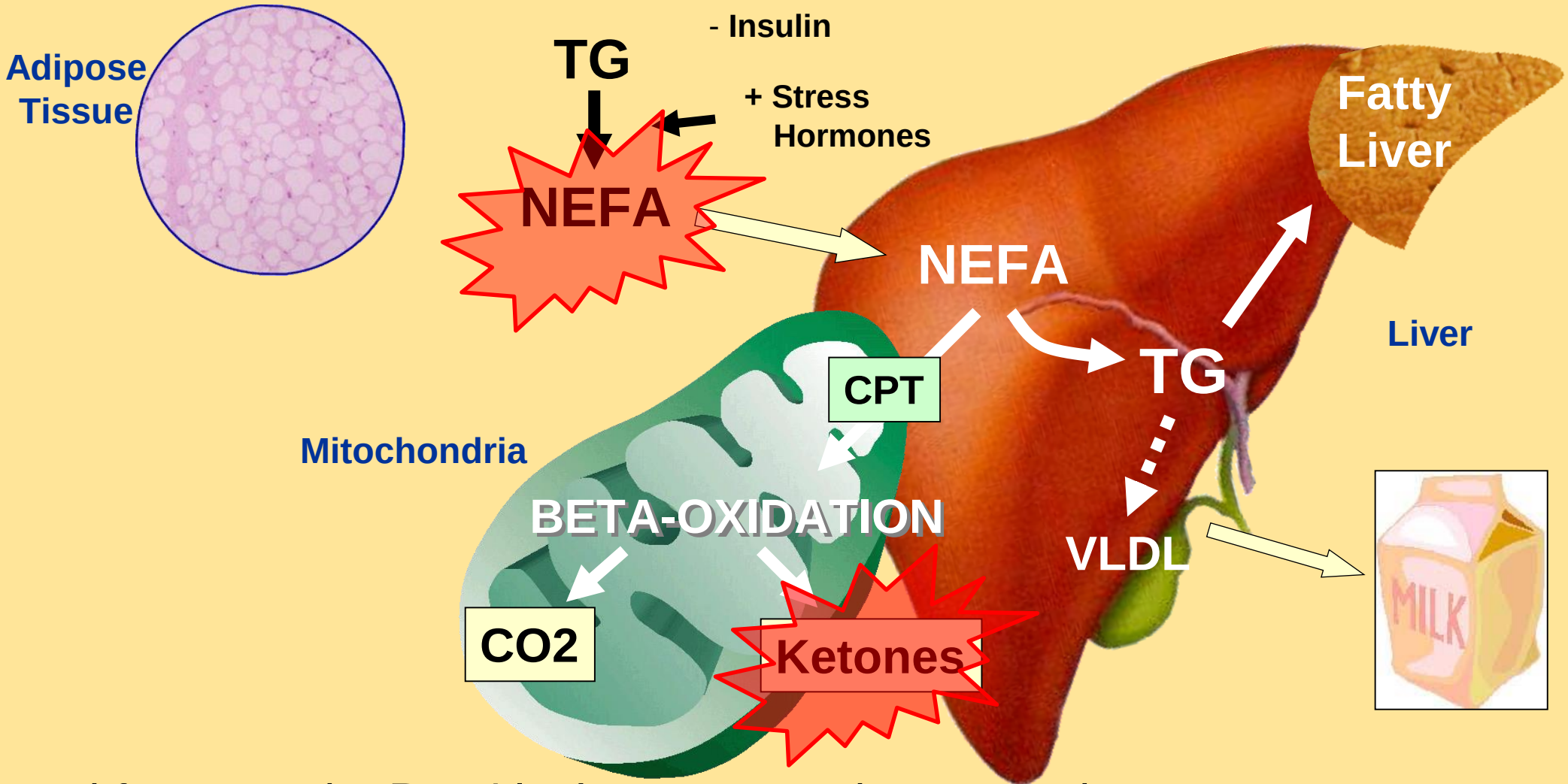


Source: 2002, Steve Stewart, DVM, Dipl.-ABVP, Univ. of Minnesota, College of Vet. Med.

Transition Period Energy Balance



Liver Lipid Metabolism During the Transition Period



Adapted from Dr. Jim Drackley's papers and presentations

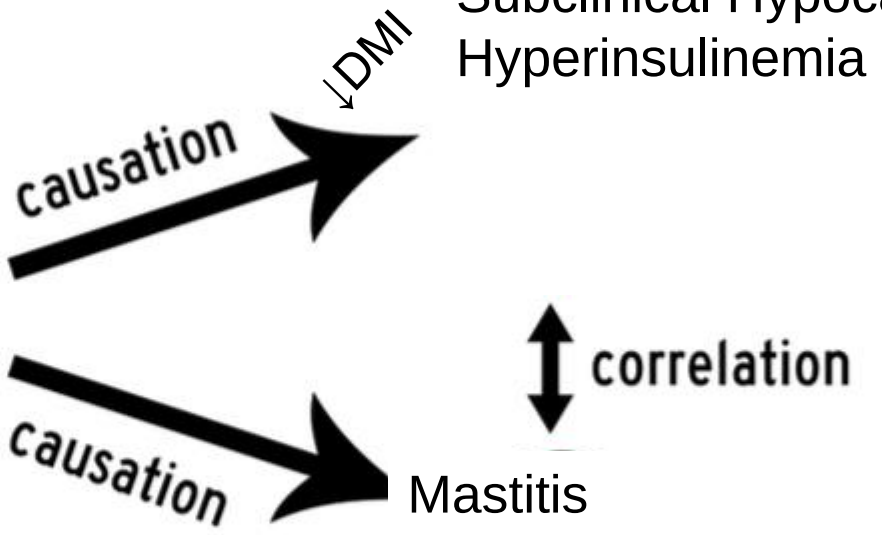
Retrospective and Observational Studies

- Hundreds of studies *associate* and correlate NEFA, BHBA and Ca with:
  - Increased risk of ketosis, decreased milk yield, LDA, metritis, retained placenta, laminitis, or poor reproduction
    - Chapinal et al., 2011; Huzzey et al., 2011; Ospina et al., 2010a, 2010c; Duffield et al., 2009; LeBlanc et al., 2005
- Many papers do not agree…..inconsistencies in the literature
  - Unlike the overwhelming and converging lines of evidence demonstrating smoking causes cancer.
    - Claiming NEFA and ketone skepticism is akin to questioning whether smoking causes cancer is bewildering
- Plasma NEFA are markedly increased (>700 mEq/L) following calving in almost all cows
  - ~15-20% get clinical ketosis
  - What makes these cows more susceptible to ketosis?
    - Predisposition to developing fatty liver?
- Reductionist approach (one metabolite = one disease)

Cause and Effect??

- The incidence of health problems is highest in the first month of lactation
- The largest swings in energetic metabolites, hormones and minerals occurs in the first month of lactation
- Thus…a lot of moving parts and events occurring simultaneously
  - Consequently they will all be correlated
- Causality and correlation are incorrectly interchanged when an observational relationship between 2 events is claimed to be inevitable rather than coincidental.

<u>Transition Period</u>
Poor dry-off procedure
Dirty pre-fresh pens
Filthy calving pens
Rumen acidosis
Hind gut acidosis
Overcrowding
Out of feed events



High NEFA
Hyperketonemia
Subclinical Hypocalcemia
Hyperinsulinemia

Mastitis
Metritis
Infertility
DA

This correlation interpretation then causes suspect decision making and unnecessary farm expenses

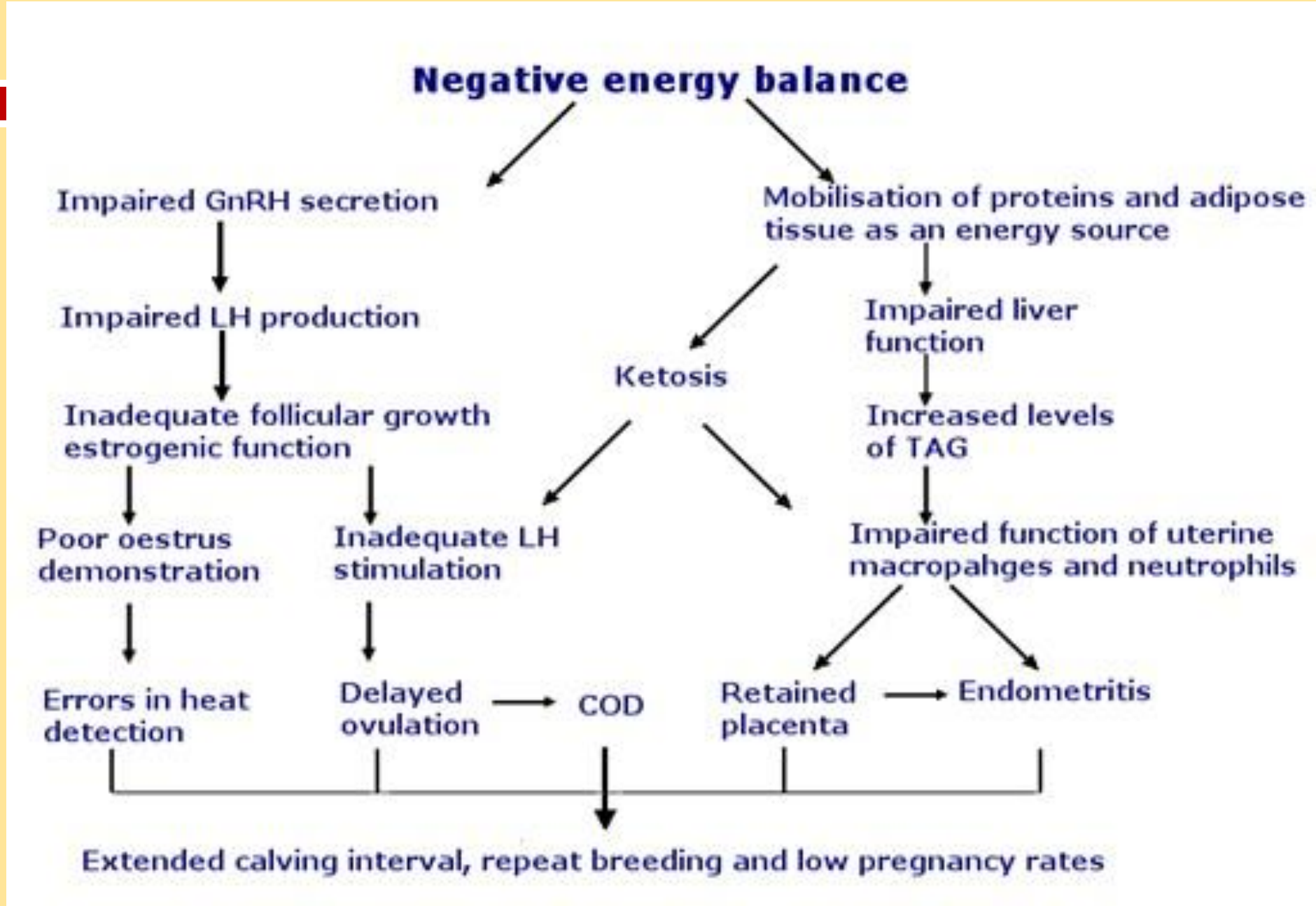
Traditional Belief

Assuming Correlation Equals Causation

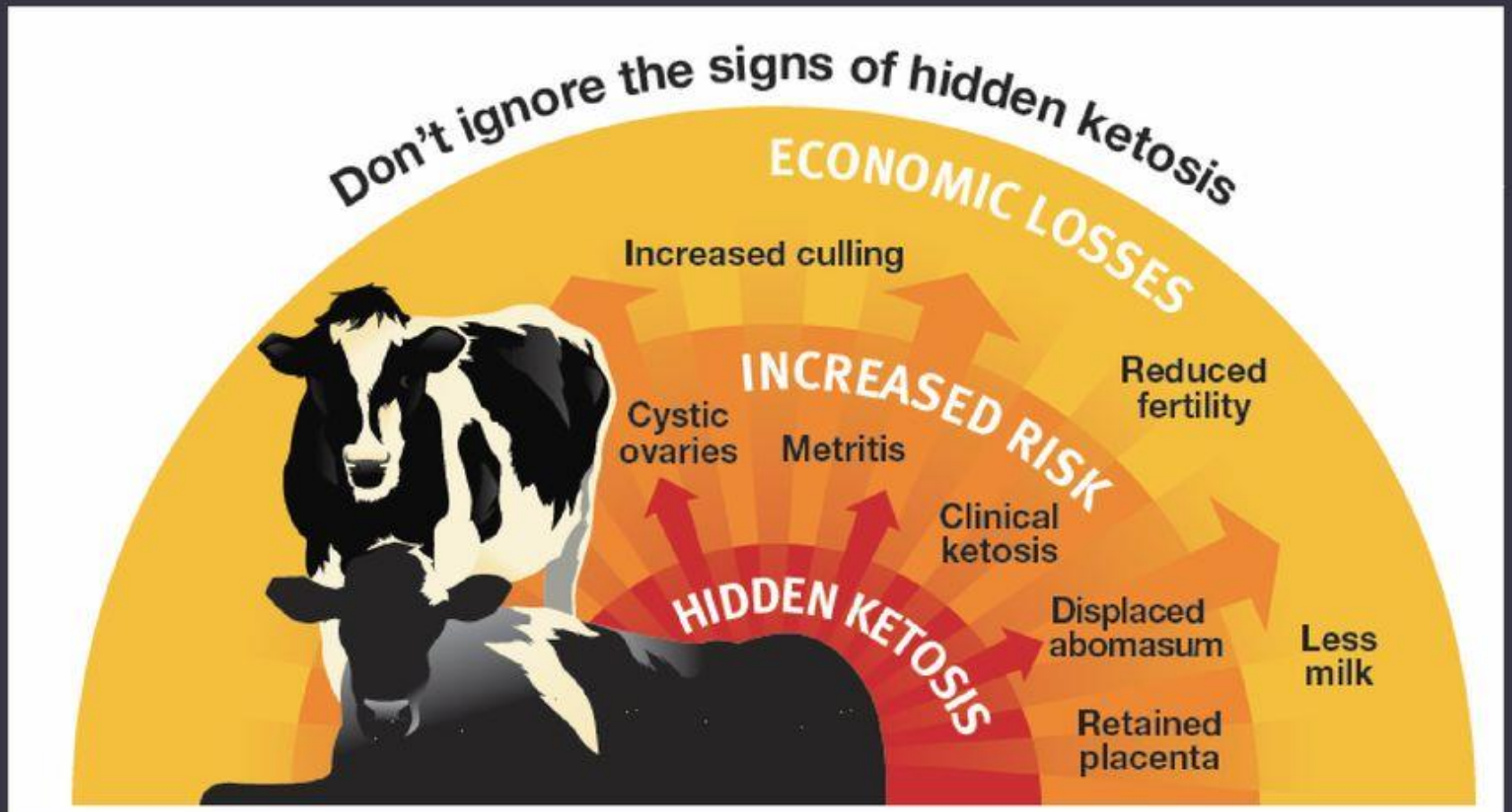
Increased NEFA, Hyperketonemia, and Hypocalcemia…..**CAUSE** production and health problems

Dogma: Negative Energy Balance CAUSES problems

An example model



Dogma: Ketones cause problems



https://slideplayer.com/slide/13774593/

How (and why) do NEFA, Hyperketonemia and Hypocalcemia cause problems

- Biological plausibility?
  - Why would evolution favor a scenario where the mother endangers herself and compromises her ability to nourish her young?

- There remains little mechanistic evidence for how NEFA, ketones and Ca can directly have such a large influence on a variety of seemingly unconnected systems and diseases

- Best line of evidence is extrapolated from their purported role in immunosuppression.

If hyperketonemia, high NEFA and subclinical hypocalcemia are pathological….it stands to reason that therapeutically treating these disorders would improve cow health

Culling Trends Over Time

Culling Reason	NAHMS (1996)	NAHMS (2002)	NAHMS (2014)
Voluntary Reasons	21.3	19.3	21.1
Re			
Injury	4.1	6.0	5.2
Death	3.8	4.8	4.2
Disposition			
Lameness	14.2	16.3	16.8
Other	3.9	4.1	

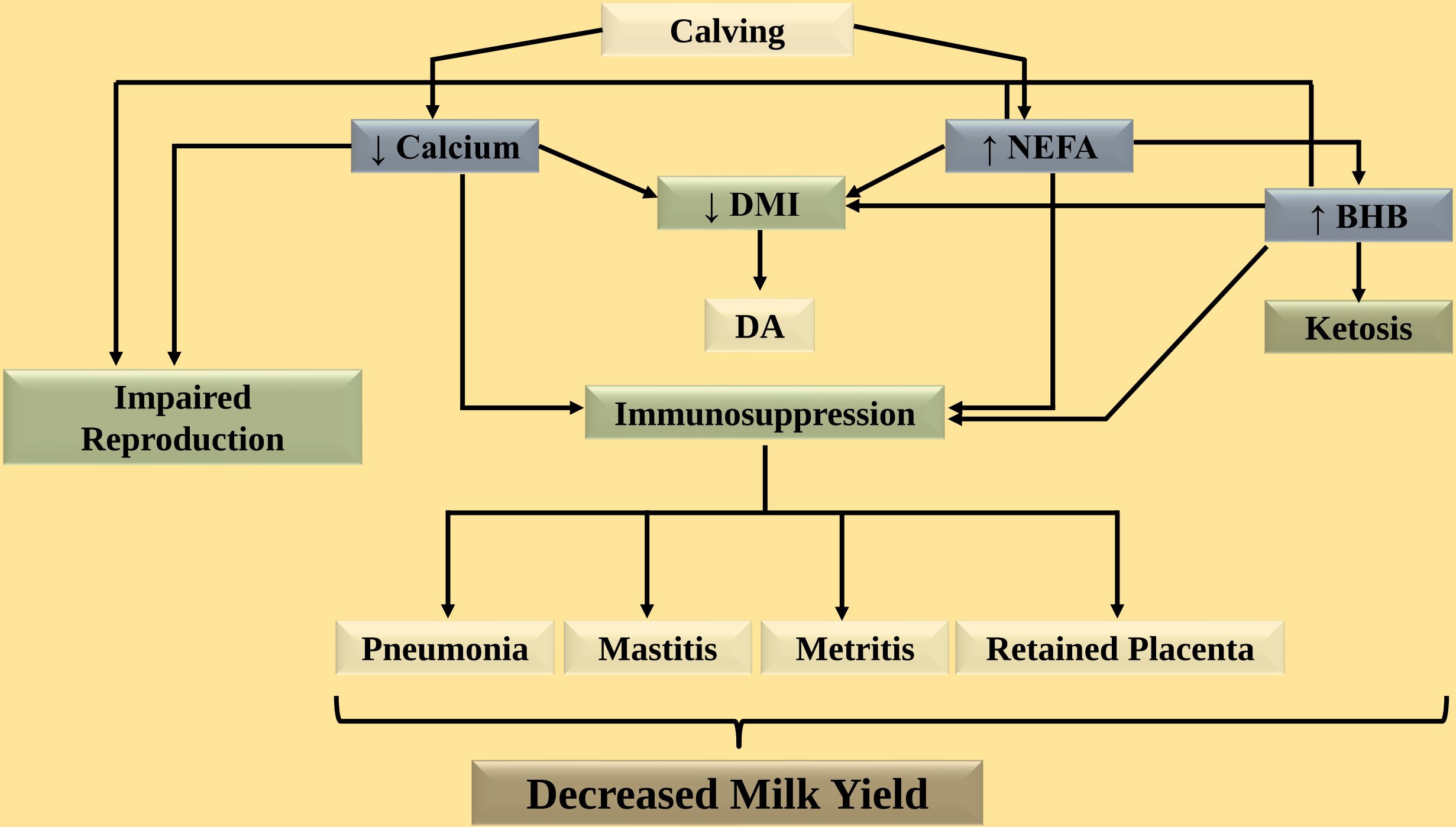
Despite emphasis, time and money spent on preventing high NEFA, hyperketonemia and subclinical hypocalcemia herd health is not improving

Maybe we're "medicating" the wrong things??

National Animal Health Monitoring Systems

Traditional Belief

Increased NEFA, Hyperketonemia, and Hypocalcemia…..**CAUSE** production and health problems


Calving
↓ Calcium
↑ NEFA
↓ DMI
↑ BHB
DA
Ketosis
Impaired Reproduction
Immunosuppression
Pneumonia
Mastitis
Metritis
Retained Placenta
Decreased Milk Yield

Observations that should have been red flags:

1) Associations and correlations
   - No cause and effect…..and the correlations are weak anyway…not probative
2) Infusing ketones or NEFA does not cause negative outcomes
   - In nature, animals ebb and flow out of ketosis ALL the time
3) Ketotic cows are not hypoinsulinemic
   - Often times they are hyperinsulinemic
4) Ketones do not decrease feed intake
   - Otherwise a starving animal would not have an appetite
5) Preventing adipose mobilization reduces milk yield
   - Transition period hyperinsulinemia is associated with immediate and long-term low milk yield
   - Insulin or TZD administration
6) Some females do not consume any food after parturition
   - Ocean mammals
7) Regional differences in the rate of clinical ketosis
   - Clinical ketosis rates in Arizona are less than 1%. Some dairy producers in AZ have never treated a ketotic cow…….”Arizona Ketosis Paradox”

Partitioning of Nutrients During Pregnancy and Lactation: A Review of Mechanisms Involving Homeostasis and Homeorhesis

DALE E. BAUMAN and W. BRUCE CURRIE
Department of Animal Science
Cornell University
Ithaca NY 14853

Introduced the Homeorhesis concept

ABSTRACT

Control of metabolism during preg-
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tions and physiological processes in which food is transformed into body tissues and activities

Lave
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sustenance involves a series of chemical reac-

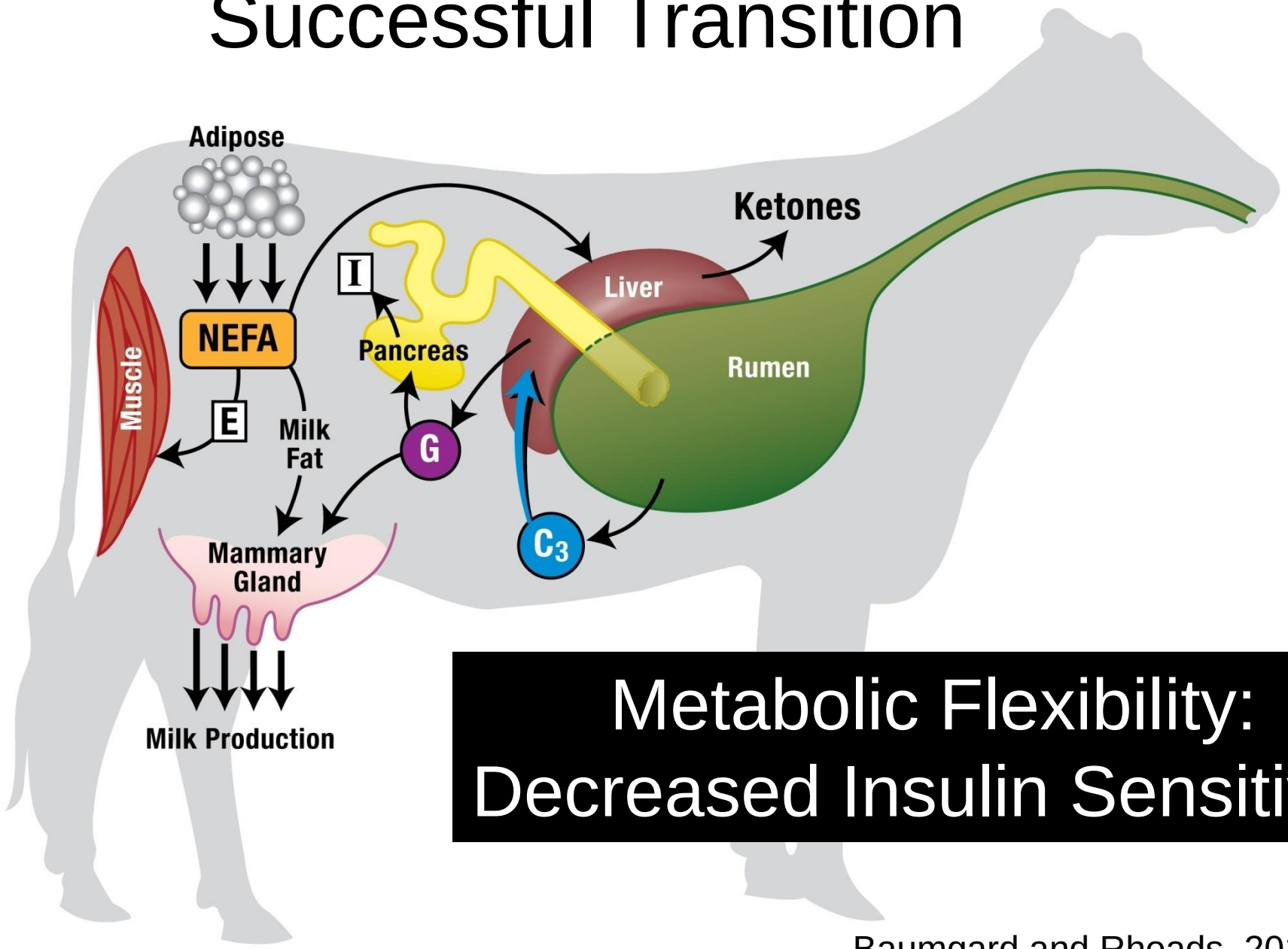
um or constant conditions in the internal environment (Figure 2). There are many well established examples of homeostasis, such as regulation to maintain constancy of body

Received January 28, 1980.

Summary of these Reviews

Mobilization of adipose tissue and partial conversion of NEFA into Ketones is ESSENTIAL for maximum milk yield in early lactation

Successful Transition



Metabolic Flexibility:
Decreased Insulin Sensitivity

Baumgard and Rhoads, 2013

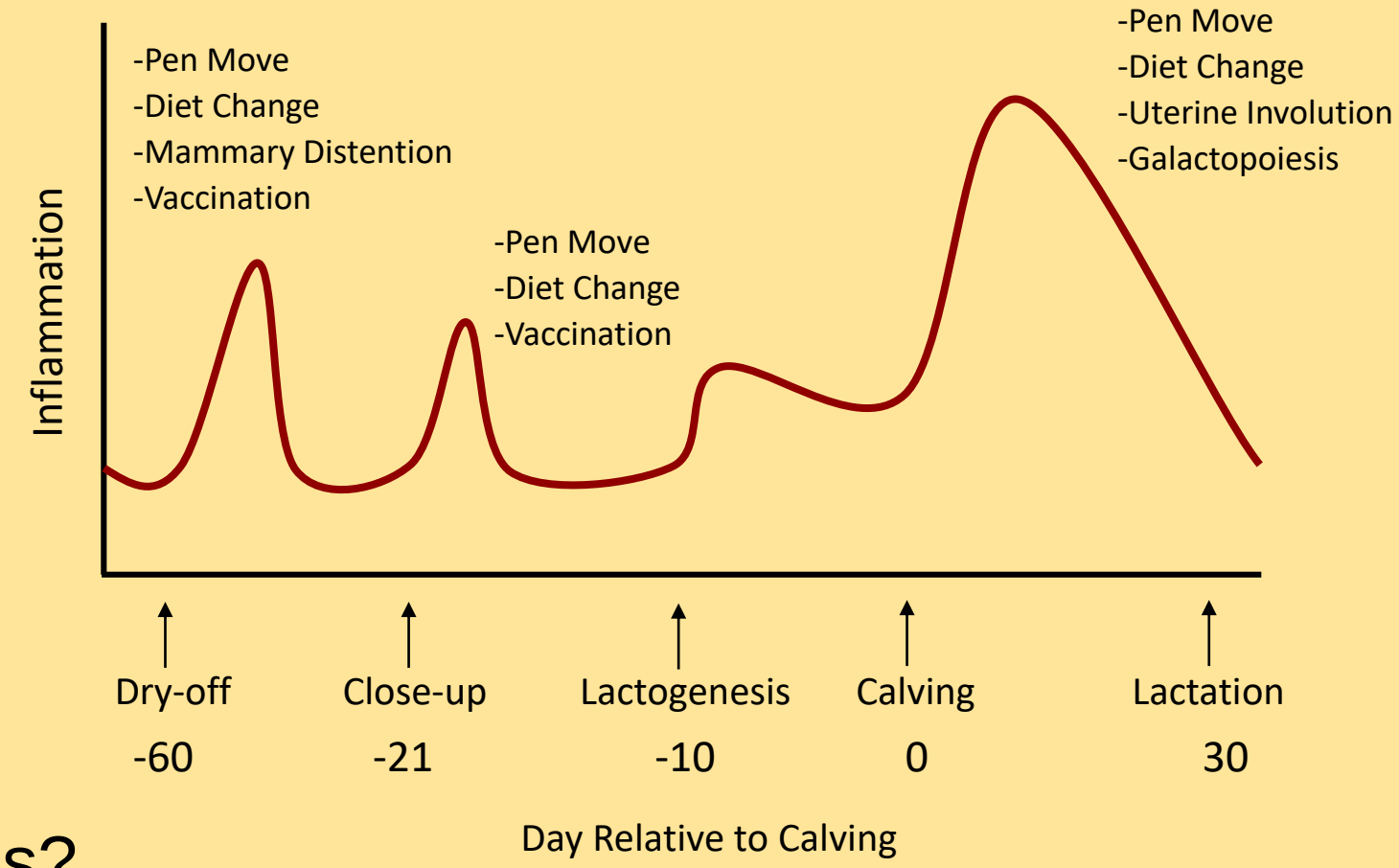
Inflammation in Transition Cows

- Observed in all cows

(Bertoni et al., 2008; Trevisi and Minuti, 2018)

- What is the source?
  - Mammary Gland
  - Uterus
  - Gastrointestinal tract

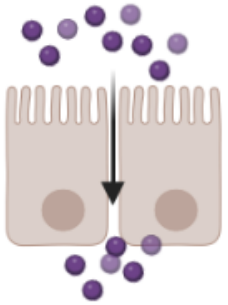
- What are the consequences?



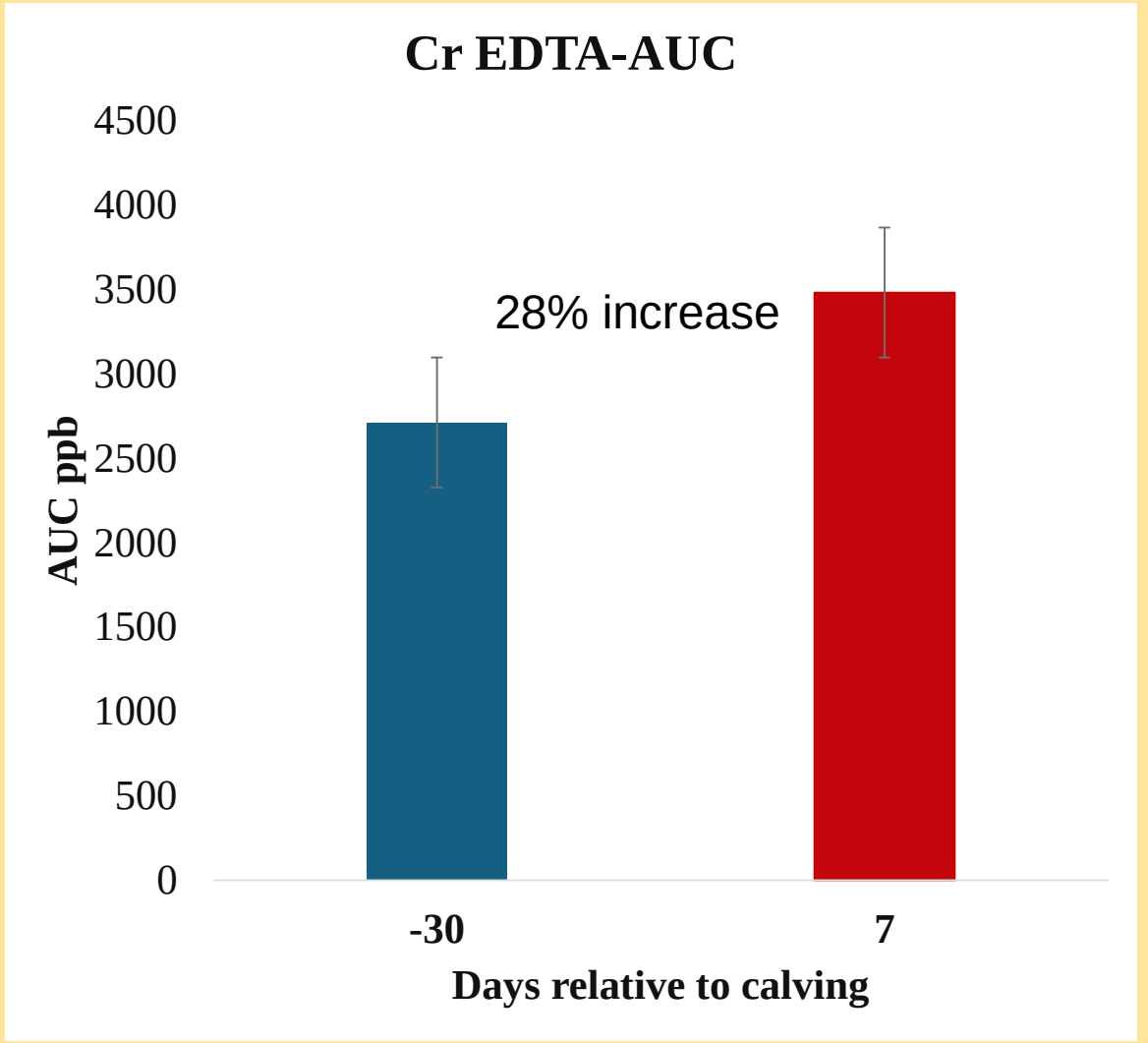
Dr. B. Goetz

GIT Permeability Increases Post Calving

Professor Michael Steele



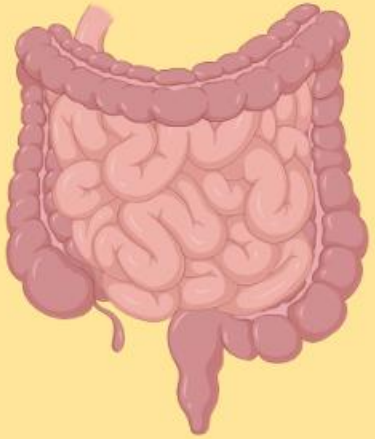
Gut permeability measurement based on Cr-EDTA recovery rate in plasma



Jantzi et al. (Unpublished data)

Inflammation sources:

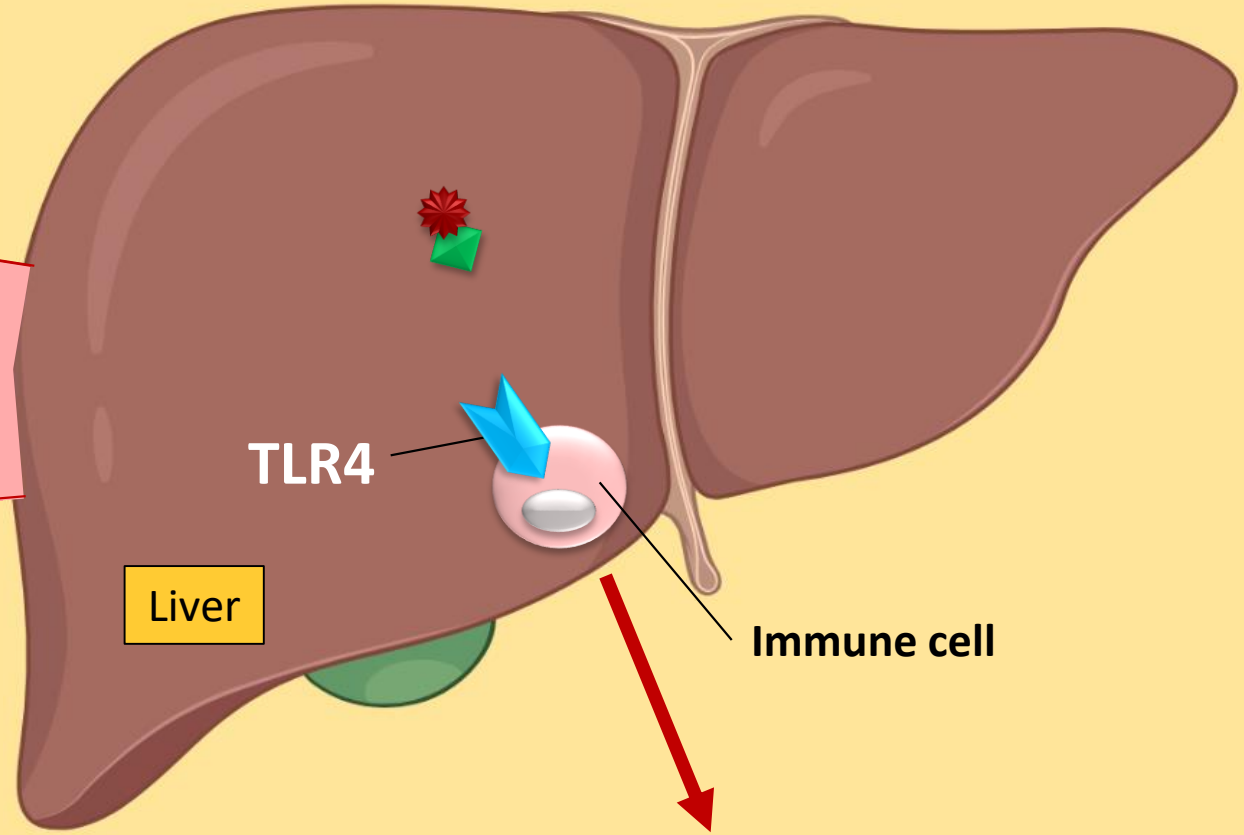
LPS



Complex LPS/LBP

LBP

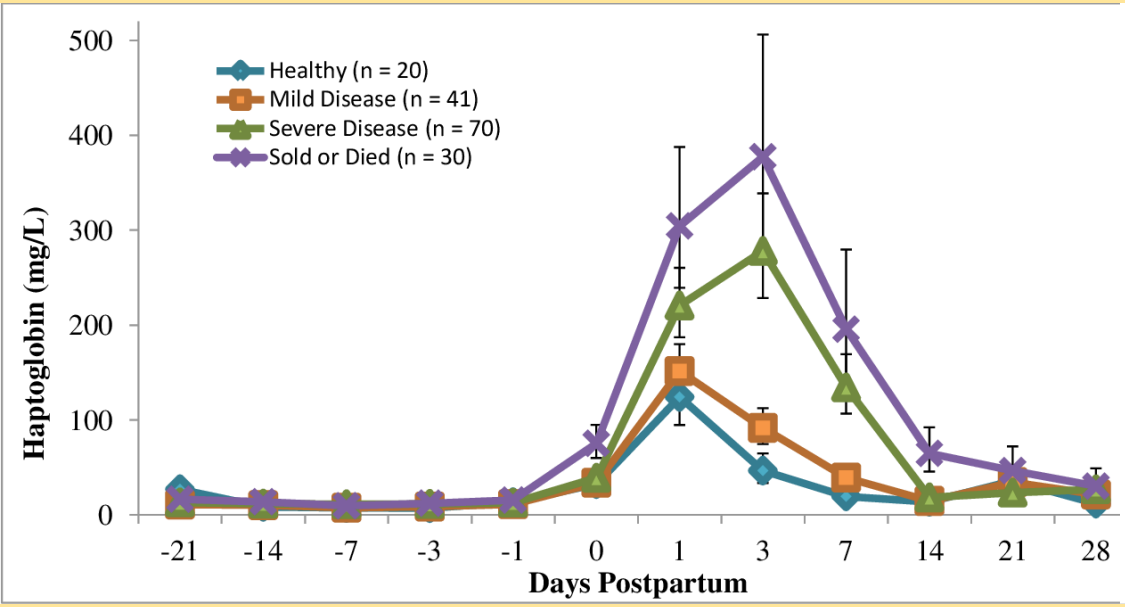
Circulation



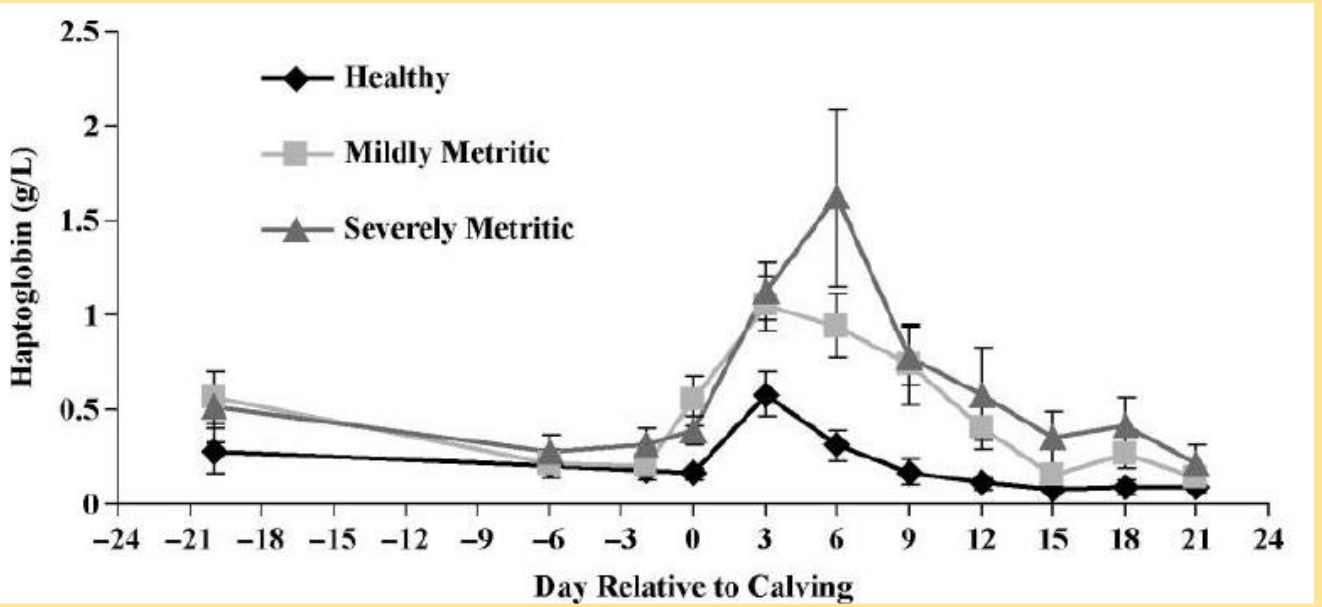
↑ Inflammatory response
↑ Cytokines
↑ APPs:
- SAA
- Hp
- LBP

Rodriguez Jimenez & Kvidera

Immune Activation (Haptoglobin) Precedes Clinical Disease

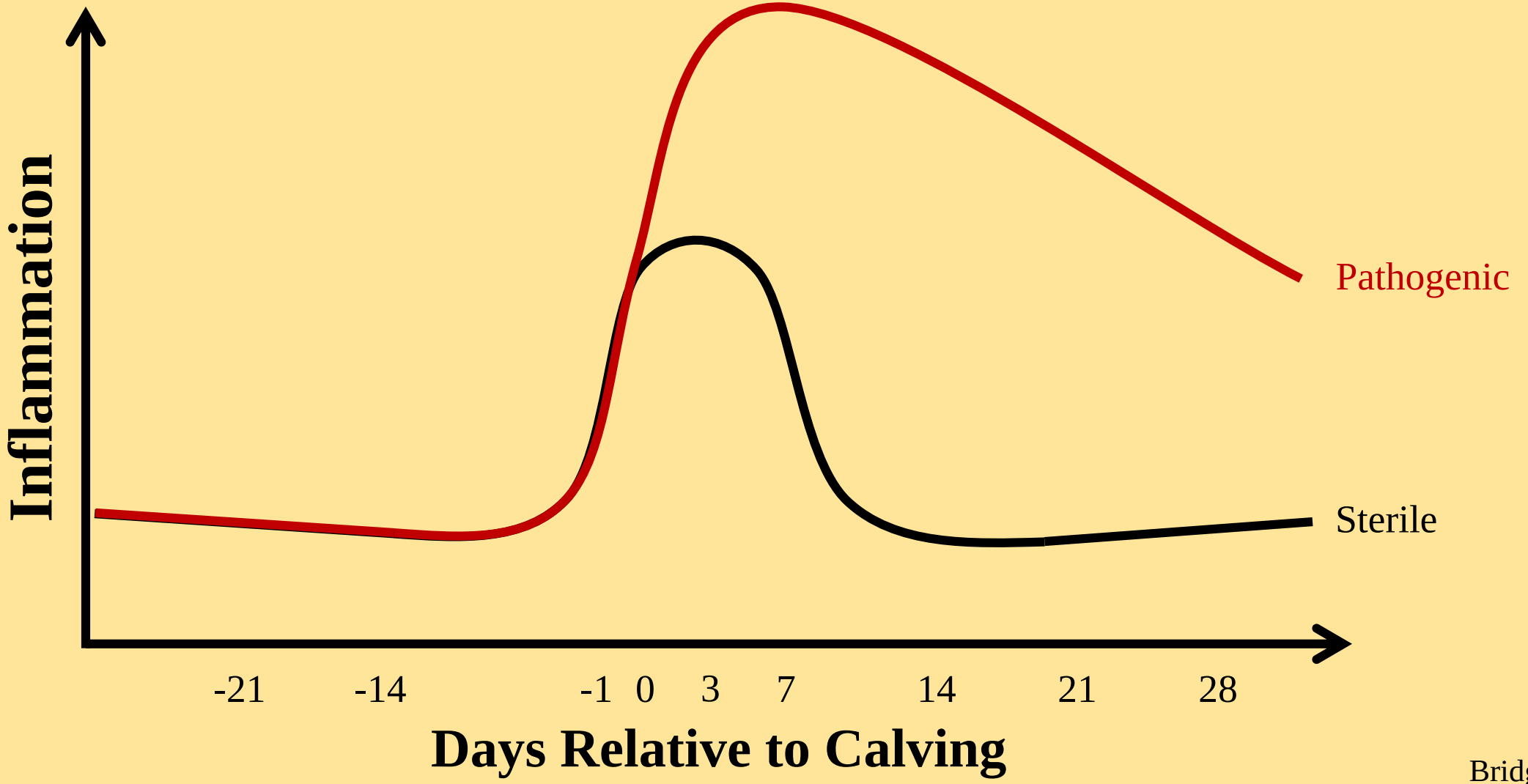


Sebedra 2012



Huzzey et al., 2012

Transition Cow Inflammation



Bridget Buol

Inflammation’s Role in Suboptimal DMI

Immune activation induced hypophagia is KEY

Immune Activation and Feed Intake

- Inflammatory mediators are potent anorexic compounds Kushibiki et al., 2003
- Reduced feed intake is a highly conserved species response to infection (Aubert et al., 1997; Wang et al., 2016)
- Infection decreases feed consumption, even in insects (Adamo, 2005)
- Cows with increased inflammation have decreased DMI (Trevisi et al., 2002)
  - ….and also increased NEFA and BHB (Trevisi et al., 2010, 2012; Zhou et al., 2016)
  - **Inflammation is the simplest and most logical explanation for why some cows don't eat well before and following calving**

Inflammation and Fatty Liver

World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v18.i21.2609

World J Gastroenterol 2012 June 7; 18(21): 2609-2618
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

Leaky gut and the liver: A role for bacterial translocation in nonalcoholic steatohepatitis

Yaron Ilan

- Humans with intestinal barrier dysfunction have fatty liver….but do not have increased [NEFA]

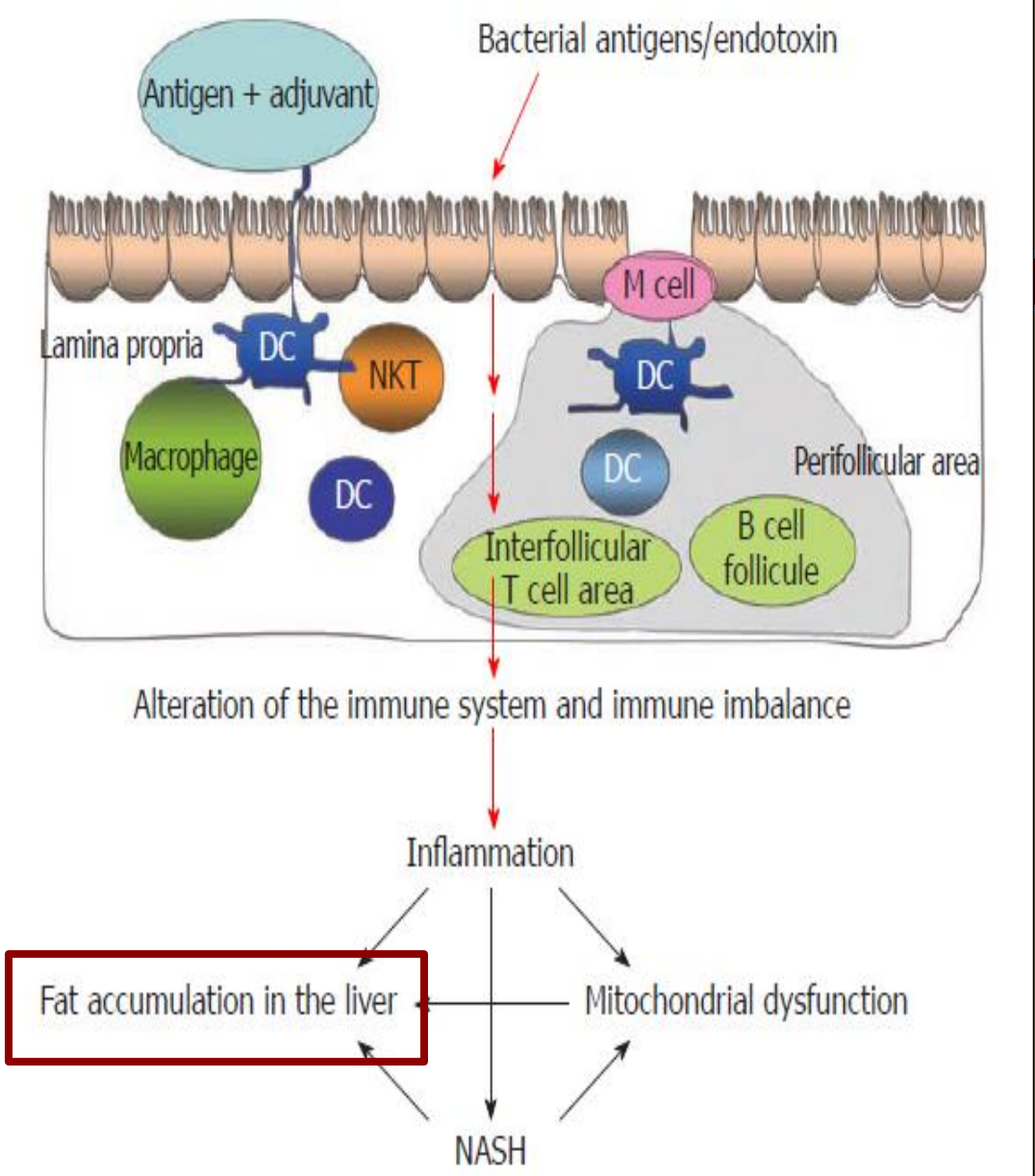
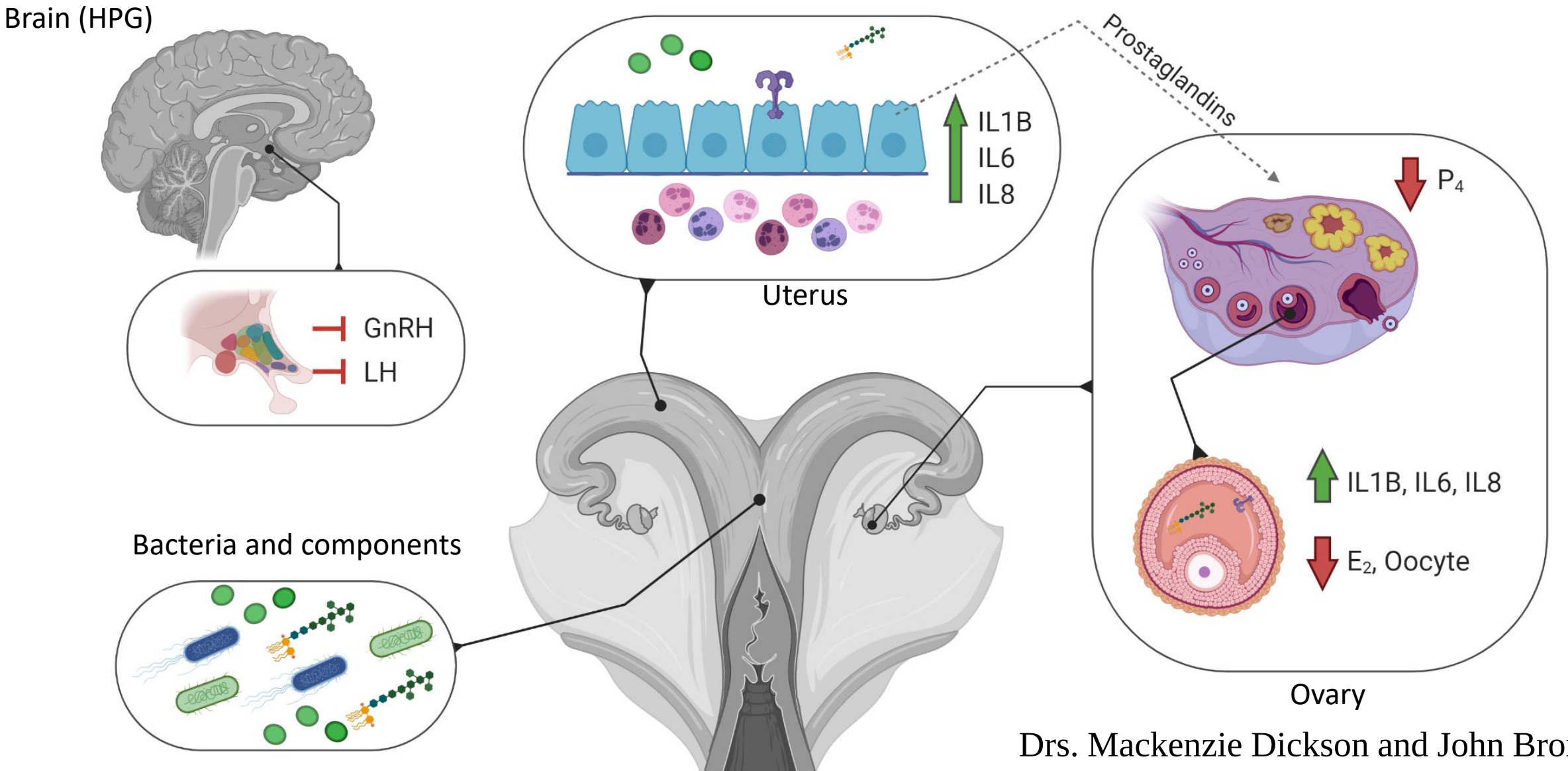


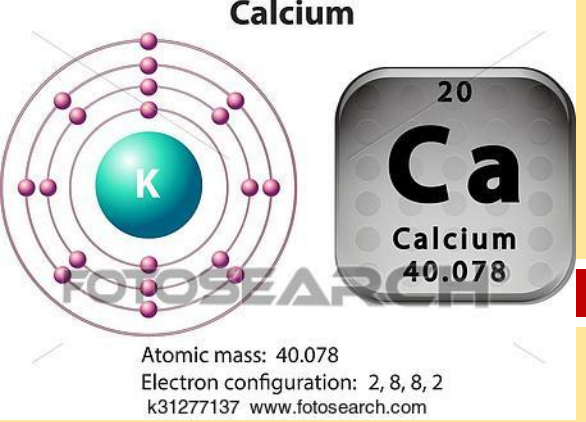
Figure 1 Bacterial translocation is associated with the development of nonalcoholic steatohepatitis. NASH: Nonalcoholic steatohepatitis.

Inflammation and Reproduction?

LPS Negative Effects Repro From Multiple Angles



Drs. Mackenzie Dickson and John Bromfield



https://www.fotosearch.com/CSP142/k31277137/

Hypocalcemia Dogma

https://www.farmersjournal.ie/milk-fever-the-problem-of-low-blood-calcium-in-cattle-319488

- Milk uptake of Ca is so quick and extensive that it exceeds the homeostatic capacity to replenish it.

- Academic & Industry Goal: <u>Minimize postcalving hypocalcemia</u>

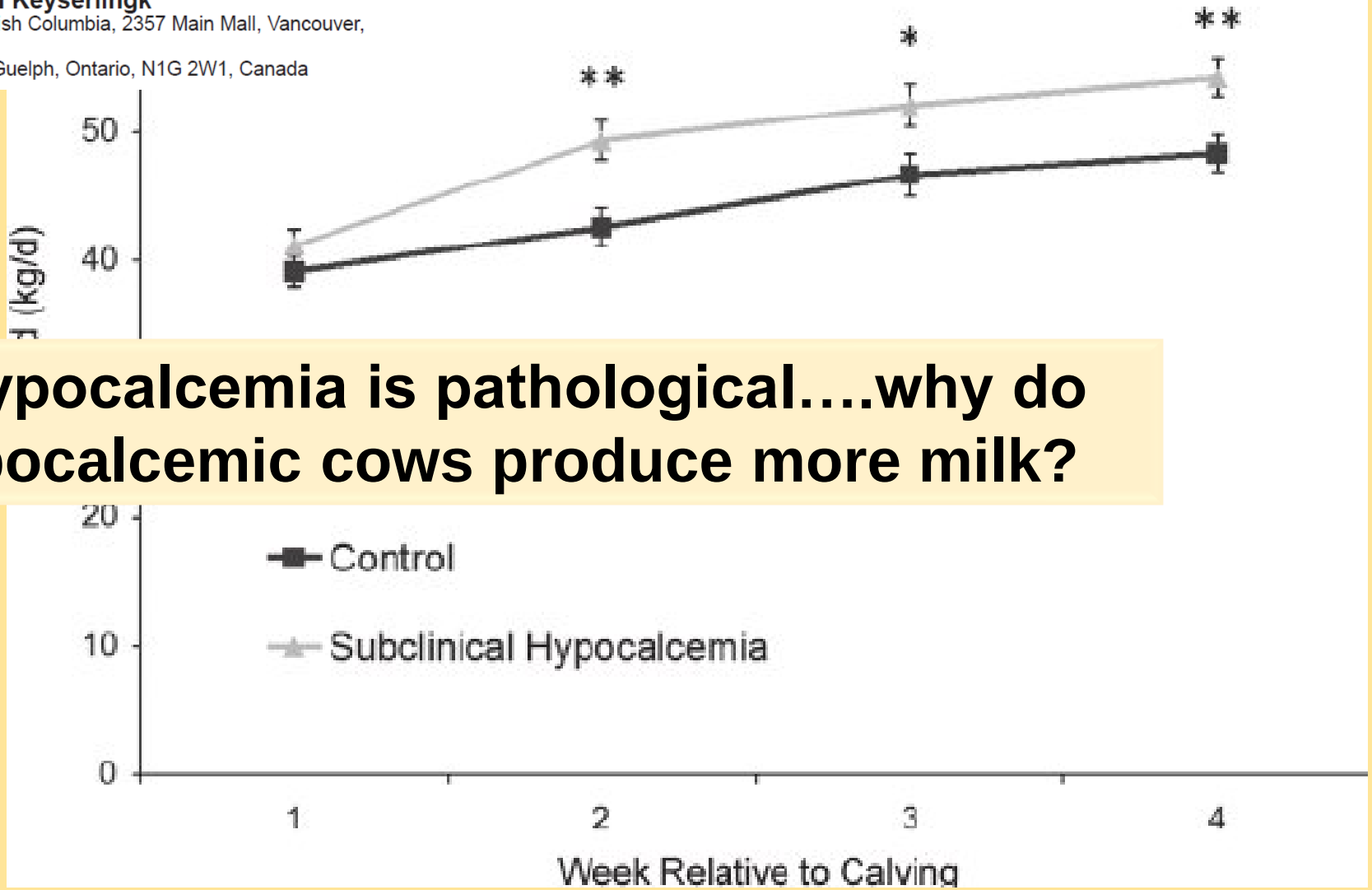
Hypocalcemia

- Clinical hypocalcemia (milk fever) needs a pre-calving dietary strategy
  - The marked reduction in clinical milk fever is arguably the biggest advancement in dairy nutrition in the last 40 years
- Clinical hypocalcemia is pathological
  - It warrants immediate intervention
- Is subclinical hypocalcemia pathological?
  - Is it detrimental to health, productivity and profitability?

J. Dairy Sci. 95:1240–1248
http://dx.doi.org/10.3168/jds.2011-4586

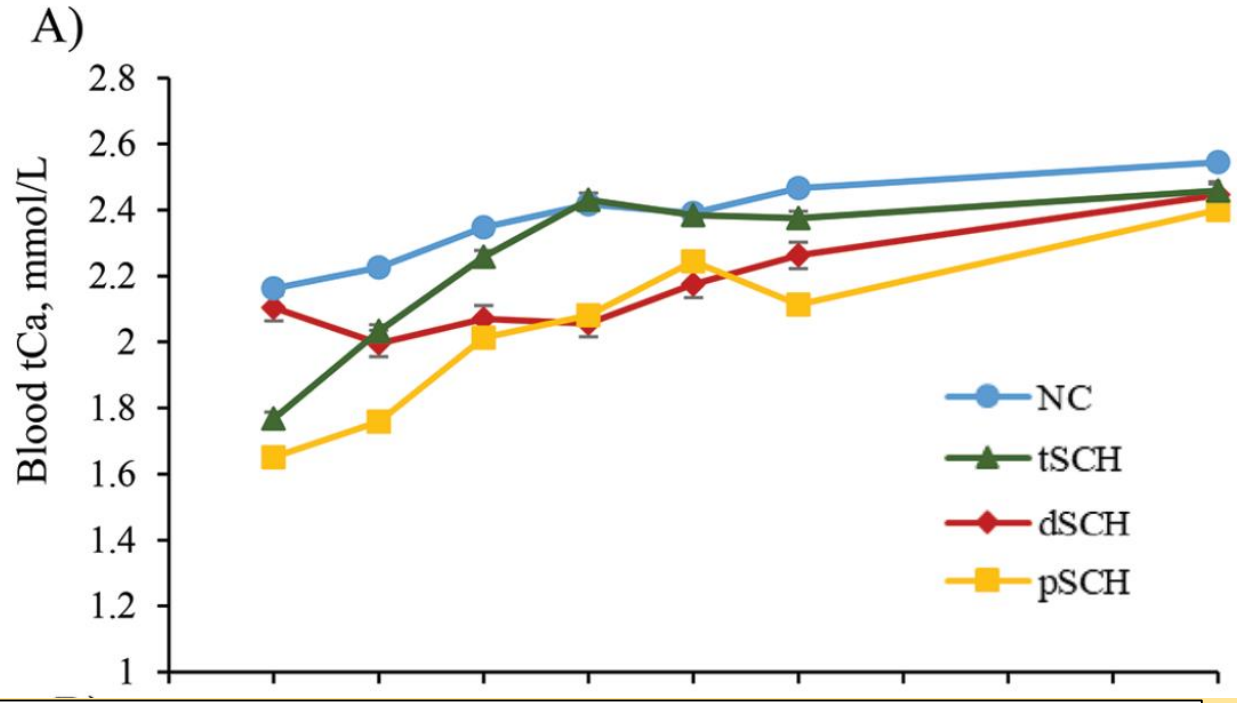
Associations of subclinical hypocalcemia at calving with milk yield, and feeding, drinking, and standing behaviors around parturition in Holstein cows

P. E. Jawor,*[1] J. M. Huzzey,* S. J. LeBlanc,† and M. A. G. von Keyserlingk*[2]
*Animal Welfare Program, Faculty of Land and Food Systems, University of British Columbia, 2357 Main Mall, Vancouver, British Columbia, V6T 1Z4, Canada
†Department of Population Medicine, Ontario Veterinary College, University of Guelph, Ontario, N1G 2W1, Canada



If subclinical hypocalcemia is pathological….why do subclinical hypocalcemic cows produce more milk?

Subclinical hypocalcemia is often associated with <u>increased</u> productivity

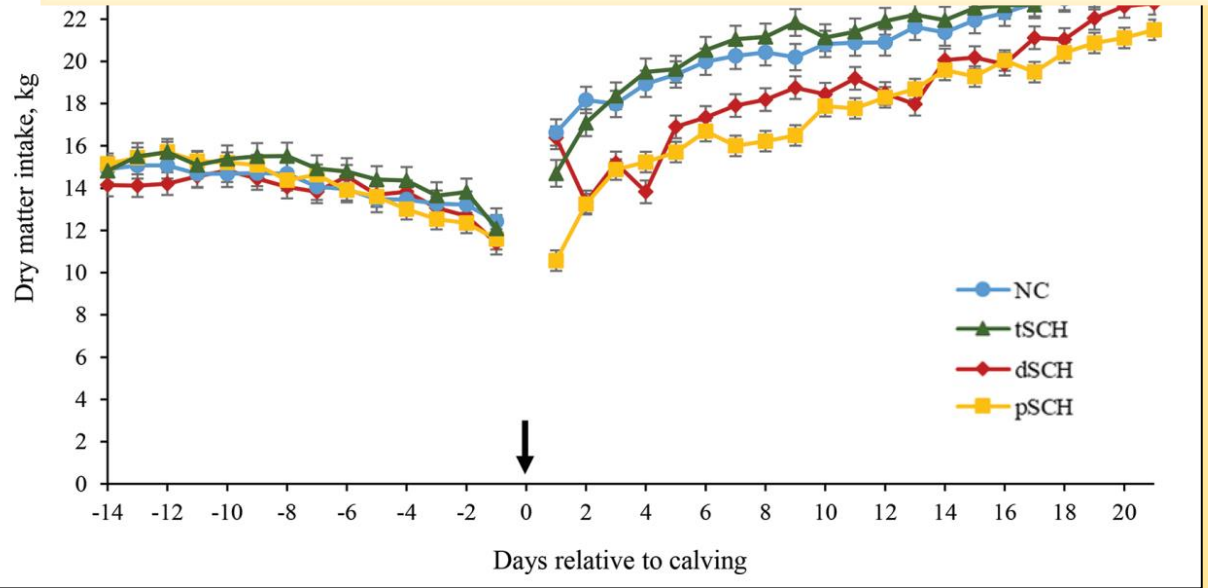


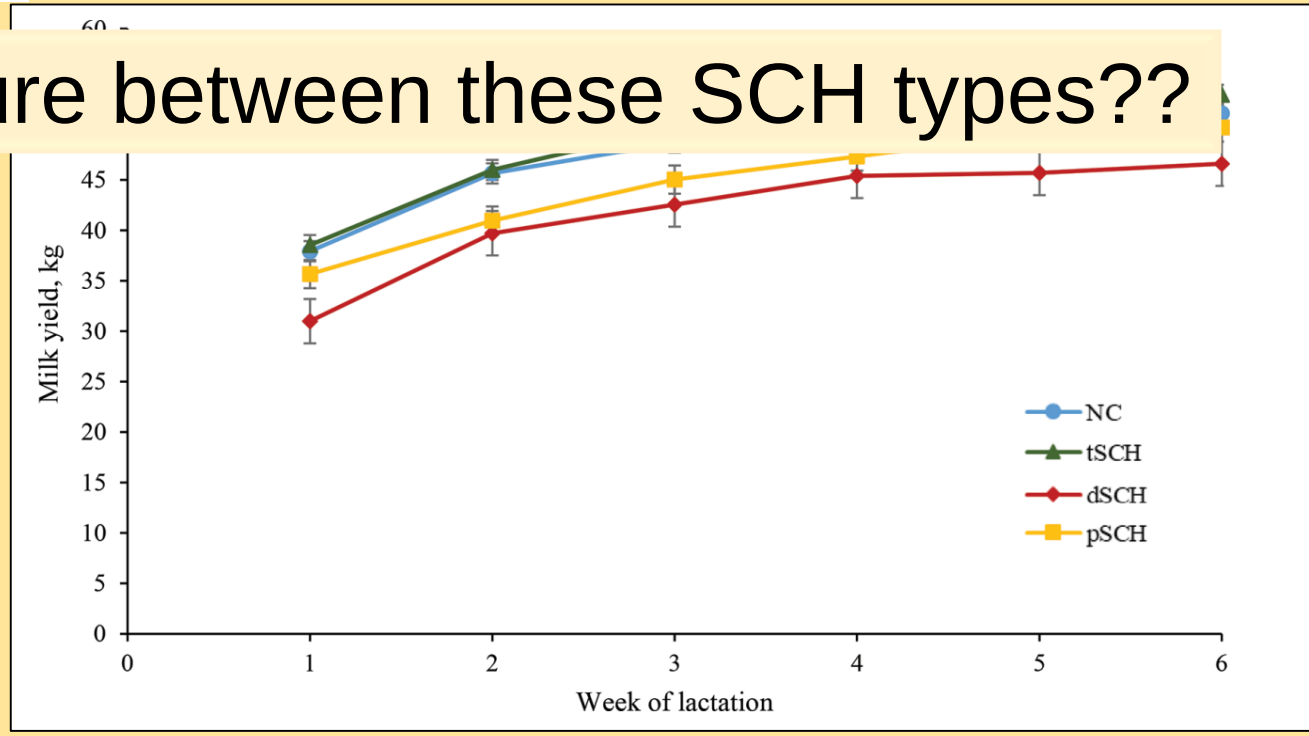
J. Dairy Sci. 104:4692–4702
https://doi.org/10.3168/jds.2020-19344

Association of subclinical hypocalcemia dynamics with dry matter intake, milk yield, and blood minerals during the periparturient period

C. R. Seely,[1] B. M. Leno,[2] A. L. Kerwin,[2] T. R. Overton,[2] and J. A. A. McArt[1]*
[1]Department of Population Medicine and Diagnostic Sciences, College of Veterinary Medicine, Cornell University, Ithaca, NY 14853
[2]Department of Animal Science, College of Agriculture and Life Sciences, Cornell University, Ithaca, NY 14853

What is the distinguishing feature between these SCH types??





Immunoactivation was identified as a cause of milk fever more than 130 years ago

MILK FEVER (PARTURIENT PARESIS) IN DAIRY COWS—A REVIEW

J. W. HIBBS

Ohio Agricultural Experiment Station, Wooster

Milk fever (parturient paresis) is an afebrile disease which typically is associated with parturition and beginning lactation. It is characterized by a sudden paralysis, gradual loss of consciousness and, if untreated, usually terminates in death. Few diseases of livestock have caused as much theoretical controversy and interest as has milk fever. Gradually, through the years, much has been learned about the nature of milk fever, and effective means of treatment have been devised, resulting in a reduction in mortality of from 60 to 70 per cent to less than 1 per cent. The basic physiological cause of milk fever has yet to be proven. The "parathyroid deficiency (hypocalcemia) theory" of Dryerre and Greig (54) seems to come the nearest of the many theories that have been advanced to accounting for the immediate cause, but many fundamental questions

THE VETERINARY JOURNAL

AND

Annals of Comparative Pathology.

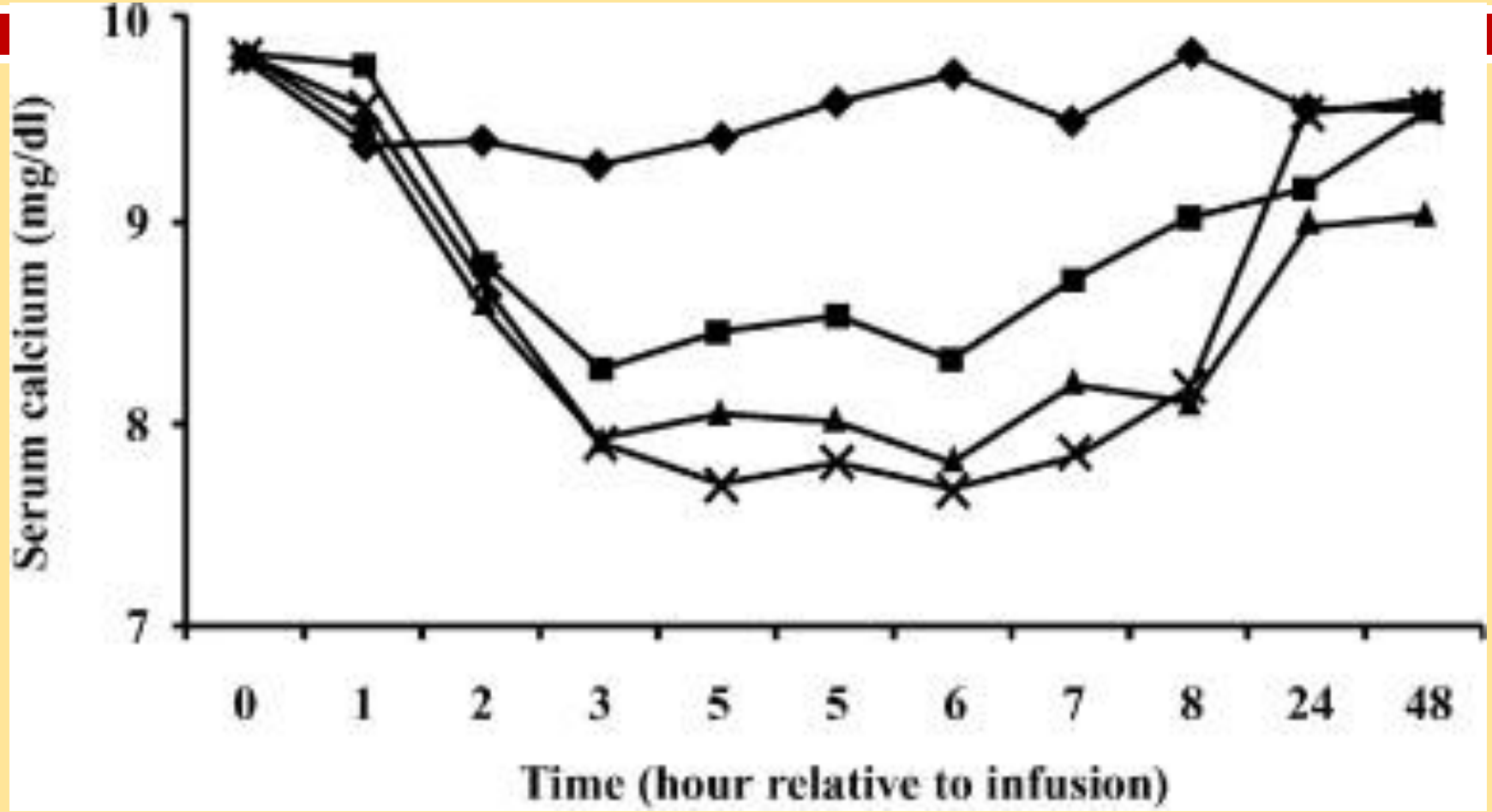
JANUARY, 1889.

PARTURIENT APOPLEXY IN COWS—A FORM OF SEPTICÆMIA.

BY A. HARRISON THOMAS, M.B., C.M., B.SC., ETC., WHITTINGHAM, PRESTON.

LPS administration, mastitis and sepsis all cause severe and acute hypocalcemia

Immune Activation (induced mastitis) Decreases Ca in Dairy Cows



Waldron et al., 2003

Technical note: A procedure to estimate glucose requirements of an activated immune system in steers

S. K. Kvidera, E. A. Horst, M. Abuajamieh, E. J. Mayorga, M. V. Sanz Fernandez, and L. H. Baumgard[1]

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ABSTRACT: Infection and inflammation impede efficient animal productivity. The activated immune system ostensibly requires large amounts of energy and nutrients otherwise destined for synthesis of agriculturally relevant products. Accurately determining the immune system's in vivo energy needs is difficult, but a better understanding may facilitate developing nutritional strategies to maximize productivity. The study objective was to estimate immune system glucose requirements following an i.v. lipopolysaccharide (LPS) challenge. Holstein steers (148 ± 9 kg; $n = 15$) were jugular catheterized bilaterally and assigned to 1 of 3 i.v. treatments: control (CON; 3 mL saline; $n = 5$), LPS-administered controls (LPS-C; *E. coli* 055:B5; 1.5 mg/kg BW; $n = 5$), and LPS + euglycemic clamp (LPS-Eu; 1.5 mg/kg BW; 50% dextrose infusion to maintain euglycemia; $n = 5$). In LPS-Eu steers, postbolus blood samples were analyzed for glucose every 10 min. Dextrose infusion rates were adjusted to maintain euglycemia for 720 min. All steers were fasted during the challenge. Samples for later analysis were obtained at 180, 360, 540, and 720 min relative to LPS administration. Rectal temperature was increased ~0.5°C in both LPS treatments relative to CON steers ($P = 0.01$). Steers in both LPS treatments were hyperglycemic for followed the same pattern; however, trophils were decreased in LPS-Eu co resulting in a decreased neutrophil-to (54%; $P = 0.03$). The large amount of maintain euglycemia indicates extens of nutrients away from growth and t glucose as a fuel for the immune syst

Key words: glucose homeostasis, immune challenge, lipopolysacchari

J. Anim. Sci. 201
doi:10.252

J. Dairy Sci. 100:2360–2374
https://doi.org/10.3168/jds.2016-12001

Glucose requirements of an activated immune system in lactating Holstein cows

S. K. Kvidera, E. A. Horst, M. Abuajamieh, E. J. Mayorga, M. V. Sanz Fernandez, and L. H. Baumgard[1]
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J. Dairy Sci. 101:5515–5530
https://doi.org/10.3168/jds.2017-13899

Effect of chromium on bioenergetics and leukocyte dynamics following immunoactivation in lactating Holstein cows

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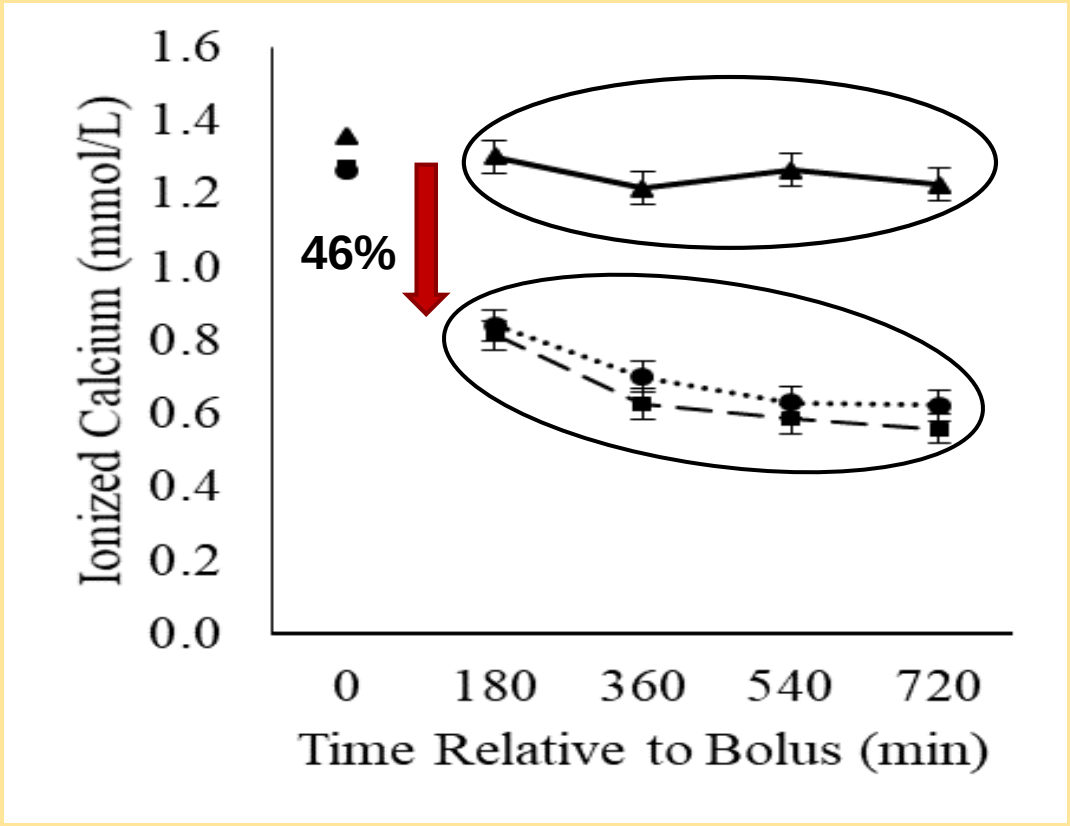
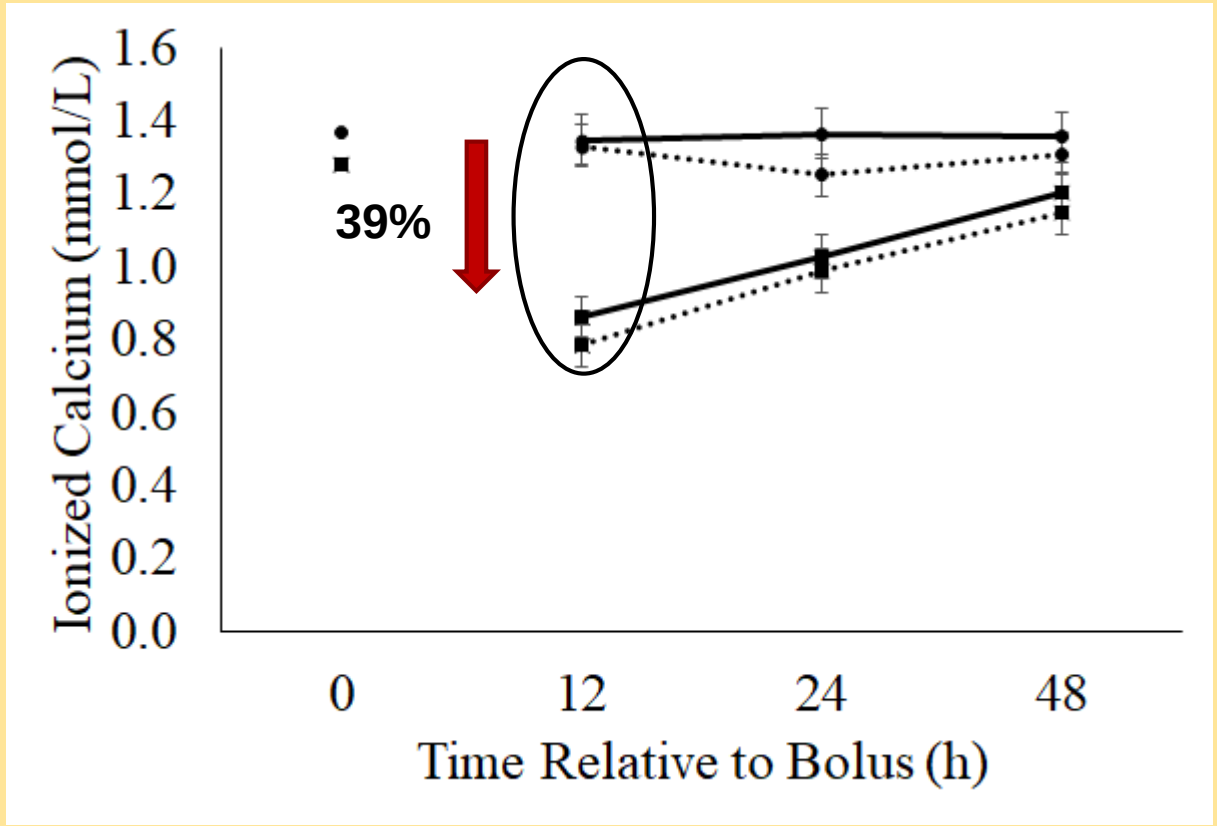
Ca and Immune System

- Immune Activation decreases circulating Ca (Kvidera et al., 2017; Horst et al., 2017)



Kvidera et al., 2017



Horst et al., 2017

J. Dairy Sci. TBC
https://doi.org/10.3168/jds.2024-25300

Acute phase responses in clinically healthy multiparous Holsteins with and without calcium dysregulation during the early postpartum period

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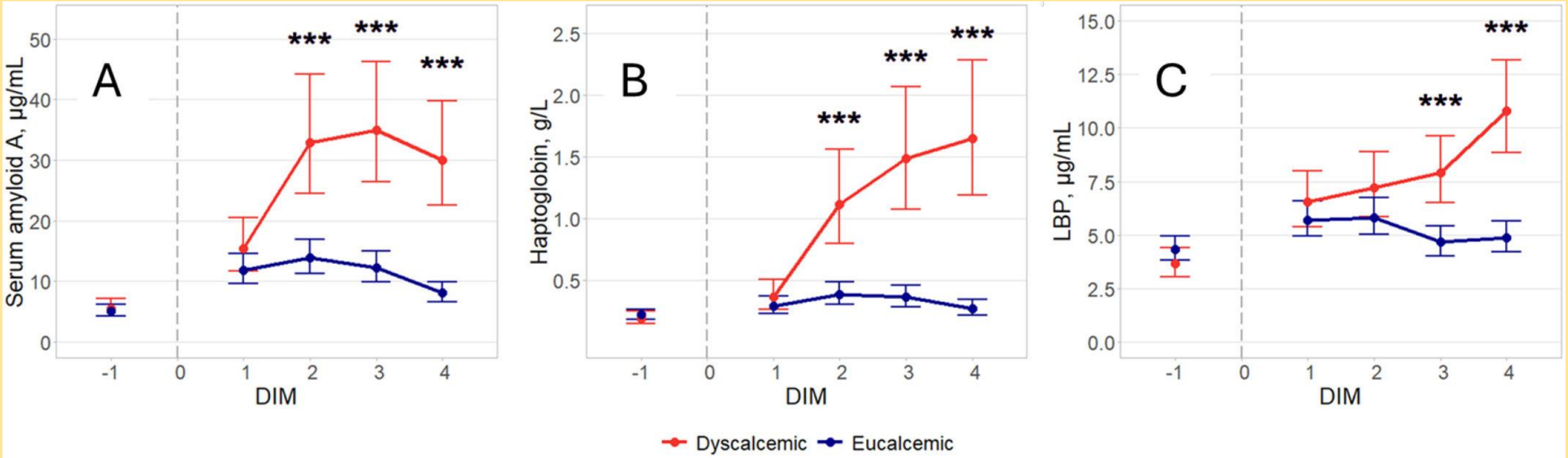


Immune Activation and Hypocalcemia

- Immune activation causes a marked and unexplainable decrease in ionized Ca
  - Response is conserved across species:
    - (Naylor and Kronfeld, 1986; Elsasser et al., 1996; Carlstedt et al., 2000; Toribio et al., 2005)
  - Paradoxical response as Ca regulates leukocyte activation and function
    - (Hendy and Canaff, 2016)
- Ca administration increases incidences of organ failure and mortality during sepsis
  - Pigs (Calstedt et al., 2000)
  - Humans (Malcolm et al., 1989)
- Hypocalcemia is a protective strategy?
  - Ca interferes with lipoprotein sequestration of endotoxins

LPS detoxification

LPS aggregates (Normocalcemia)

LPS monomers (Hypocalcemia)

Ca^{2+}

LBP

CD14

Lipoprotein

TLR4

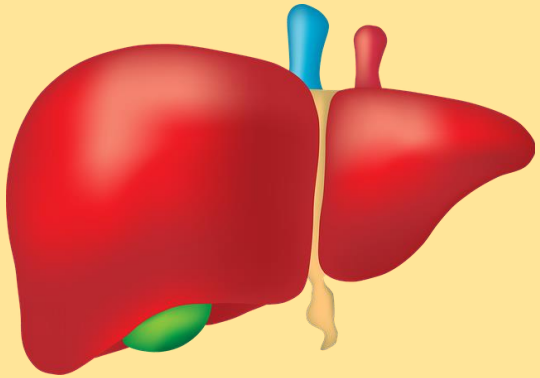
Leukocyte

Cytokines

Cytokines

Cytokines

Lipoprotein



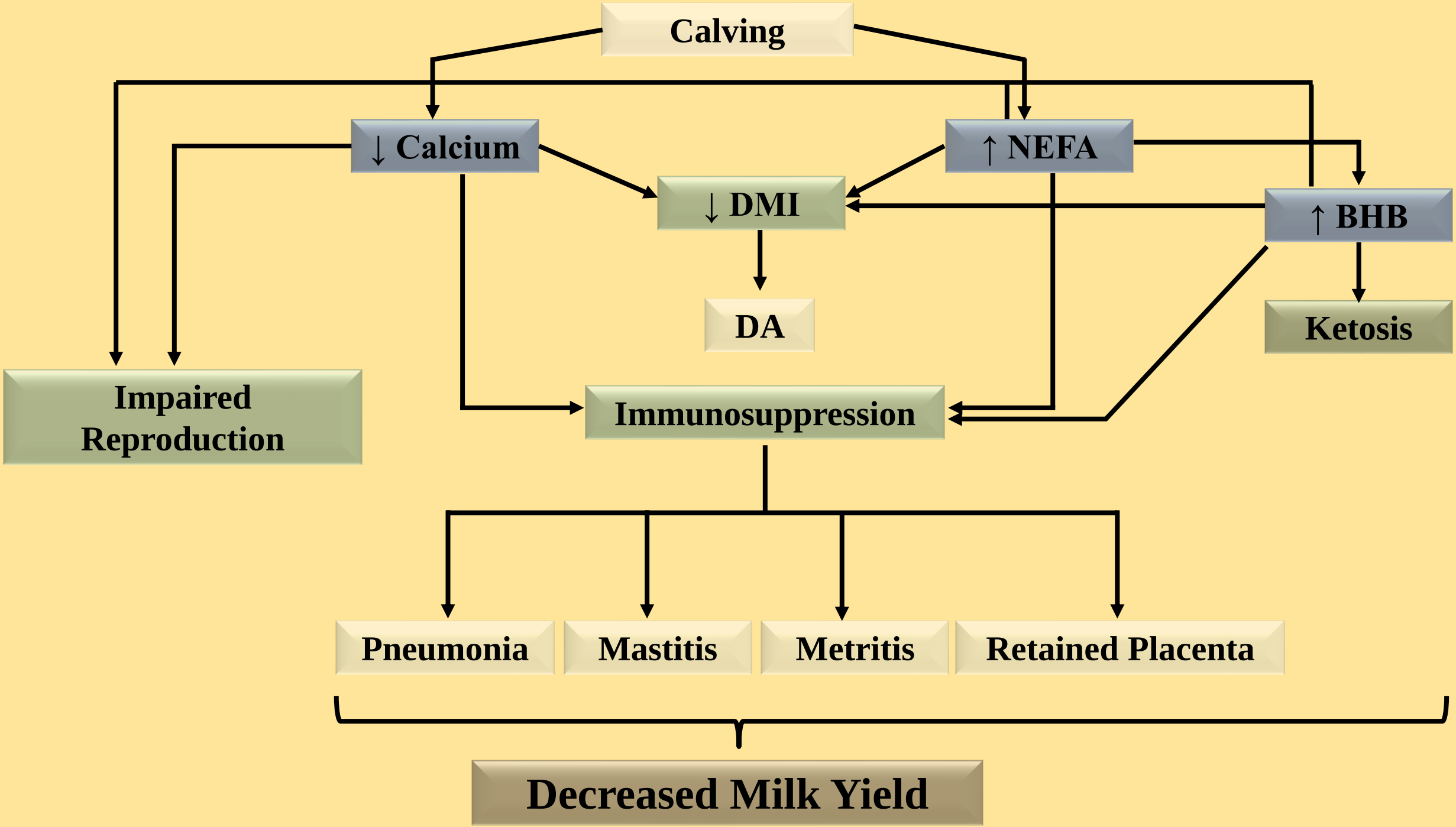
Immune Activation and Hypocalcemia

- Fact: All transition cows experience some degree of immune activation. Only the magnitude of inflammation differs
- Fact: Immune activation acutely causes hypocalcemia
- **It's reasonable to hypothesize then that immune activation contributes to some types of subclinical hypocalcemia**
  - Is this pathological…..or homeorhesis??

Traditional Belief

Increased NEFA, Hyperketonemia, and Hypocalcemia…..**CAUSE** production and health problems

This is not just an ivory tower debate, it has pragmatic and economic consequences


Calving
↓ Calcium
↑ NEFA
↓ DMI
↑ BHB
DA
Ketosis
Impaired Reproduction
Immunosuppression
Pneumonia
Mastitis
Metritis
Retained Placenta
Decreased Milk Yield

Paradigm Shifting Concept

Increased NEFA and Hyperketonemia are ca d

Low Feed Intake, high NEFA, Hyperketonemia and hypocalcemia are merely SYMPTOMS….a reflection of prior immune stimulation

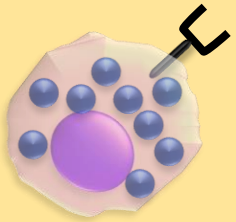
Hypocalcemia is a consequence of immune activation

Mycotoxins

Mastitis

Leaky Gut

Metritis



LPS/Inflammation

Impaired Reproduction

Fatty Liver

↓ DMI

Hypocalcemia

↑ NEFA

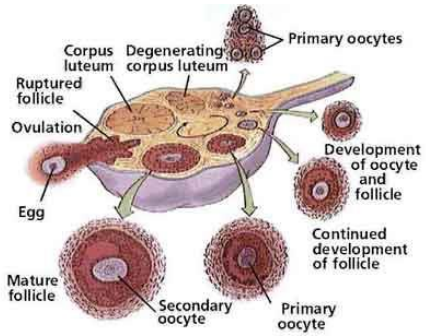
DA

↓ Milk Yield

↑ BHB

Ketosis

Unsuccessful Transition



Fatty Liver, Excessive Ketone Synthesis

Reduced DMI

Adipose

Ketone

Liver

NEFA

Pancreas

Rumen

Muscle

E

Milk Fat

G

C_3

LPS

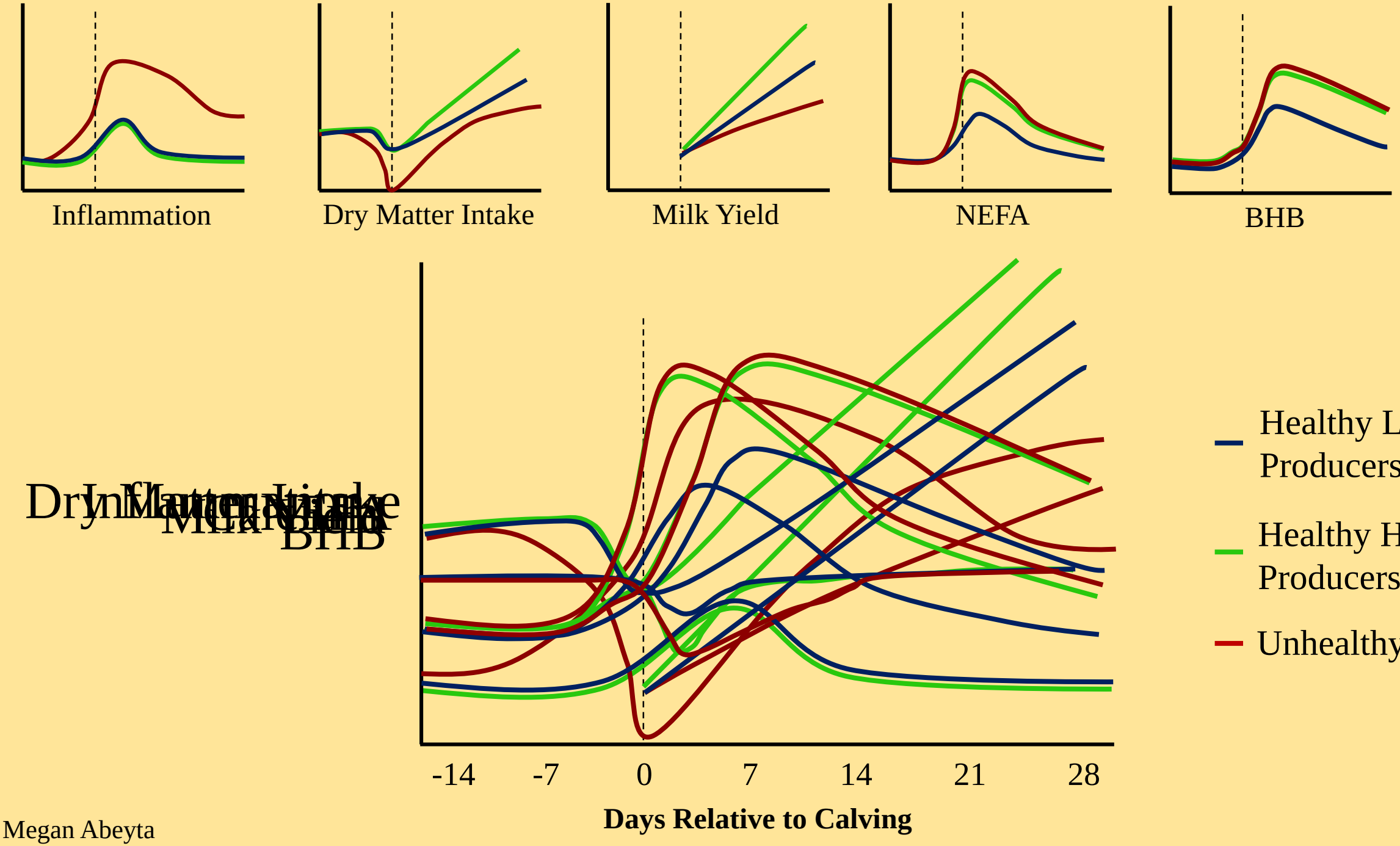
↓ Ca

Mammary Gland

Milk Production

Metabolic Flexibility:
Decreased Insulin Sensitivity
Glucose redirected to immune system

Baumgard and Rhoads, 2013



Dr. Megan Abeyta

Ketosis Scenario

- Two cows in the fresh pen
  - 10 DIM
  - Multiparous
- Both are hyperketonemic (i.e. 1.5 mmol/l)

Ketosis: When (or if) to intervene?

- Treat:
  - High ketones
  - Not coming into milk
  - Not aggressively eating
  - Looks lethargic and melancholic
  - Has a mild fever

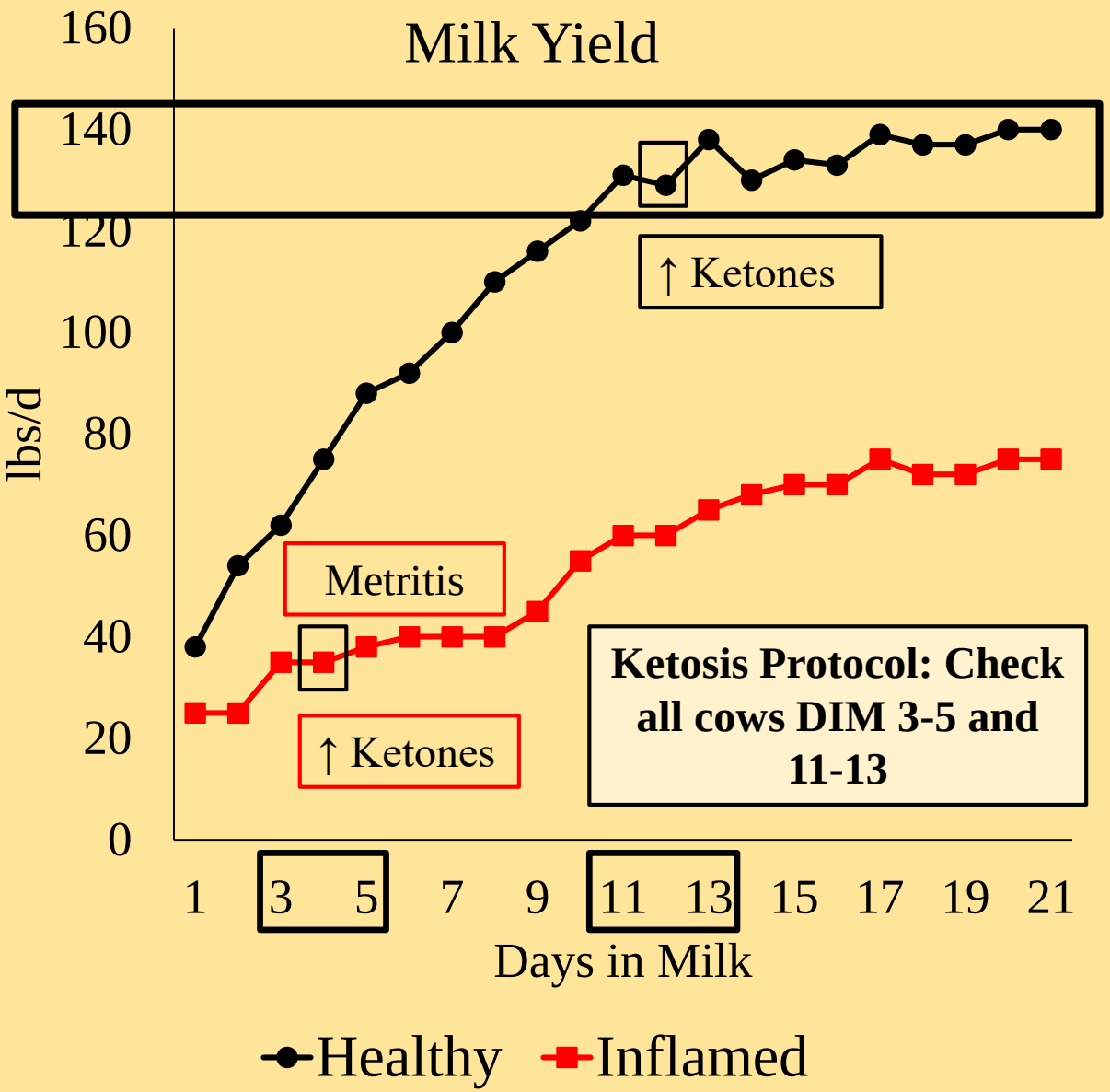
But treating with energy does nothing to address the real problem…..somewhere…..immune-activation is putting the clamp on appetite

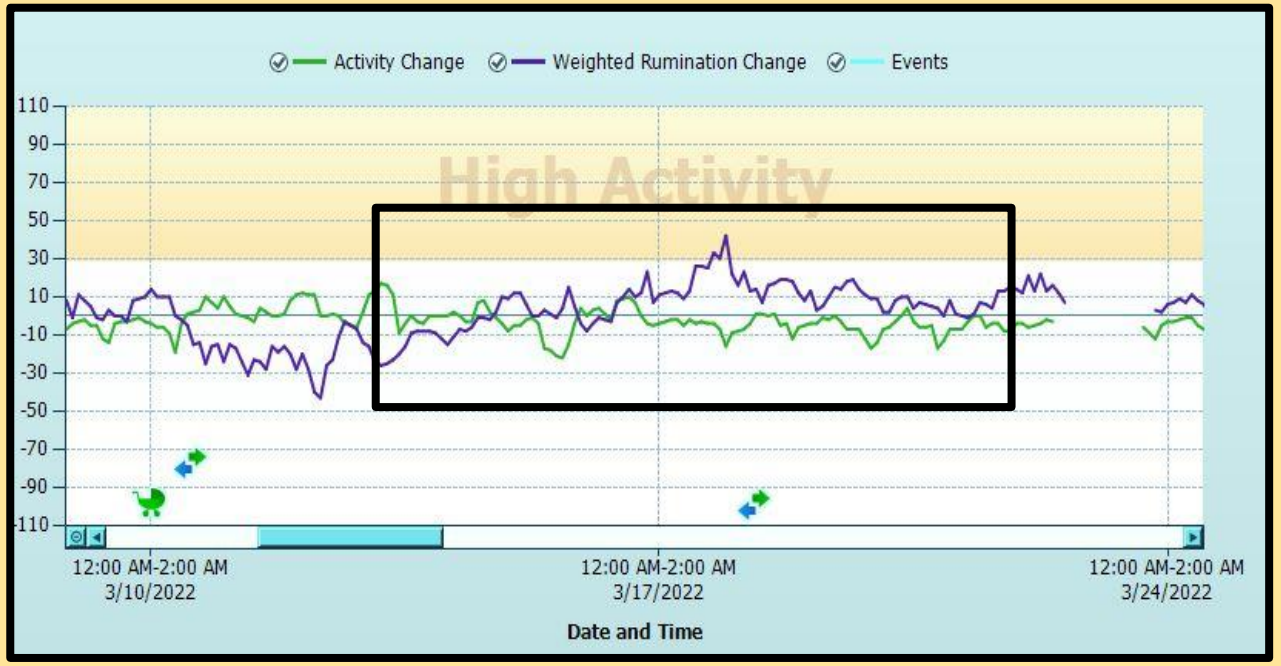
- Don’t mess with
  - High ketones….but she’s eating like a champion
  - Milking like a world-record holder
  - Looks great
  - No fever

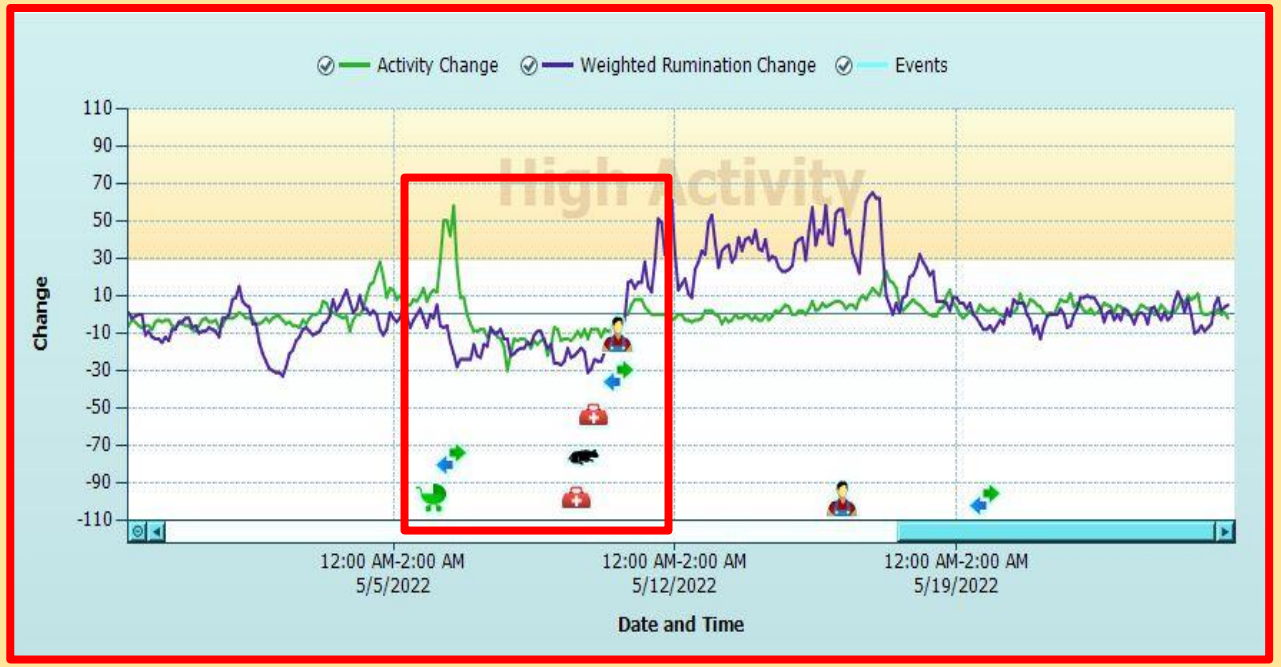
She’s the healthiest cow in the herd

Real World Example

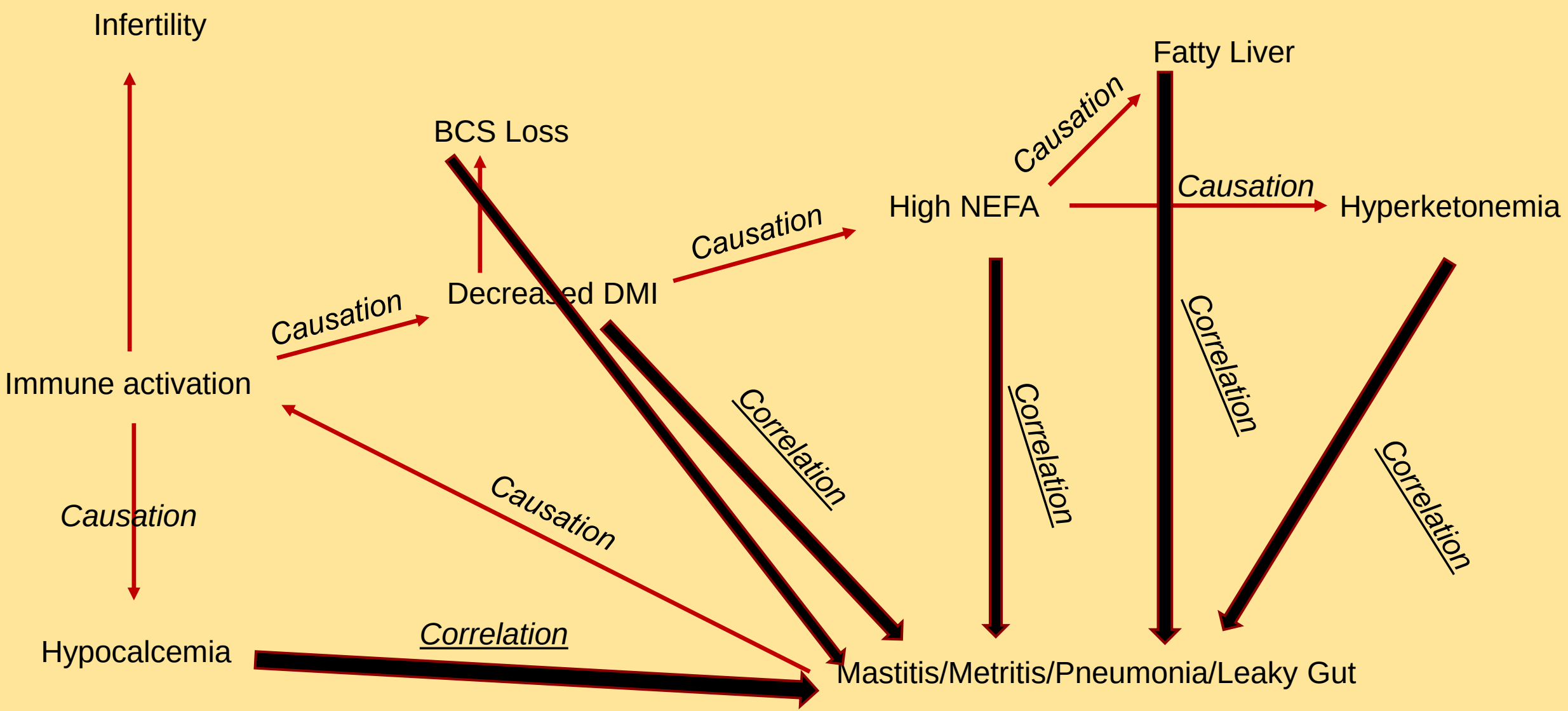
ISU Dairy Farm
Spring of 2022


Milk Yield
160
140
120
100
80
60
40
20
0
lbs/d
↑ Ketones
Metritis
↑ Ketones
Ketosis Protocol: Check all cows DIM 3-5 and 11-13
1
3
5
7
9
11
13
15
17
19
21
Days in Milk
Healthy
Inflamed


Activity Change
Weighted Rumination Change
Events
High Activity
110
90
70
50
30
10
-10
-30
-50
-70
-90
-110
12:00 AM-2:00 AM
3/10/2022
12:00 AM-2:00 AM
3/17/2022
12:00 AM-2:00 AM
3/24/2022
Date and Time


Activity Change
Weighted Rumination Change
Events
High Activity
Change
110
90
70
50
30
10
-10
-30
-50
-70
-90
-110
12:00 AM-2:00 AM
5/5/2022
12:00 AM-2:00 AM
5/12/2022
12:00 AM-2:00 AM
5/19/2022
Date and Time

Causation vs. Correlation: transition cow perspective



Transition Period: Multiple Stacked Stressors in a Small Window of Time

- Dry Off:
  - Pen change, routine change, diet change, over-crowding, far-off pen hygiene, mammary distension
- “Close-up”:
  - Pen change, diet change, impending calving, over-crowding, close-up pen hygiene
- Calving pen:
  - Parturition, diet change, pen hygiene, calf removal, routine change, clinical and endometritis
- Fresh pen:
  - Routine change, diet change, pen hygiene, over-crowding, mastitis, metritis

Minimize Stressors: Farmer's Responsibilities

- Pen hygiene (dry)
- Stall-Bed hygiene
- Over crowding
- Feeding bunk space
- Water availability
- Parlor: lighting, flooring, holding pen
- Heat-stress abatement
- Feed delivery time
- Consistent feed mixing time
- Noise and calmness
- Rough handling

What are Producers, Nutritionists and Veterinarians to do?

- Need to identify the source of infection/subclinical infection
  - Can't just show up and quickly treat subclinical hypocalcemia and hyperketonemia and hurry to next client
  - Need thorough physical evaluation…requires time

- Train farm personnel to utilize full array of information
  - Precision tools (activity, rumination, etc.)
  - Feed intake and milk yield
    - Create bench marks for milk production based upon parity and DIM
  - Cow appearance

Minimize Stressors: Vet's Responsibilities

- Don't encourage lock-up
- Don't unnecessarily "handle" cows
  - Stop touching the cows
    - They aren't pets
- Avoid vaccinations during the transition
- Allow productivity to be your guide
  - Hyperketonemia and hypocalcemia are symptoms of either healthy high production or pathogenic inflammation

Minimize Stressors: Nutritionist's Responsibilities

- Feed hygiene
  - Teach importance to farmers
- Feed Management
  - Teach importance of consistent mixing and delivery time
- Rumen vs. Large intestine fermentation
  - Large intestine digestion is economically less favorable and potentially dangerous
- Choosing appropriate target molecules

Management Changes?

- Should we even be measuring blood ketones, calcium and rectal temperature during the transition period?
  - Costs money and time
  - Opportunity costs for that dedicated labor
- Instead pay more attention to feed intake (rumination/activity) and milk yield

High production can only occur in the absence of stress and morbidity

Summary: Inflammation and the Transition Period

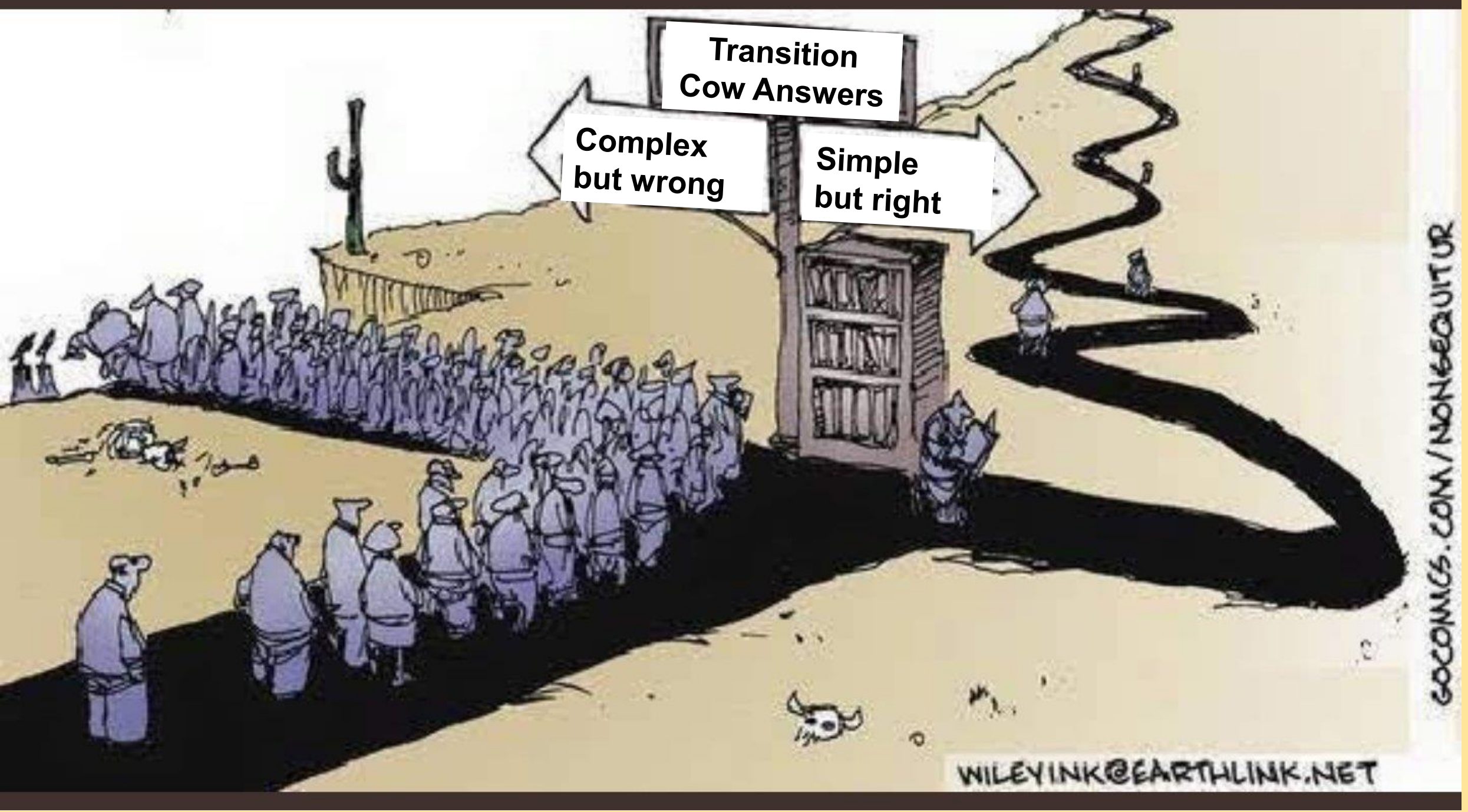
- These metabolic and mineral changes are not “dysfunctional”
- They are required to prioritize survival or required for maximum productivity
  - They aren’t to blame (they’re not the cause) for poor productivity
- Our efforts should be in preventing immune activation in the first place
  - Management
    - Minimize stress (overcrowding of prefresh and fresh pens, on time feed delivery, etc.)

Profitable Production is a Consequence of Wellness

    - Pen cleanliness
  - Dietary strategies
    - Feed hygiene/pathogen binding (microencapsulated botanicals and organic acids)
    - Prevent GIT disturbances
    - Target molecules aimed and minimizing leaky gut
    - Immune modulation

Immune Activation Causes Inflammation

- All transition cows are inflamed (just the magnitude differs)
- Inflammation appears before clinical disease (metritis, mastitis, “ketosis”)
- The immune system “pumps the brake” on feed intake
  - It’s clearly not the only reason for subclinical hypocalcemia
- LPS causes infertility
- Immune activation reduces feed intake
  - It’s the simplest and most logical explanation for why some cows don’t eat well following calving


Transition
Cow Answers
Complex
but wrong
Simple
but right
GOCOMICS.COM/NONSEQUITUR
WILEYINK@EARTHLINK.NET

Acknowledgments

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  - # 2015- 10843
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  - # 2017- 10843
  - # 2019- 07859
  - # 2020- 02716
  - # 2021- 09507

USDA NIFA United States Department of Agriculture National Institute of Food and Agriculture

- Industry Partners

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• TechMix	United Animal Health
• Zinpro Inc.	Zoetis


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GIT Health Target Mitigation Strategies

- Prevent infection (obvious)
- Encourage feed intake
  - Ensure 100% feed availability
- Minimize psychological stress
- Maximize digestion prior to large intestine
  - Dietary strategies
- Prevent rumen acidosis
  - Dietary Strategies
- Manage intestinal permeability
  - Dietary strategies
- Manage intestinal pathogen load
- Immunomodulation

Producer's Responsibility

Nutritionist and Producer's Responsibility

Nutritionist's Responsibility