Reevaluating transition cow dogmas. It's time to question conventional thinking

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

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Department of Animal Science, Iowa State University, Ames 50011

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

Transition Period Morbidity

Disorders affects 50%:

- D
- M
- R
- M
- K
- DA
- Fatty liver
- Lameness
- Death

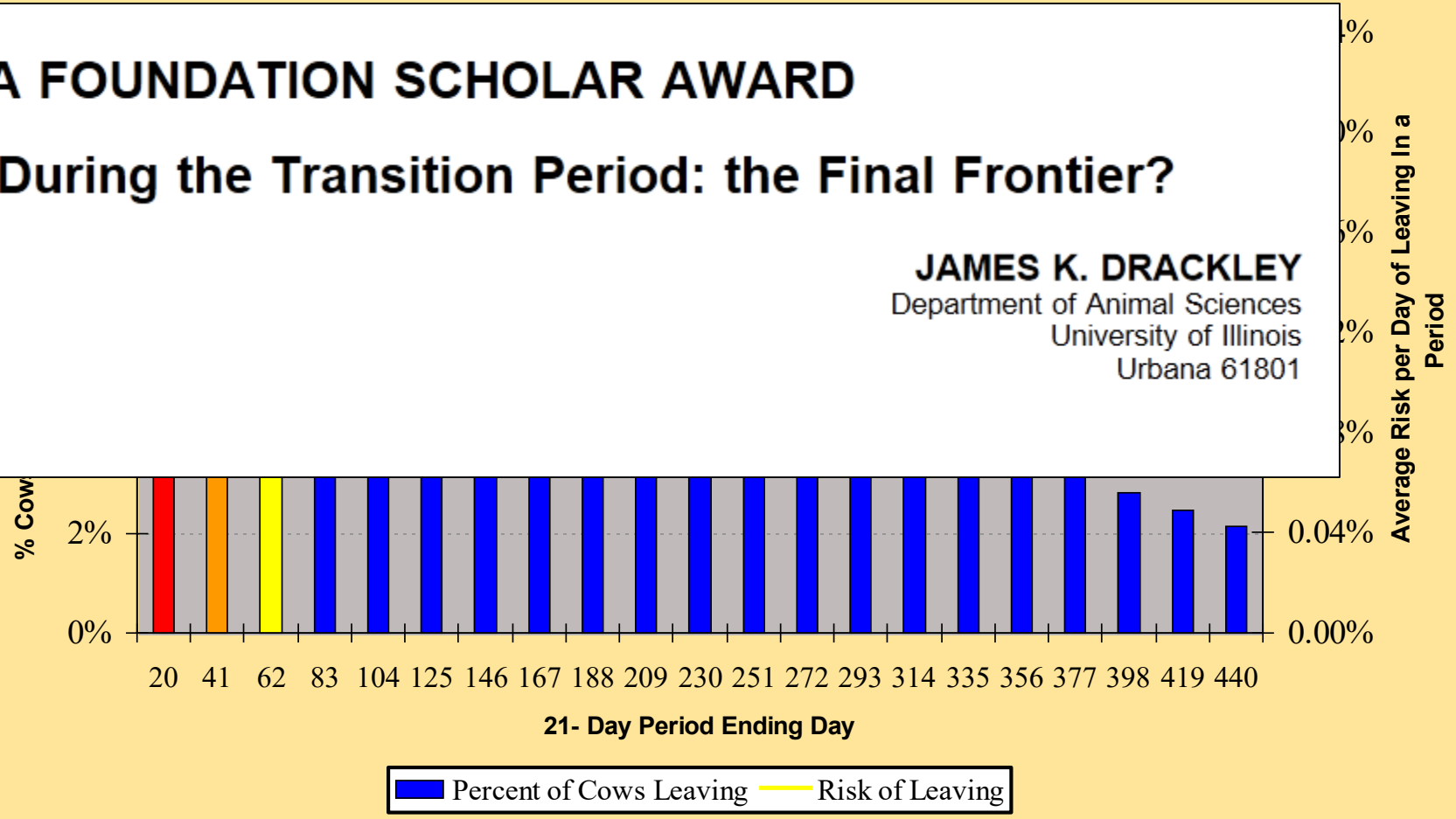
Drackley, 1999

When cows leave the herd

ADSA FOUNDATION SCHOLAR AWARD

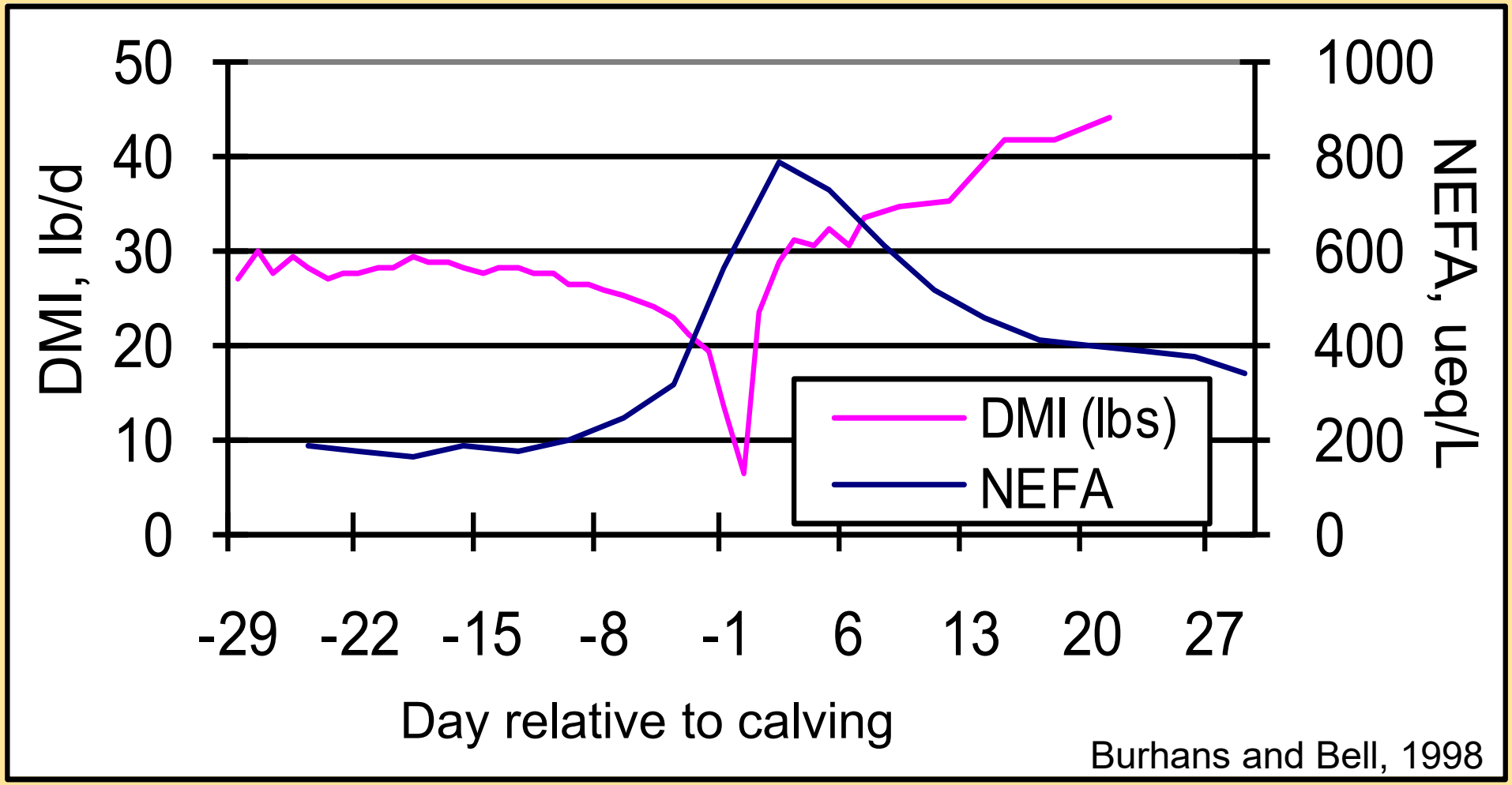
Biology of Dairy Cows During the Transition Period: the Final Frontier?

JAMES K. DRACKLEY
Department of Animal Sciences
University of Illinois
Urbana 61801

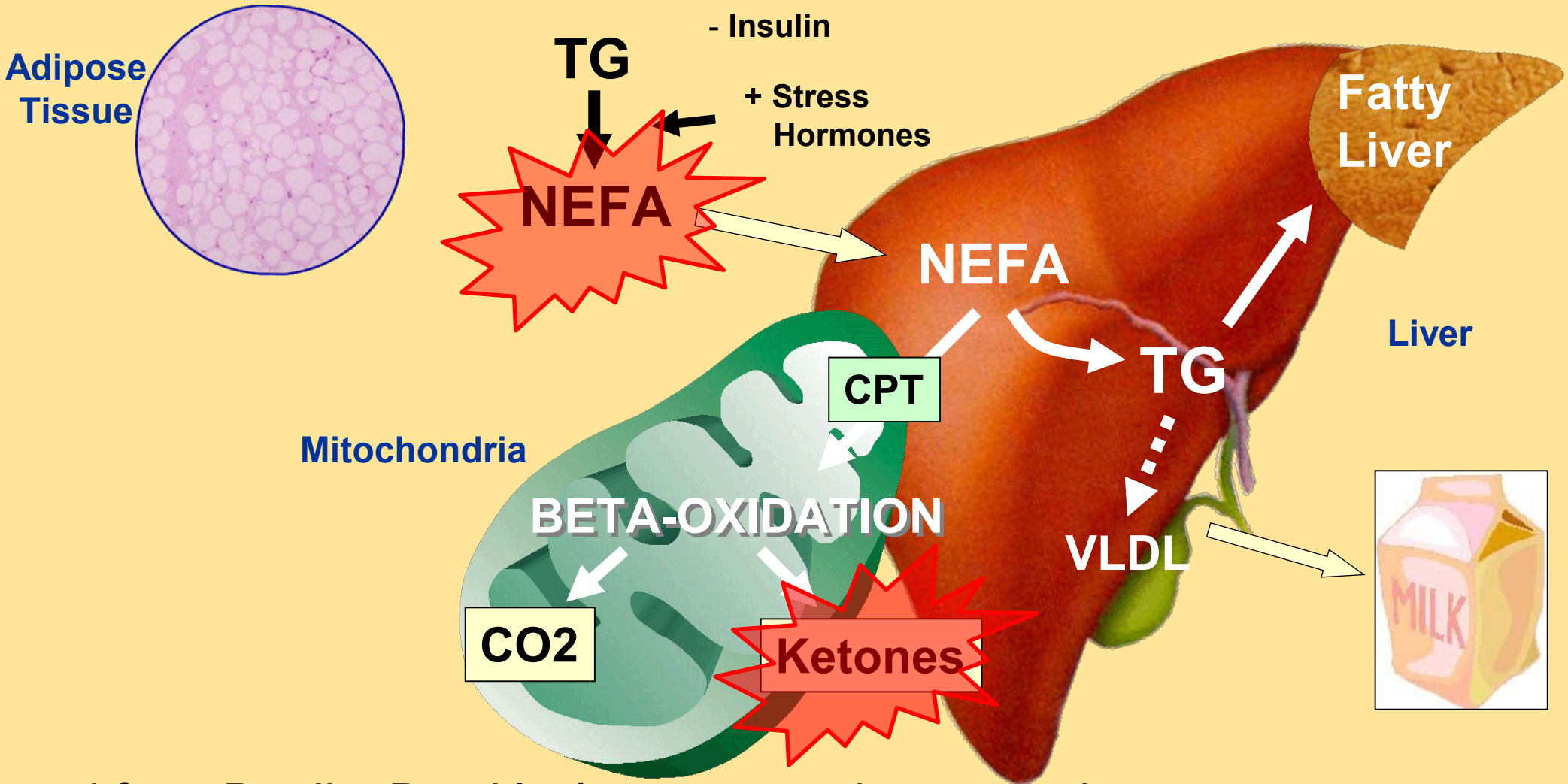


Source: 2002, Steve Stewart, DVM, Dipl.-ABVP, Univ. of Minnesota, College of Vet. Med.

Transition Period Energy Balance



Liver Lipid Metabolism During the Transition Period



Adapted from Dr. Jim Drackley's papers and presentations

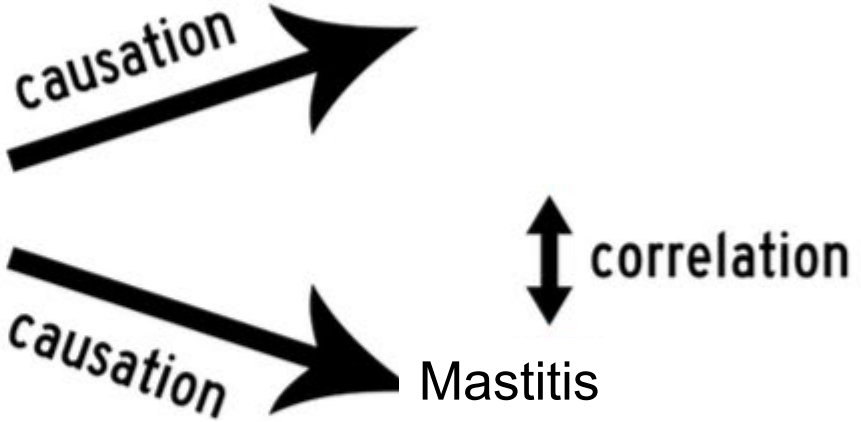
Retrospective and Observational Studies

- 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

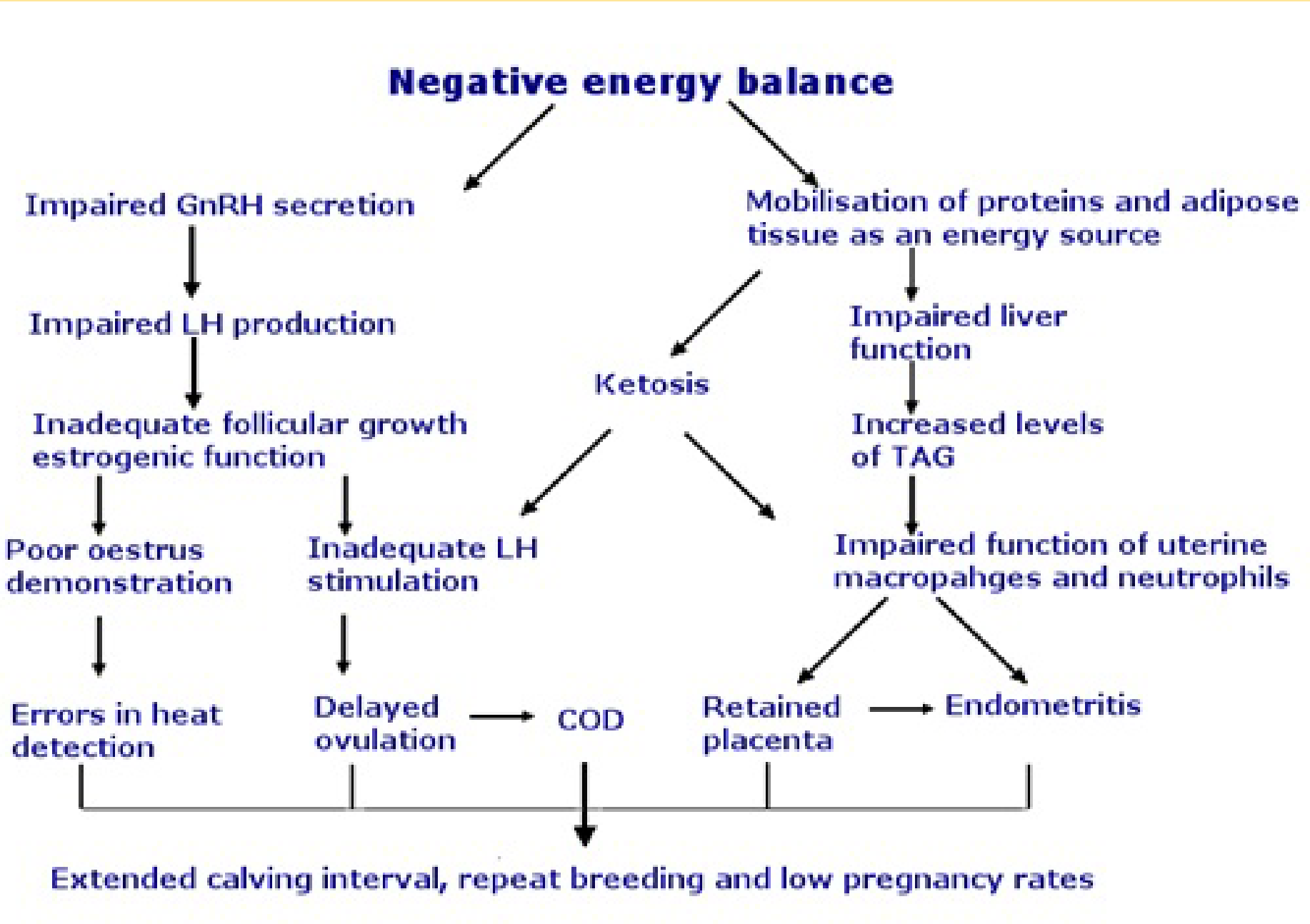
Traditional Belief

Assuming Correlation Equals Causation

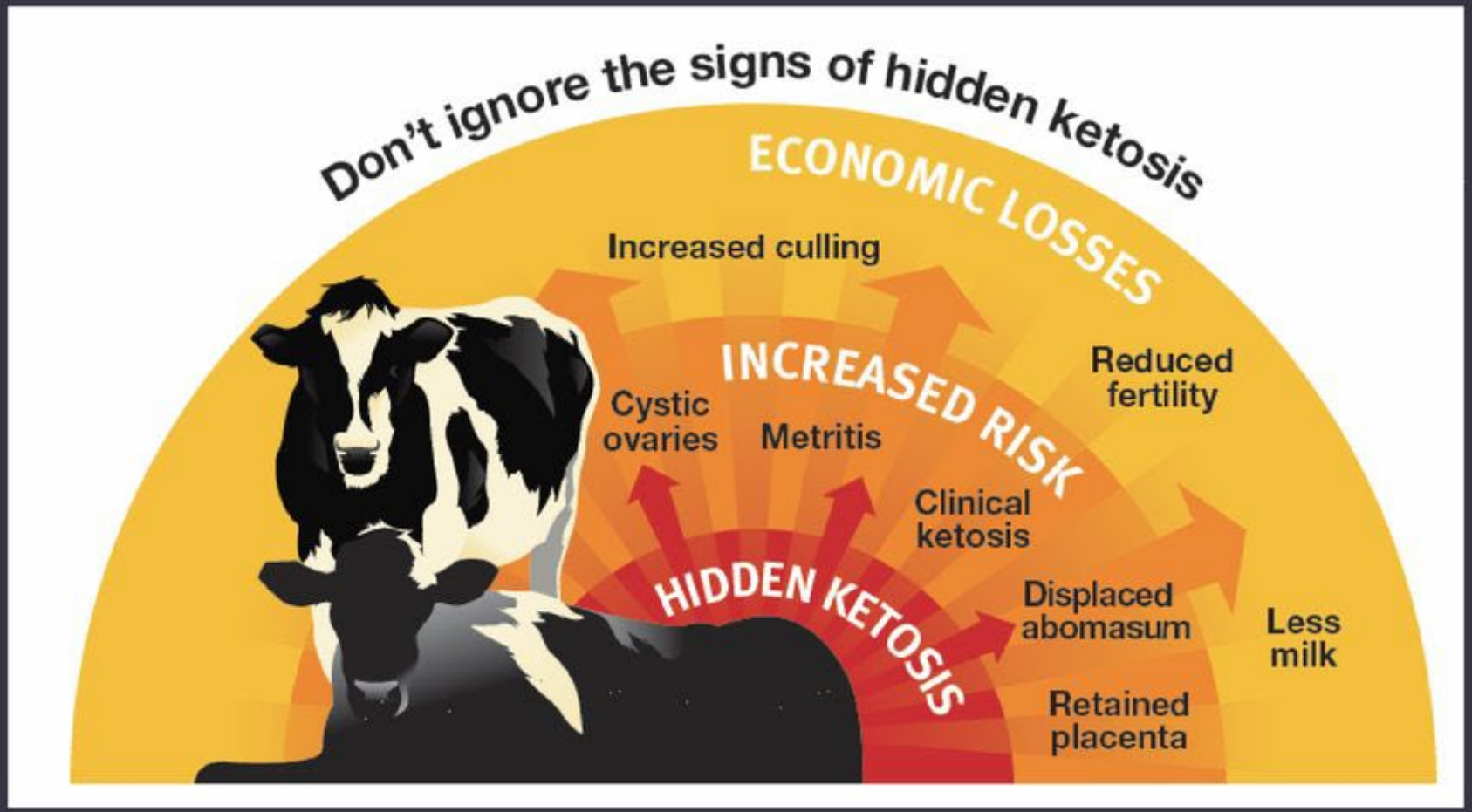
Increased NEFA, Hyperketonemia, and Hypocalcemia…..**CAUSE** production and health problems

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	

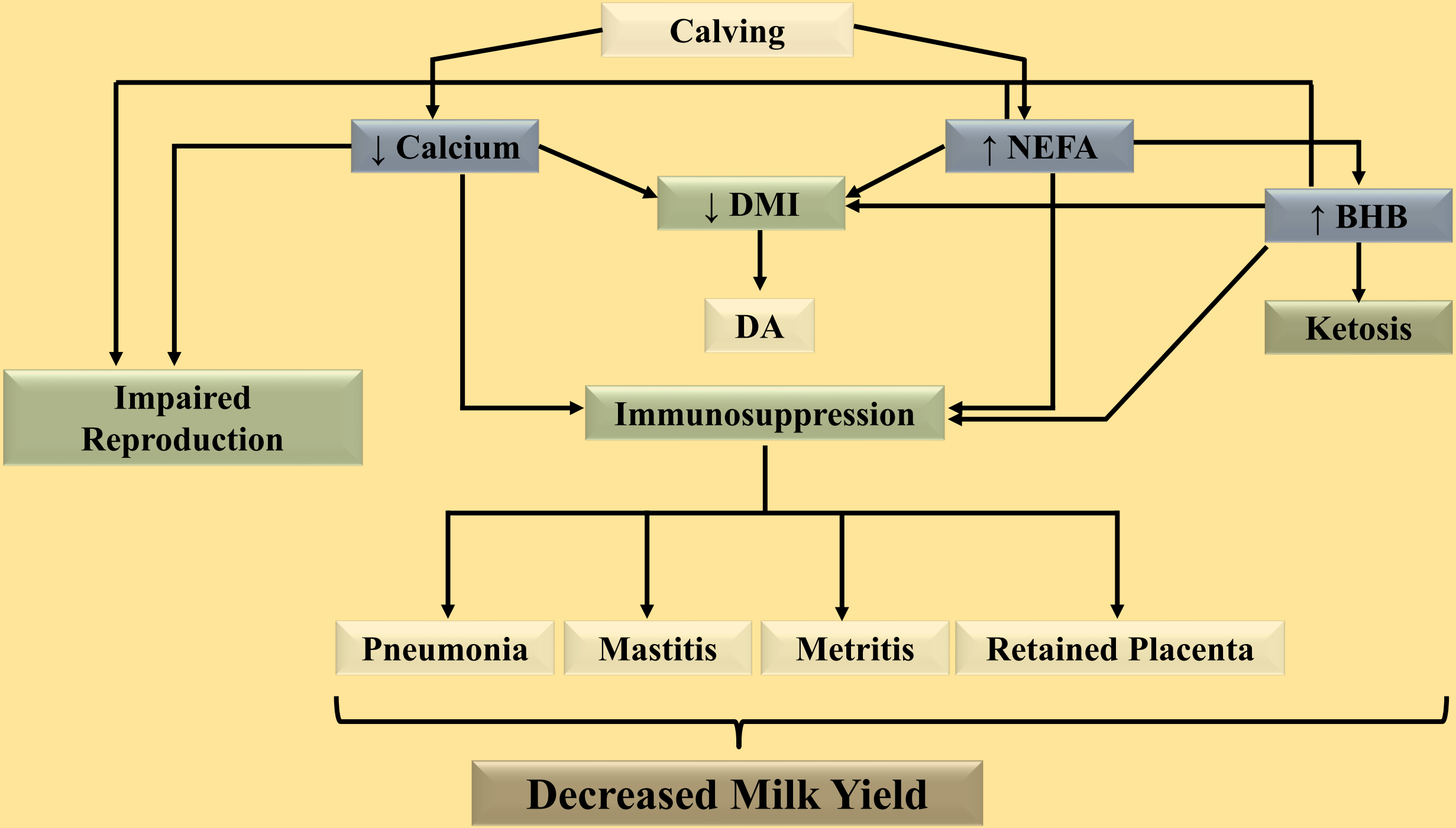
Despite emphasis, time and money spent on preventing high NEFA, hyperketonemia and subclinical hypocalcemia herd health is not improving

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

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
a chem
sustenance involves a series of chemical reac-

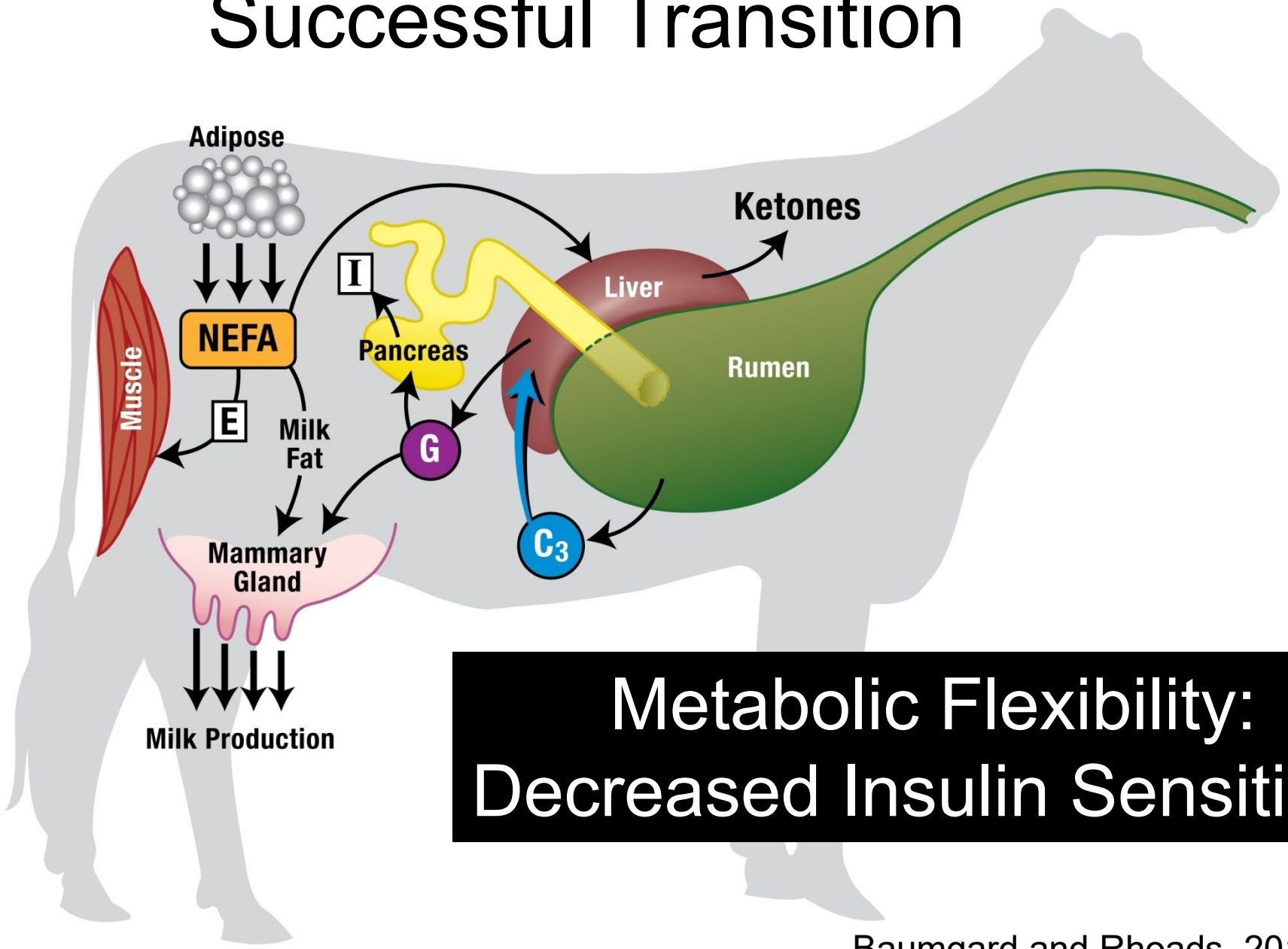
involves maintenance of physiological equilibri-
um or constant conditions in the internal environment (Figure 2). There are many well established examples of homeostasis, such as regulation to maintain constancy of body

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

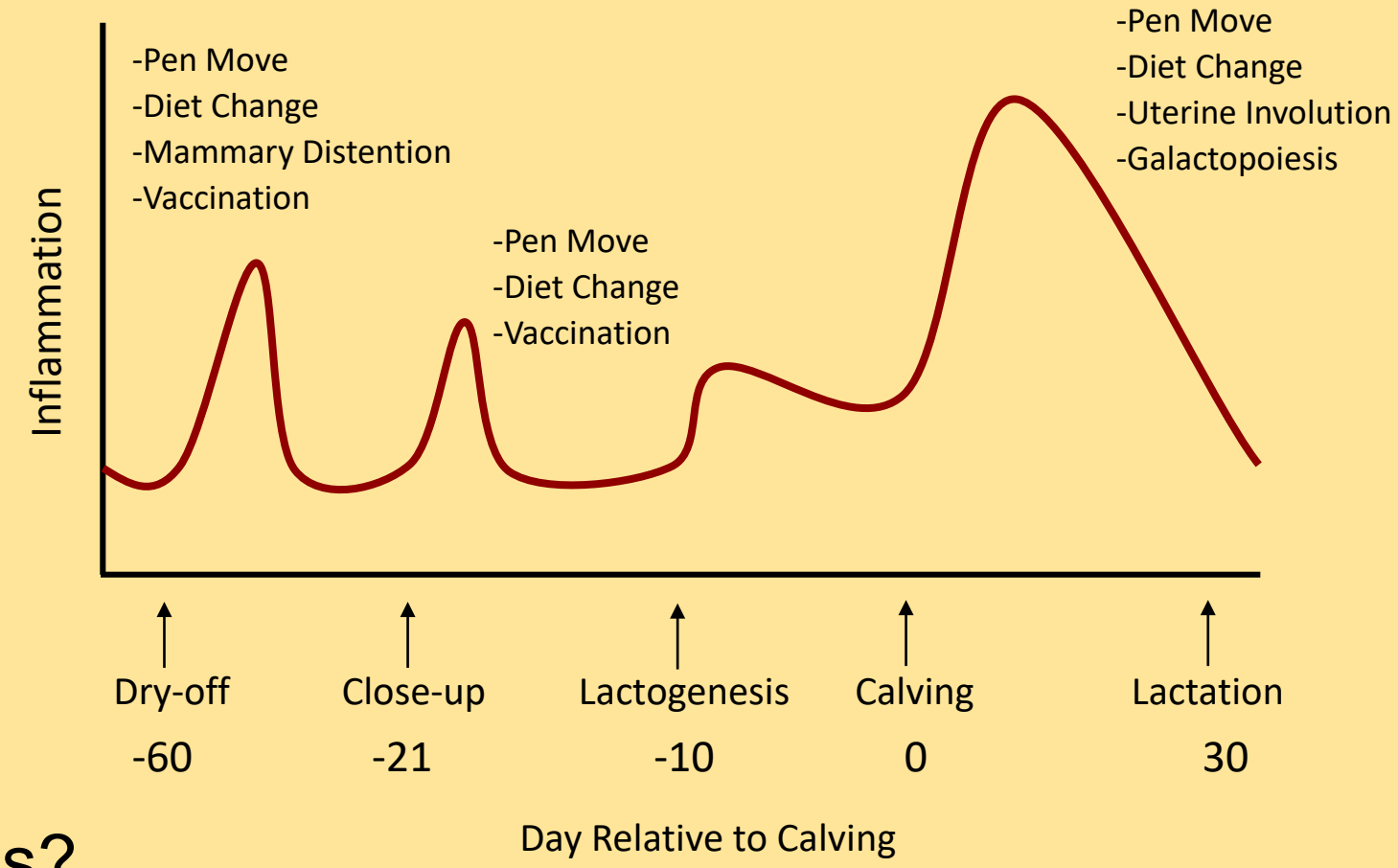
Inflammation in Transition Cows

- Observed in all cows

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

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

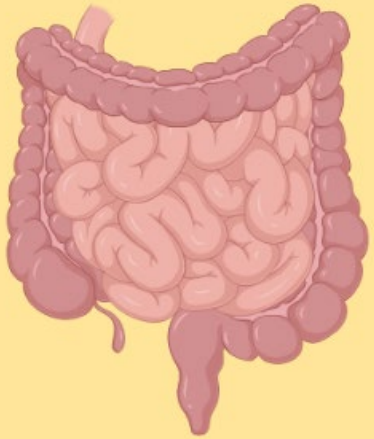
- What are the consequences?



Dr. B. Goetz

Inflammation sources:

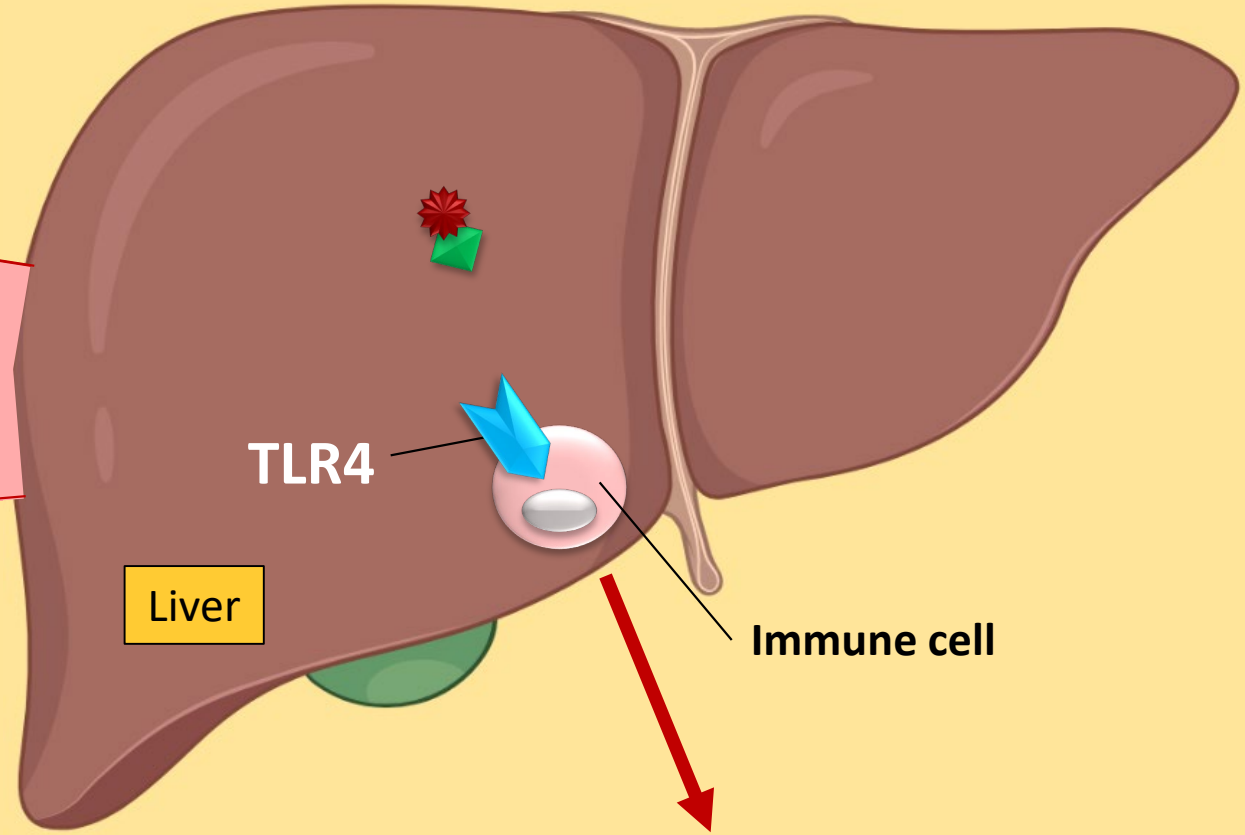
LPS



Complex LPS/LBP

LBP

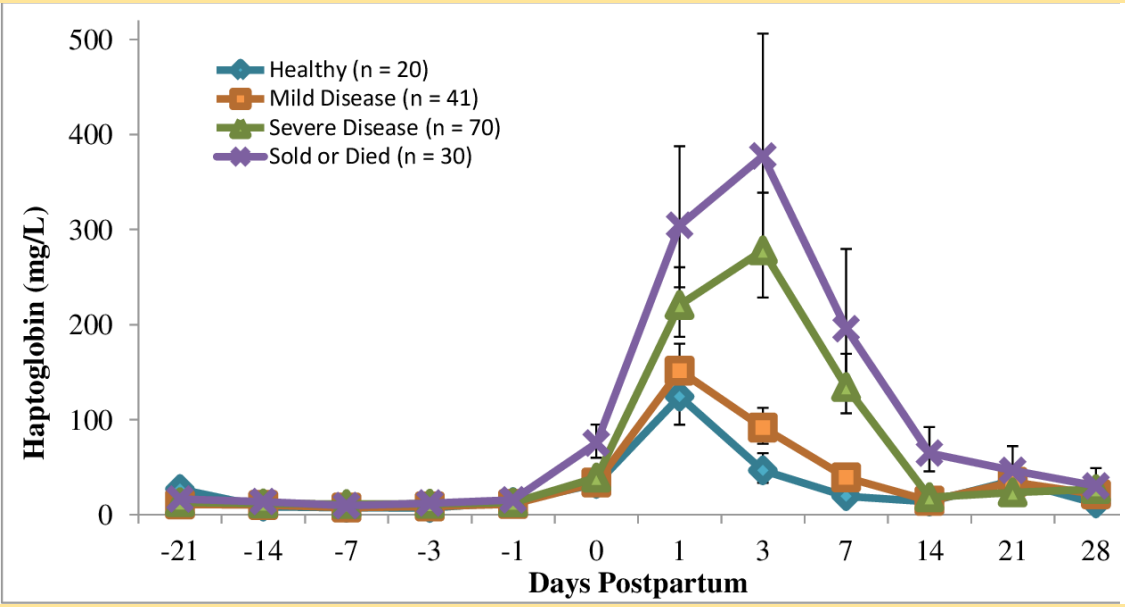
Circulation



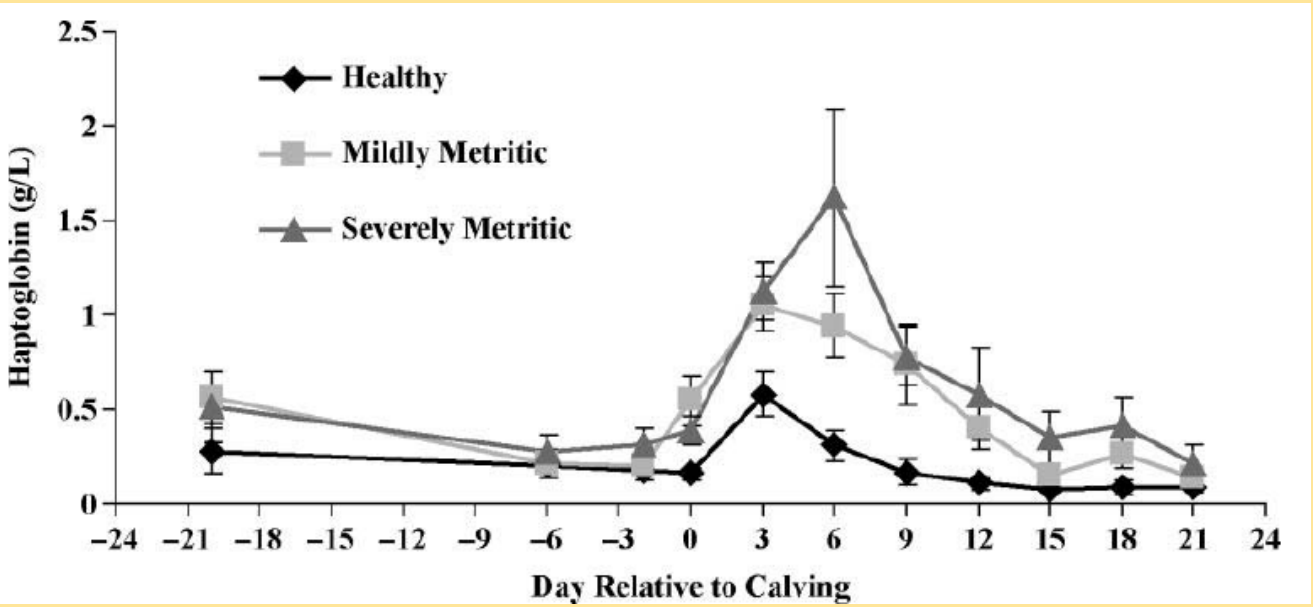
↑ Inflammatory response
↑ Cytokines
↑ APPs:
- SAA
- Hp
- LBP

Rodriguez Jimenez & Kvidera

Immune Activation (Haptoglobin) Precedes Clinical Disease

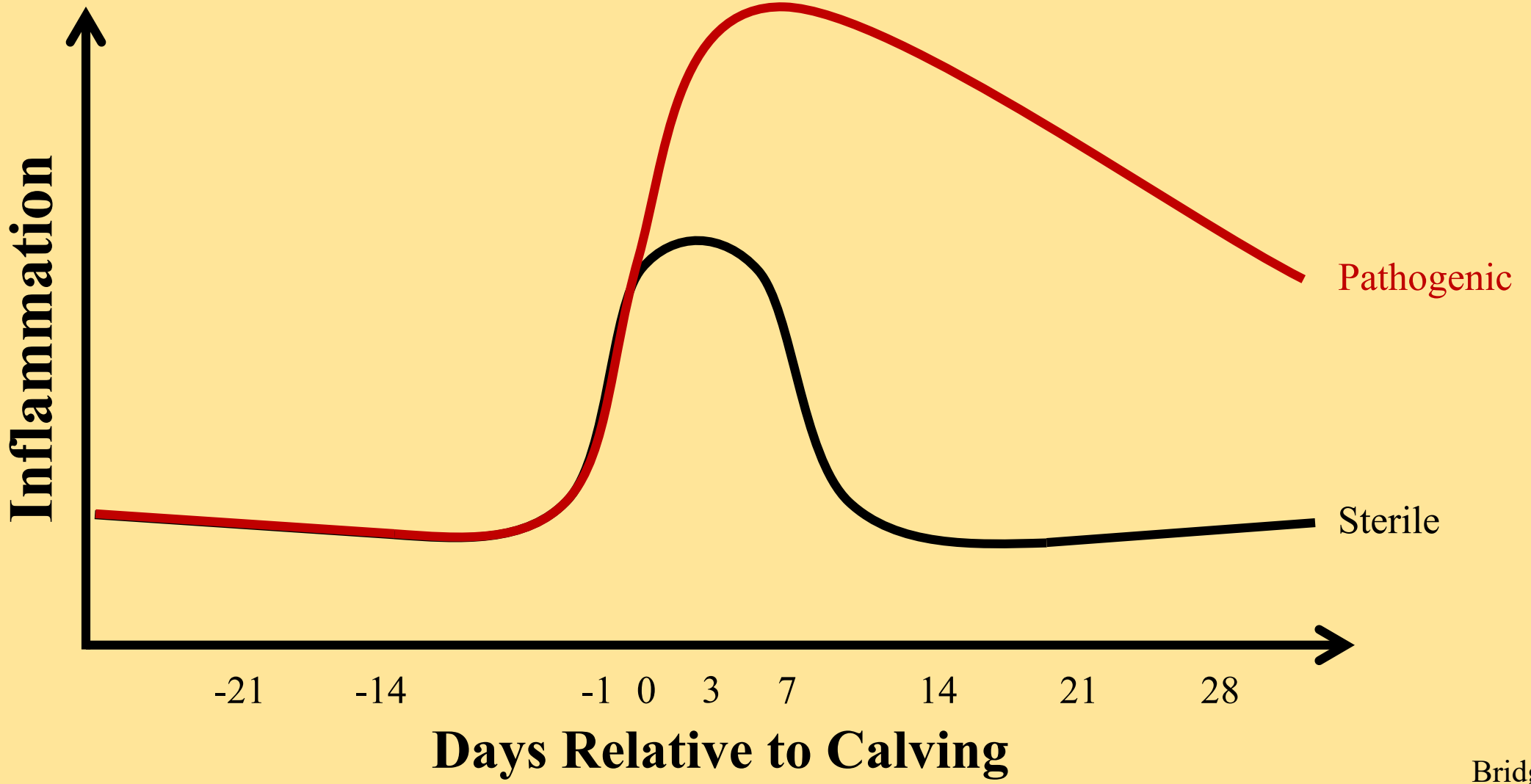


Sebedra 2012



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

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wjg@wjgnet.com
doi:10.3748/wjg.v18.i21.2609

World J Gastroenterol 2012 June 7; 18(21): 2609-2618
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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]

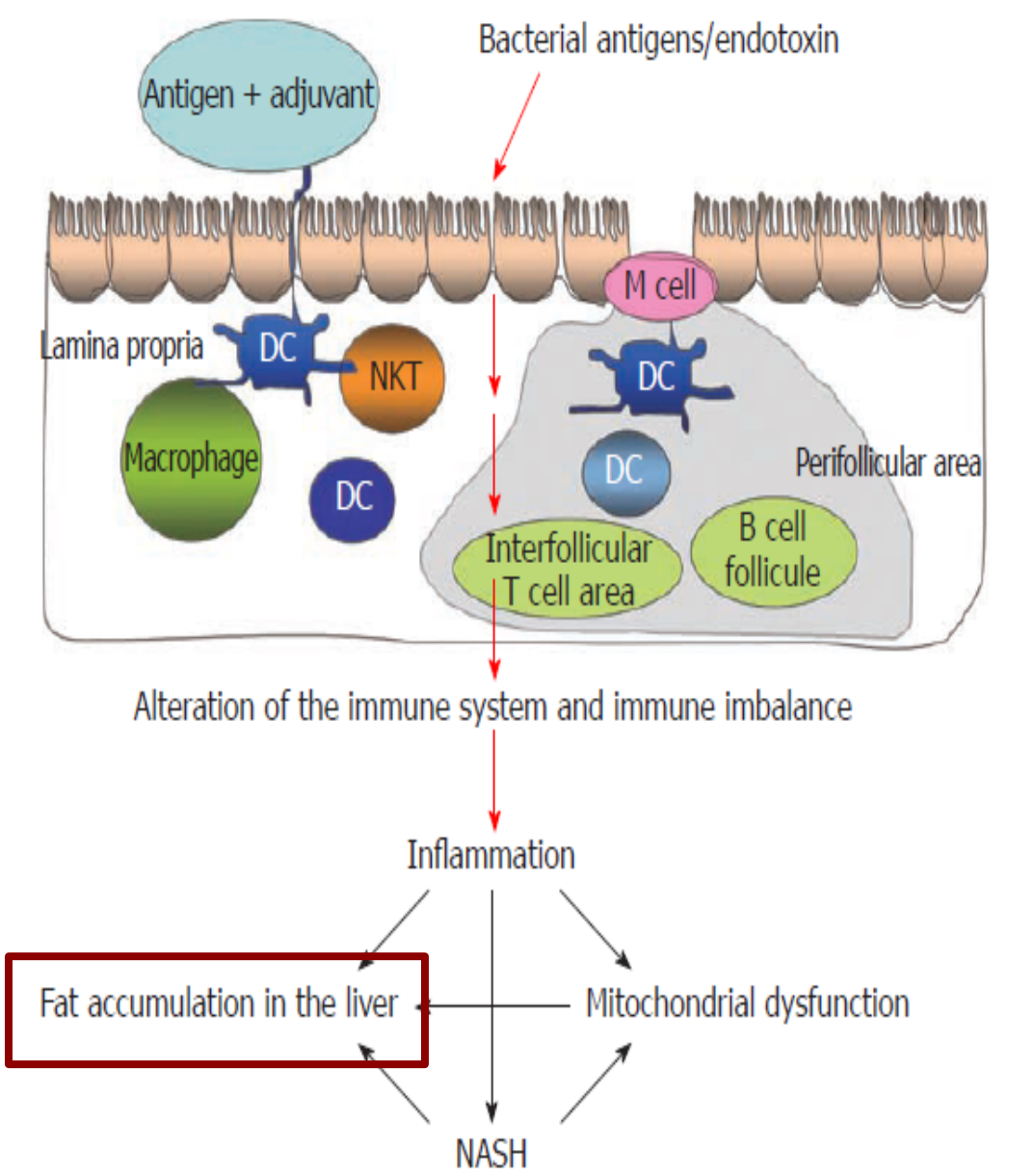
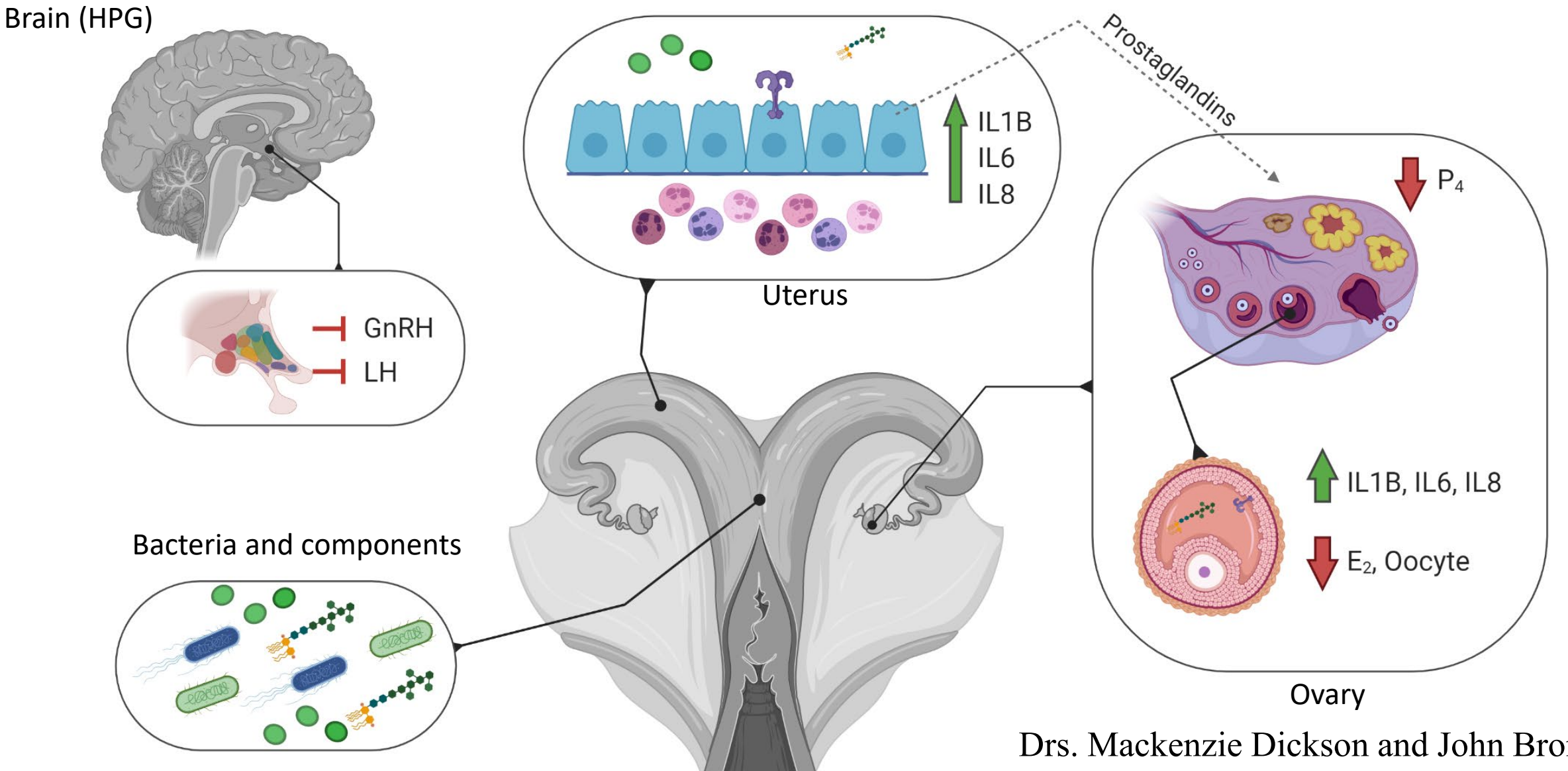


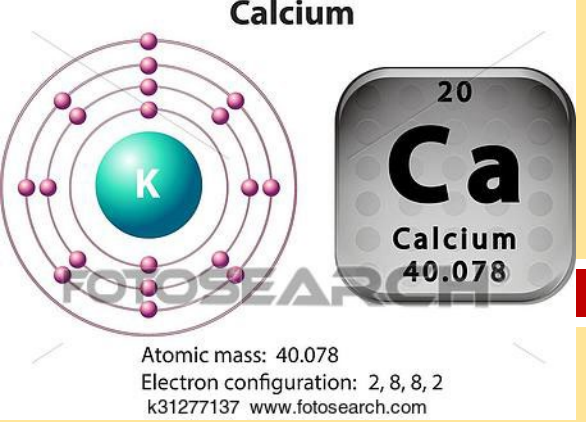
Figure 1 Bacterial translocation is associated with the development of nonalcoholic steatohepatitis. NASH: Nonalcoholic steatohepatitis.

Inflammation and Reproduction?

LPS Negative Effects Repro From Multiple Angles



Drs. Mackenzie Dickson and John Bromfield



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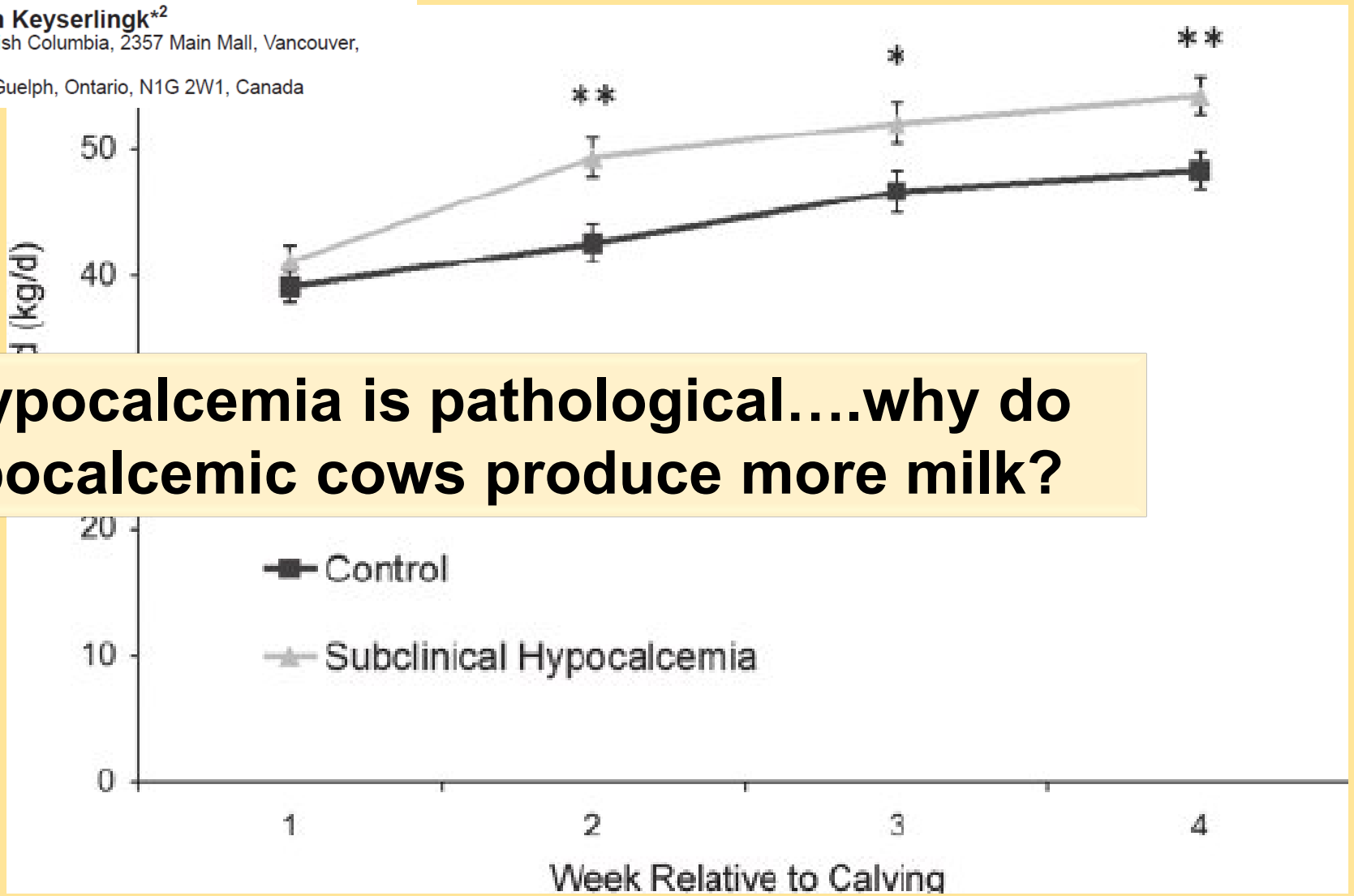
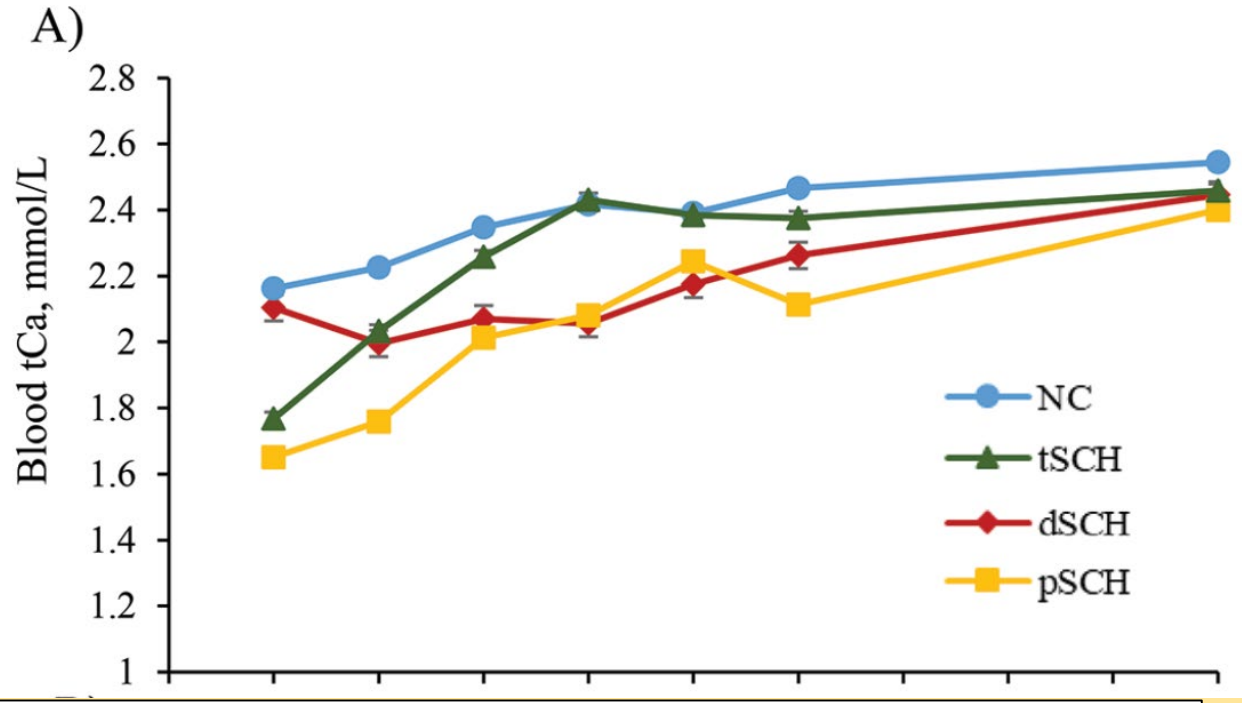
Associations of subclinical hypocalcemia at calving with milk yield, and feeding, drinking, and standing behaviors around parturition in Holstein cows

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



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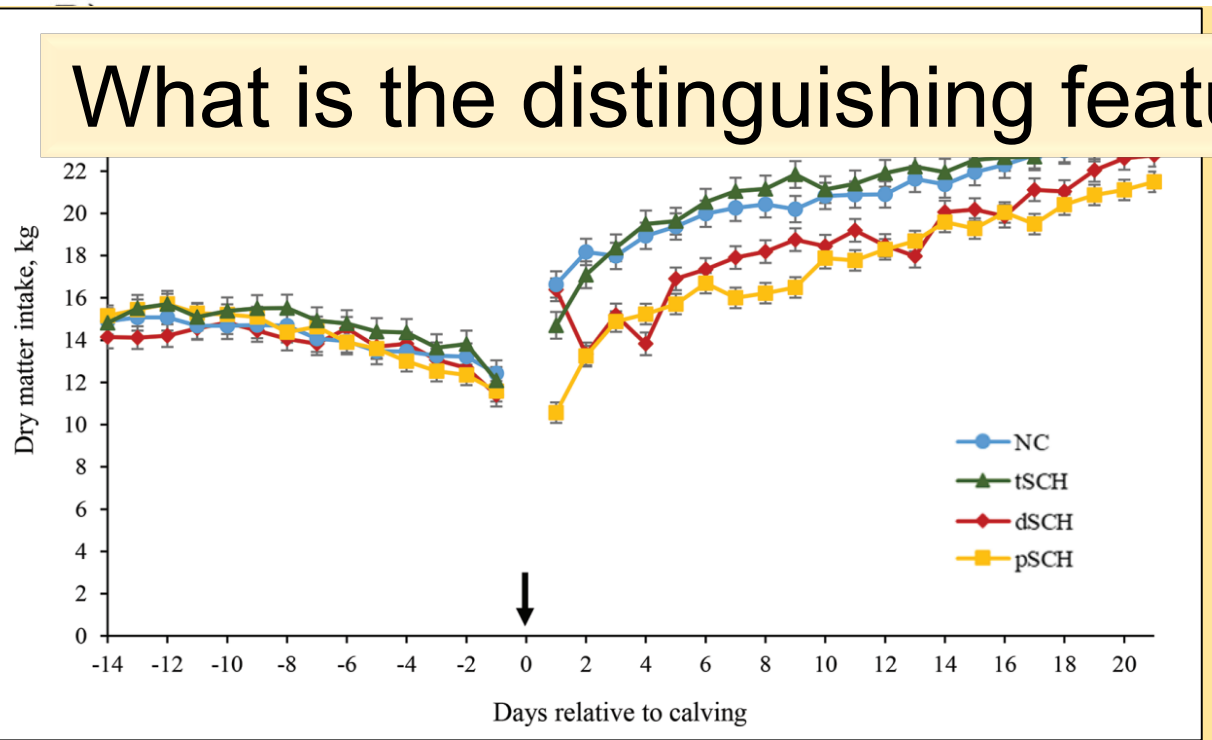
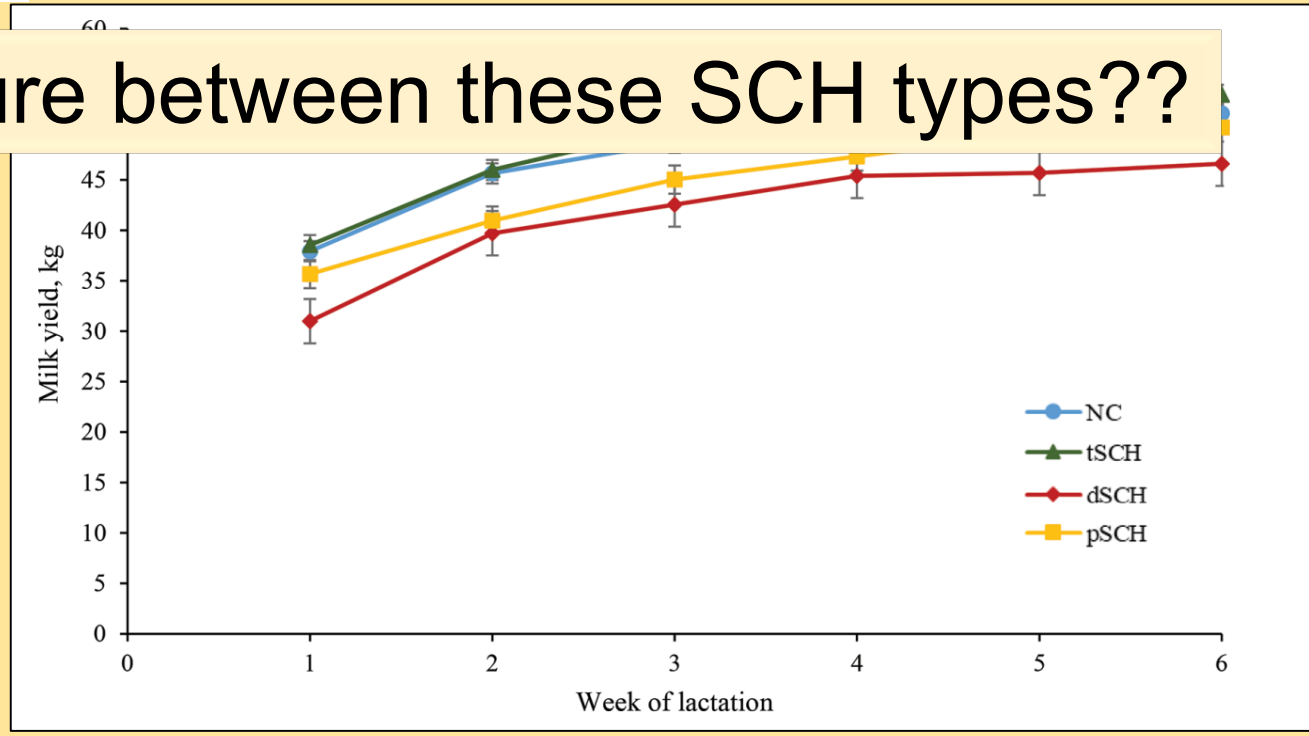
Association of subclinical hypocalcemia dynamics with dry matter intake, milk yield, and blood minerals during the periparturient period

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 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 <u>some</u> types of subclinical hypocalcemia**

J. Dairy Sci. TBC
https://doi.org/10.3168/jds.2024-25300
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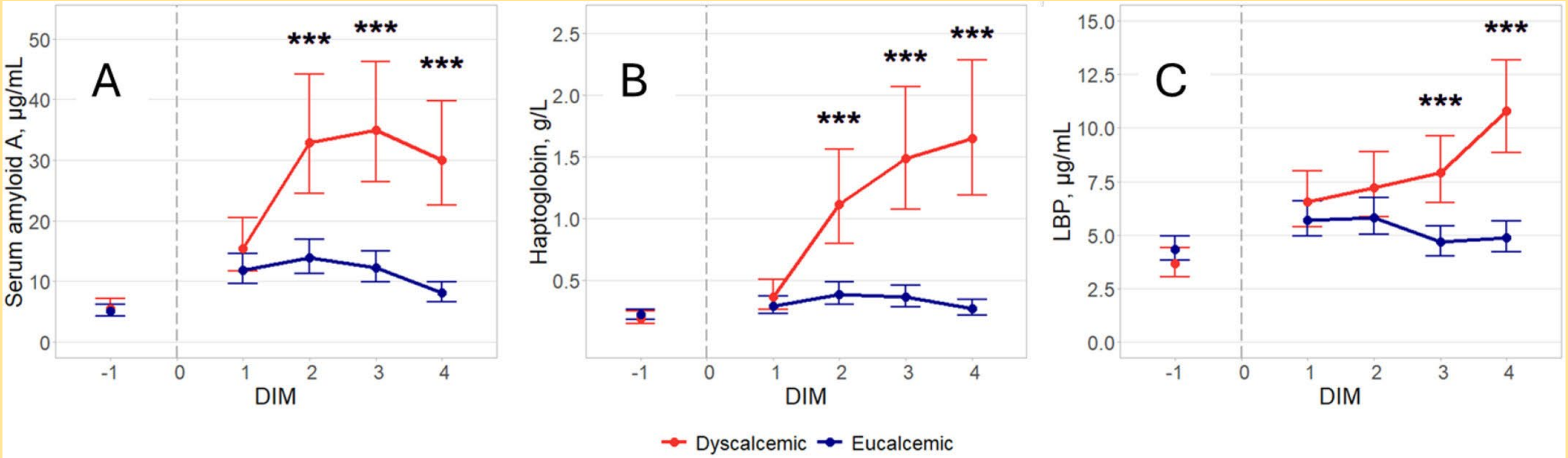
Acute phase responses in clinically healthy multiparous Holsteins with and without calcium dysregulation during the early postpartum period

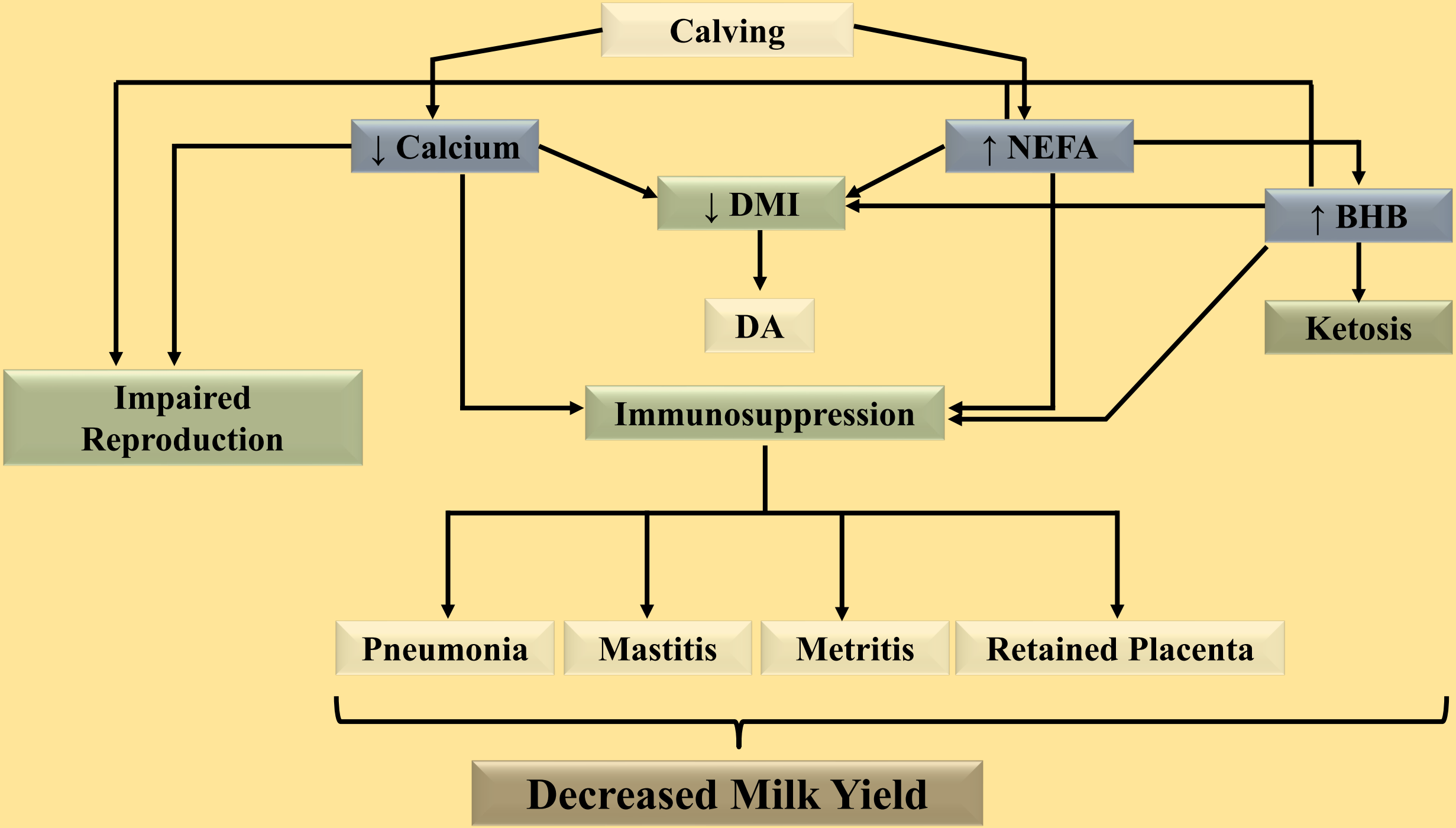
J. A. Seminara,[1] C. R. Seely,[2] and J. A. A. McArt[1]*
[1]Department of Population Medicine and Diagnostic Sciences, College of Veterinary Medicine, Cornell University, Ithaca, NY
[2]Department of Agriculture, Nutrition, and Food Systems, College of Life Sciences and Agriculture, University of New Hampshire, Durham, NH



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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↓ Calcium
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↓ DMI
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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

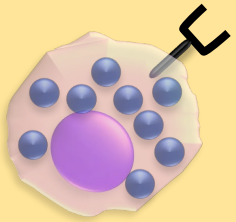
Hypocalcemia is a consequence of immune activation

Mycotoxins

Mastitis

Leaky Gut

Metritis



LPS/Inflammation

Impaired Reproduction

Fatty Liver

↓ DMI

Hypocalcemia

↑ NEFA

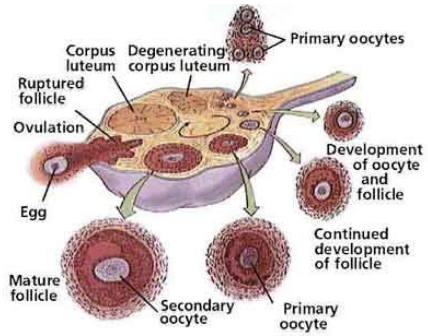
DA

↓ Milk Yield

↑ BHB

Ketosis

Unsuccessful Transition



Fatty Liver, Excessive Ketone Synthesis

Reduced DMI

Adipose

NEFA

Muscle

E

Milk Fat

Liver

Ketone

Rumen

G

C3

LPS

↓ Ca

Mammary Gland

Milk Production

Metabolic Flexibility:
Decreased Insulin Sensitivity
Glucose redirected to immune system

Baumgard and Rhoads, 2013

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

Rethinking Immunity in Transition Cows: Are They Truly Suppressed?

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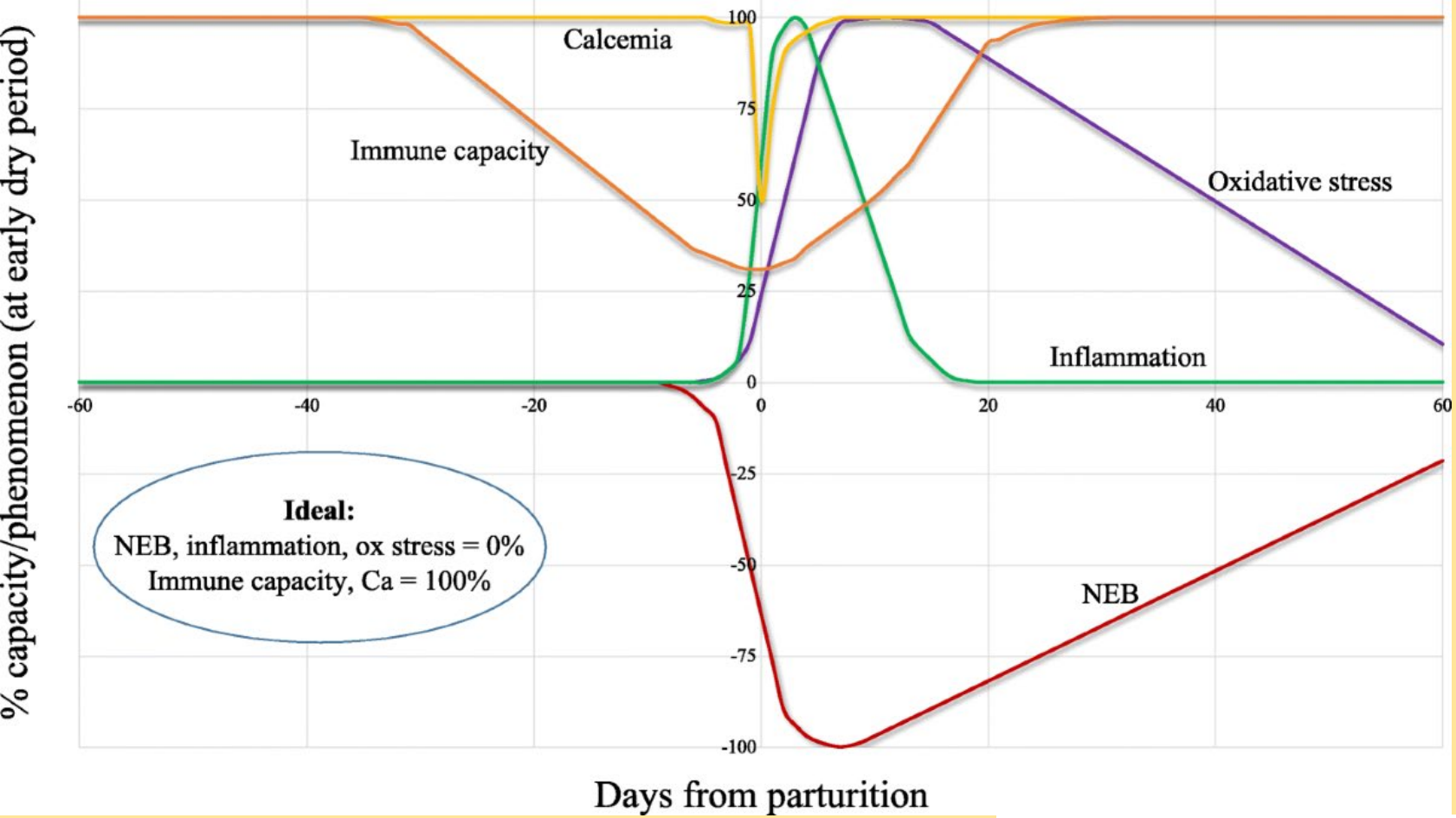
Department of Animal Science



Lopreiato *et al. Journal of Animal Science and Biotechnology* (2020) 11:96
https://doi.org/10.1186/s40104-020-00501-x

Journal of Animal Science and Biotechnology

REVIEW Open Access

Role of nutraceuticals during the transition period of dairy cows: a review

Vincenzo Lopreiato[1], Matteo Mezzetti[1], Luca Cattaneo[1], Giulia Ferronato[1], Andrea Minuti[1,2] and Erminio Trevisi[1,2*]

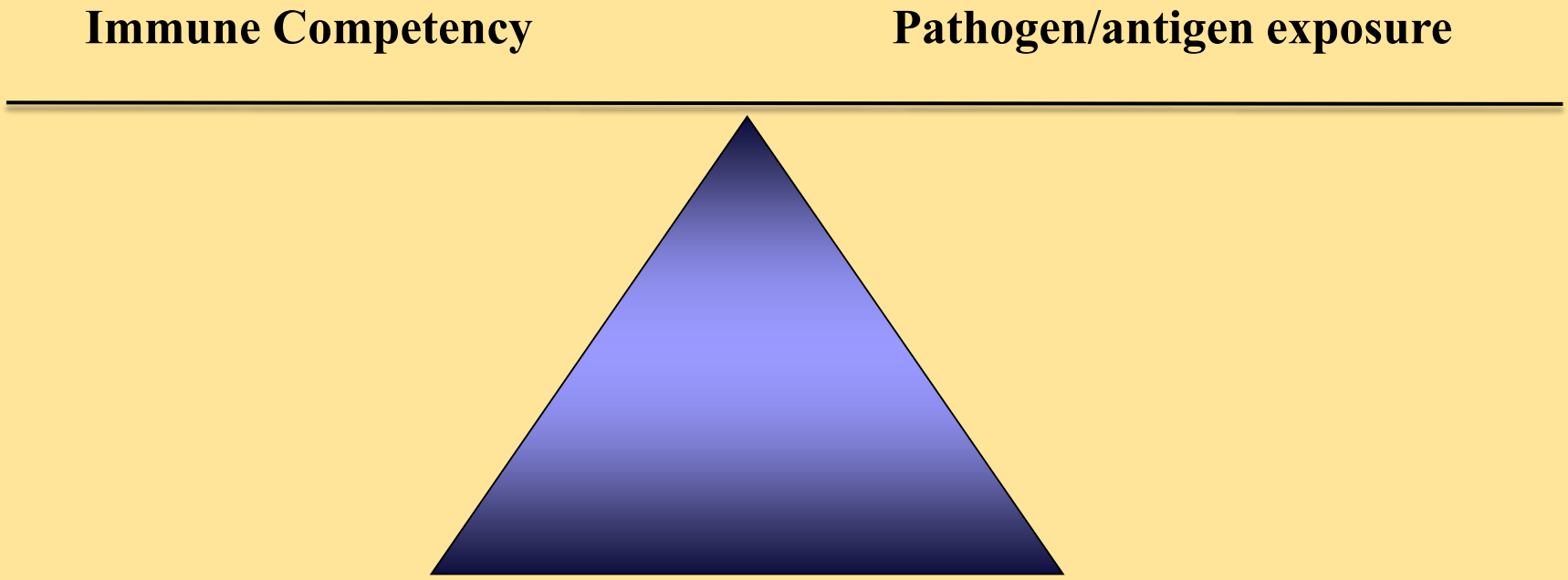
Transition Cow Morbidity

- Highest rates of illness occurs within the first 30 days
- Highest rates of culling occurs within the first 60 days

- This has traditionally been assumed to be caused by “immune suppression”.

- Dogma: The reason why transition cows get sick is because of a dysfunctional immune system.
  - This tenant does not consider the pathogen load

Immune Competency vs. Exposure



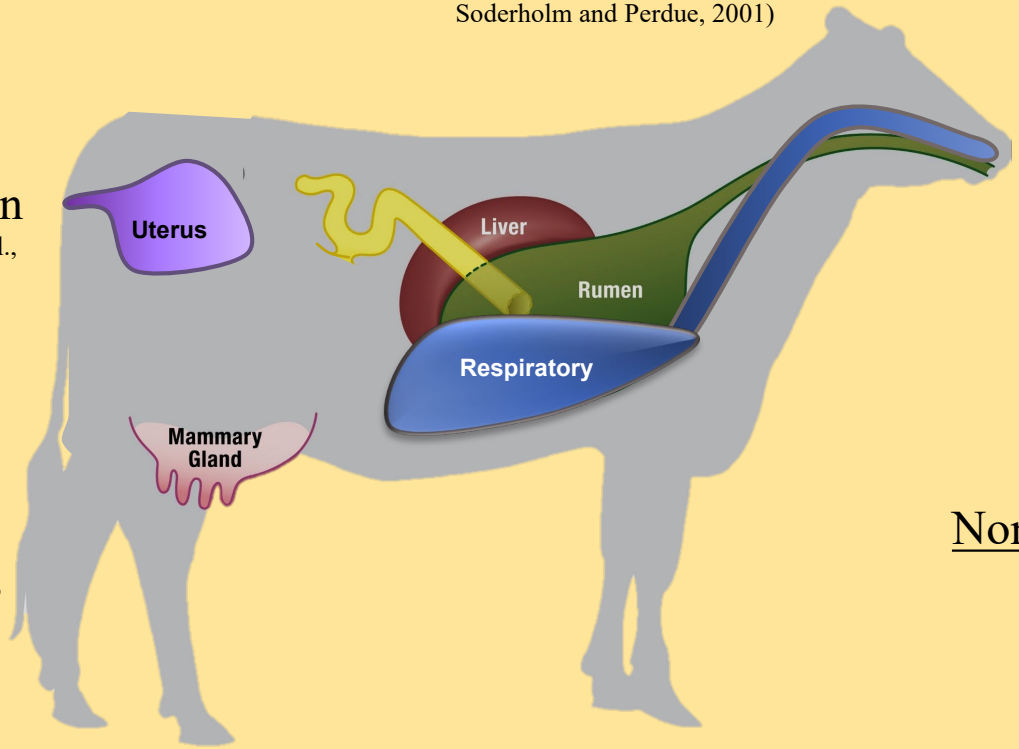
David Vetter, aka the “bubble boy”
Severe Combined Immunodeficiency (SCID)

<u>Wellness:</u>
Immune Competency vs. Pathogen Load

Heightened Risk of Pathogen Insult in Early Lactation

Increased gut permeability via diet and social changes
(Emmanuel et al., 2007; Khafipour et al., 2009; Soderholm and Perdue, 2001)

Uterine bacterial contamination post-parturition
(Paisley et al., 1986; Földi et al., 2006; Norman et al., 2007; Sheldon et al., 2008)



Lactogenesis and galactopoeisis
(Akers and Nickerson, 2011)

<u>Non-pathogenic/Sterile Inflammation</u>
Parturition
Placenta Expulsion
Uterine Involution

J. Dairy Sci. 107:6225–6239
https://doi.org/10.3168/jds.2023-24350
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Intravenous lipopolysaccharide challenge in early- versus mid-lactation dairy cattle. I: The immune and inflammatory responses

J. Opgenorth,[1] E. J. Mayorga,[1] M. A. Abeyta,[1] B. M. Goetz,[1] S. Rodriguez-Jimenez,[1] A. D. Freestone,[1] J. L. McGill,[2] and L. H. Baumgard[1]*
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Intravenous lipopolysaccharide challenge in early- versus mid-lactation dairy cattle. II: The production and metabolic responses

J. Opgenorth, E. J. Mayorga, M. A. Abeyta, S. Rodriguez-Jimenez, B. M. Goetz, A. D. Freestone, and L. H. Baumgard*
Department of Animal Science, Iowa State University, Ames

J. Dairy Sci. 107:6252–6267
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Intramammary lipopolysaccharide challenge in early- versus mid-lactation dairy cattle: Immune, production, and metabolic responses

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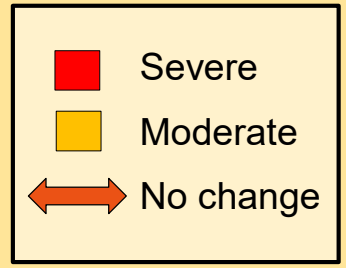
Immune Activation: Early vs. Mid Lactation Cow

Parameter	Early-Lactation Cow	Mid-lactation Cow
Febrile Response	↑↑↑	↑
Inflammatory/Chemotactic Cytokines	↑↑↑	↑
Leukocytosis	↑↑↑	↑
Acute Phase Proteins	↑↑↑	↑
Ionized Calcium	↓↓↓	↓
Insulin	↑	↑↑↑
Glucagon	↑↑↑	↑
NEFA	↑↑↑	↓
BHB	↔	↓
BUN (muscle mobilization)	↑↑↑	↑
Dry Matter Intake	↓↓↓	↓
Milk Yield	↓	↓



Opgenorth and Baumgard, 2024

What About Cell Mediated Immunity?

T-Cell $CD4^+$, $CD28^+$ and $CD8^+$ Cell Types increased immediately post-calving.

Not supportive of Adaptative Immune System Suppression

2066 Effect of supplementation of *Saccharomyces cerevisiae boulardii* CNCM I-1079 on cell-mediated immunity during early lactation period in Holstein dairy cows. T. Fernandez Wallace*[1], M. Boerefyn[2], S. Cartwright[2], S. Jantzi[2], K. Dekraker[2], A. Pineda[2], C. Villot[3], S. K. Kvidera[4], M. A. Steele[2], and L. R. Cangiano[1], [1]*Department of Animal and Dairy Sciences, University of Wisconsin–Madison, Madison, WI,* [2]*Department of Animal Biosciences, University of Guelph, Guelph, ON, Canada,* [3]*Lallemand SAS, Blagnac, France,* [4]*Elanco Animal Health, Greenfield, IN.*

The objective of this study was to evaluate the effect of supplementation

Abstracts of the
2024 American Dairy Science Association®
Annual Meeting

Journal of Dairy Science®
Volume 107, Supplement 1

PDPW Webinar
https://mediasiteconnect.com/site/pdpw-dairy-signal/watch/9e89c5f8-3537-4579-73e3-08dd192a3aa2

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journal homepage: www.elsevier.com/locate/vetmic

Mucosal immune responses in peri-parturient dairy cattle

Victor S. Cortese [a,*], Amelia Woolums [b], Merrilee Thoresen [b], P.J. Pinedo [c], Thomas Short [d]

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[b] Mississippi State University, College of Veterinary Medicine Mississippi State, MS 39762, USA
[c] Department of Animal Sciences, Colorado State University, Fort Collins, CO 80523, USA
[d] Zoetis, Inc. Parsippany, NJ, USA

"Contrary to previous reports of systemic immune-suppression, bovine mucosal responses appear to be intact during the peripartum period"

"The increases in local IFN-beta in the pre-partum period, and the IgA in the post-partum, despite published evidence of decreased systemic immune responsiveness during the same time frame (Heiser et al., 2015), provides support for further research to confirm whether there is an upregulation of mucosal immunity during the peripartum period."

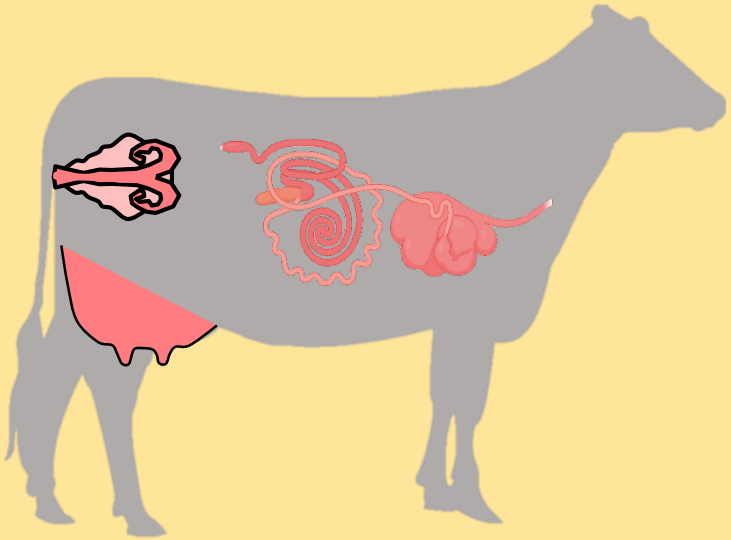
Practical on-farm Examples Supporting)ur Tenet that Transition Cows Are Not Immune Suppressed

- bovine granulocyte stimulating factor (rbG-CSF)
  - Increases circulating neutrophils
    - Should benefit an immune suppressed transition cow
- Transition cows are less sensitive to high pathogenic avian bird flu
  - https://www.canr.msu.edu/news/hpai-dairy-herd-infection-case-report
  - https://www.cidrap.umn.edu/avian-influenza-bird-flu/avian-flu-detections-dairy-cows-raise-more-key-questions
  - https://wwwnc.cdc.gov/eid/article/30/7/24-0508_article
- Transition cows are less sensitive to heat stress (an immune activating event)
  - (Maust et al., 1972; Perera et al., 1986)
- Effects of anti-inflammatory (NSAIDs) administration to transition cows is inconsistent
  - (Horst et al., 2021)

Transition Cow Immune Competency

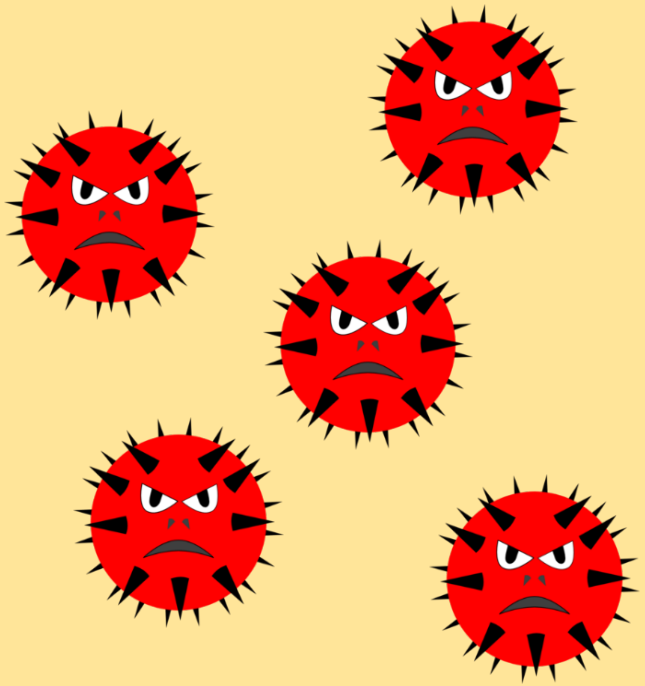
- Almost every immune variable we measured was more robust in early lactation compared to late lactation cows.
- Despite an exaggerated immune response, early lactation cows prioritized milk synthesis
  - Energetic collision of priorities (immune system AND milk synthesis)
    - Hypoglycemia, high NEFA and Hyperketonemia
  - Late lactation cows just give up trying to make milk
- Maybe if it weren't for a robust immune response morbidity would be even worse!
- If correct, what are the implications to dairy nutrition and management?
- I am not suggesting that inflammation is innocuous
  - Efforts should be to limit the peak and hasten the resolution

Immune Suppression Dogma



Immune System

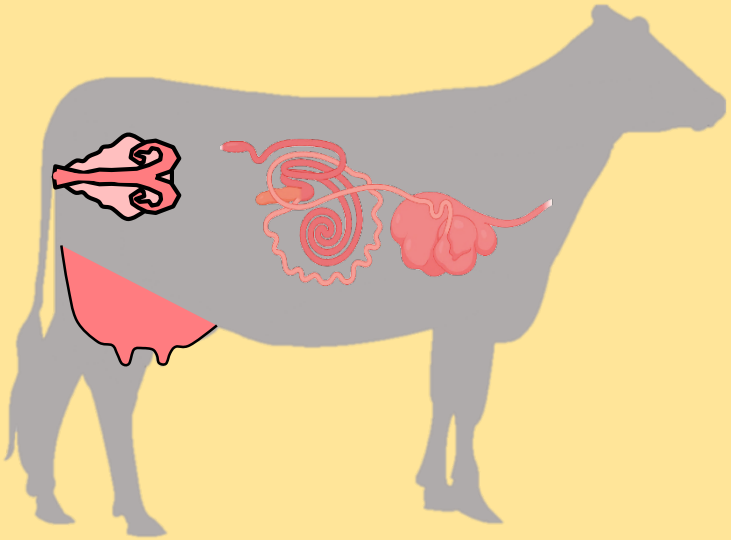
↓ Function



≈ Pathogen Load

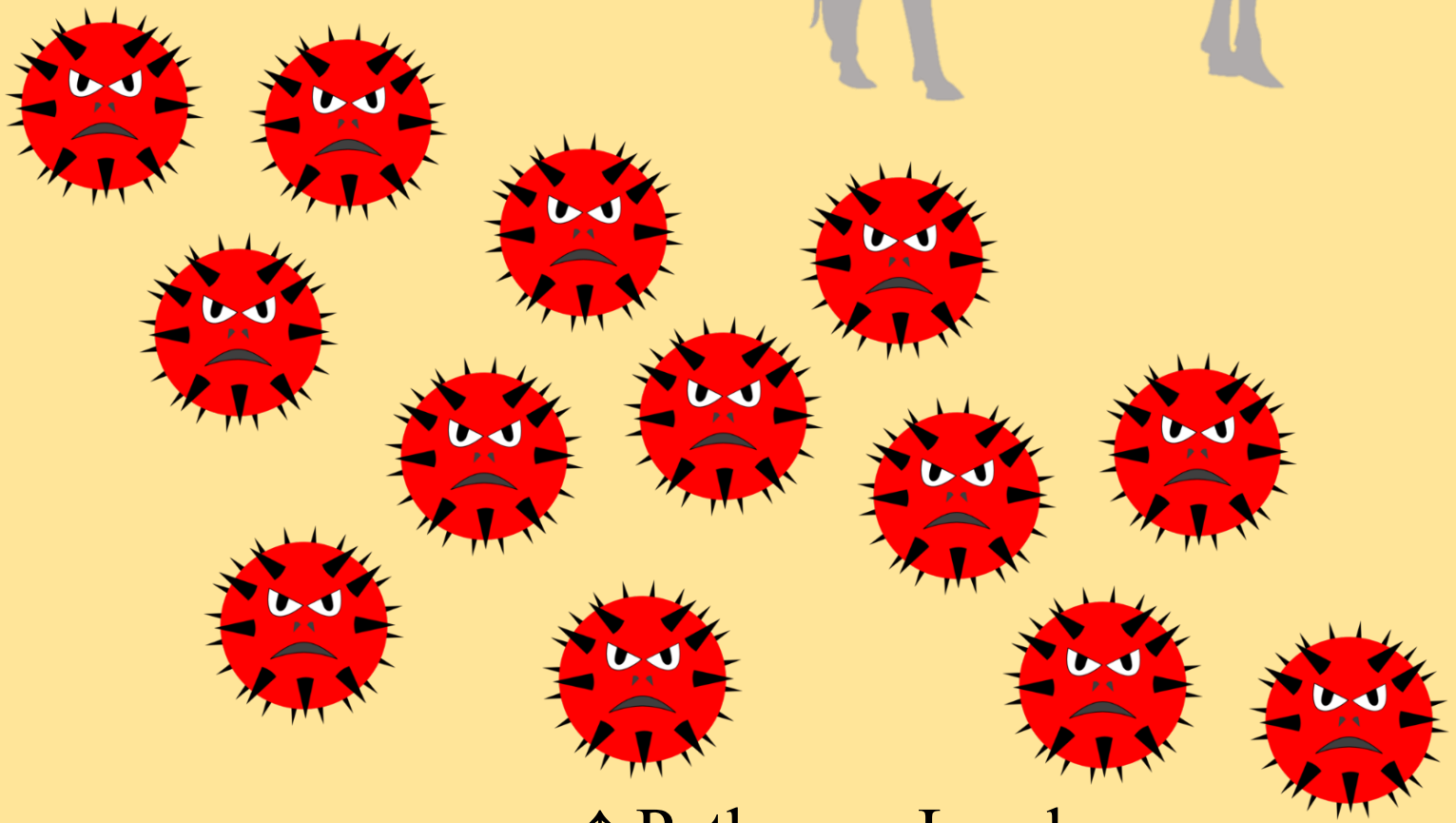
Bridget Buol and Gaelan Combs

Challenged Dogma



Immune System

Robust Function



↑ Pathogen Load

Bridget Buol and Gaelan Combs

Take Home Message

- The periparturient cow does not appear immune suppressed, BUT she is at much greater risk of antigen exposure.

The increased exposure explains the increased risk of morbidity

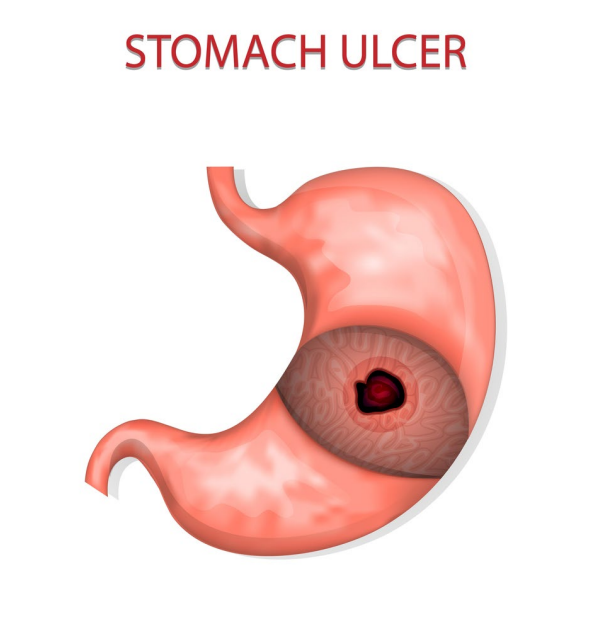
Stress Causes “Leaky Gut”

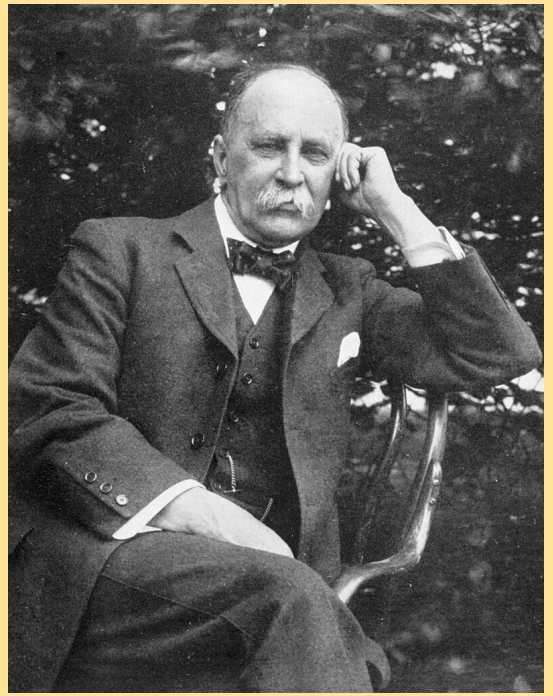
Lance Baumgard PhD
Distinguished Professor
Jacobson Professor of Nutritional Physiology
Iowa State University
Baumgard@iastate.edu

Department of Animal Science

Stress

- In the late 19th and early 20th centuries, physicians observed an increased incidence of gastric ulcers in soldiers and proposed that the extreme psychological stress of combat was the cause (Osler, 1925).





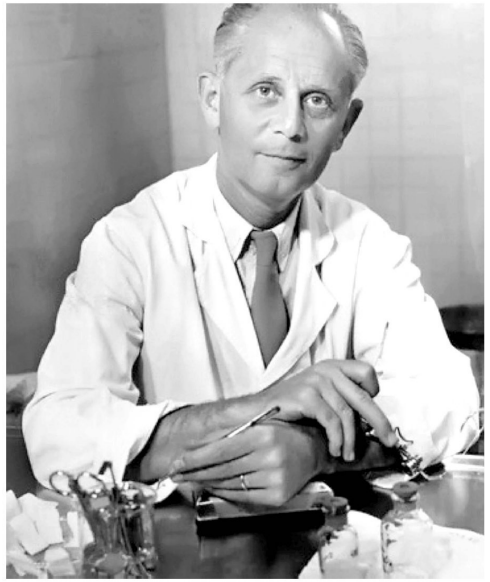
William Osler

Stress

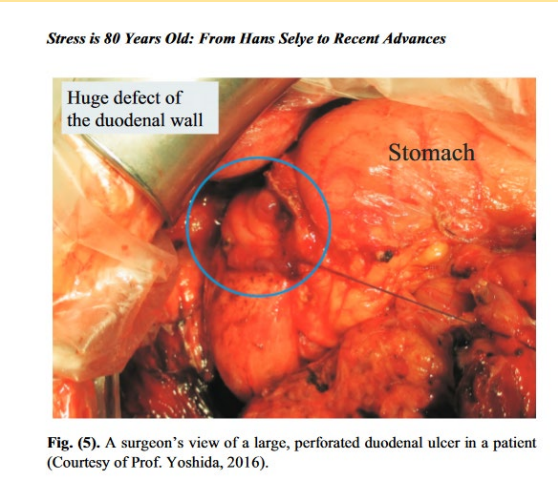
"The nonspecific response of the body to any demand."

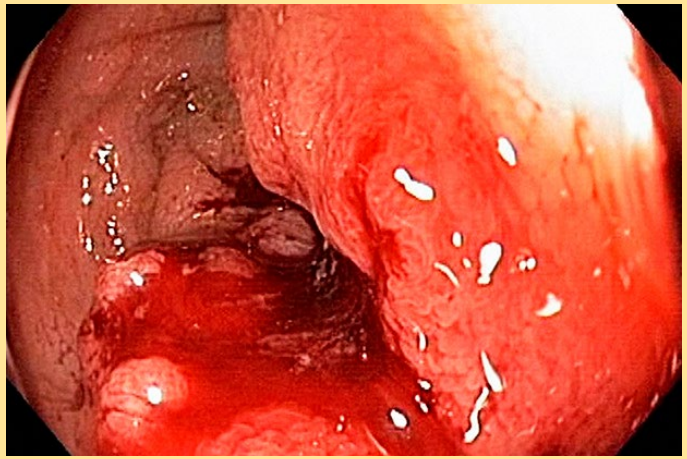
"Maintaining an internal physiological balance through homeostasis can not by itself ensure the stability of body systems under stress."

"Similar stress response to different potentially harmful stimuli."

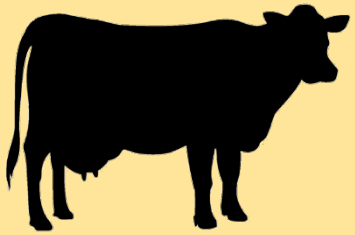


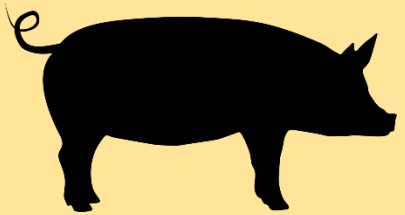
Hans Selye, 1936





Stressors: Intestinal Derived Immune Activation and Inflammation





Feed Restriction

Transition Period

Heat Stress

Rumen Acidosis

Hind Gut Acidosis

Mycotoxins & Enteric Pathogens

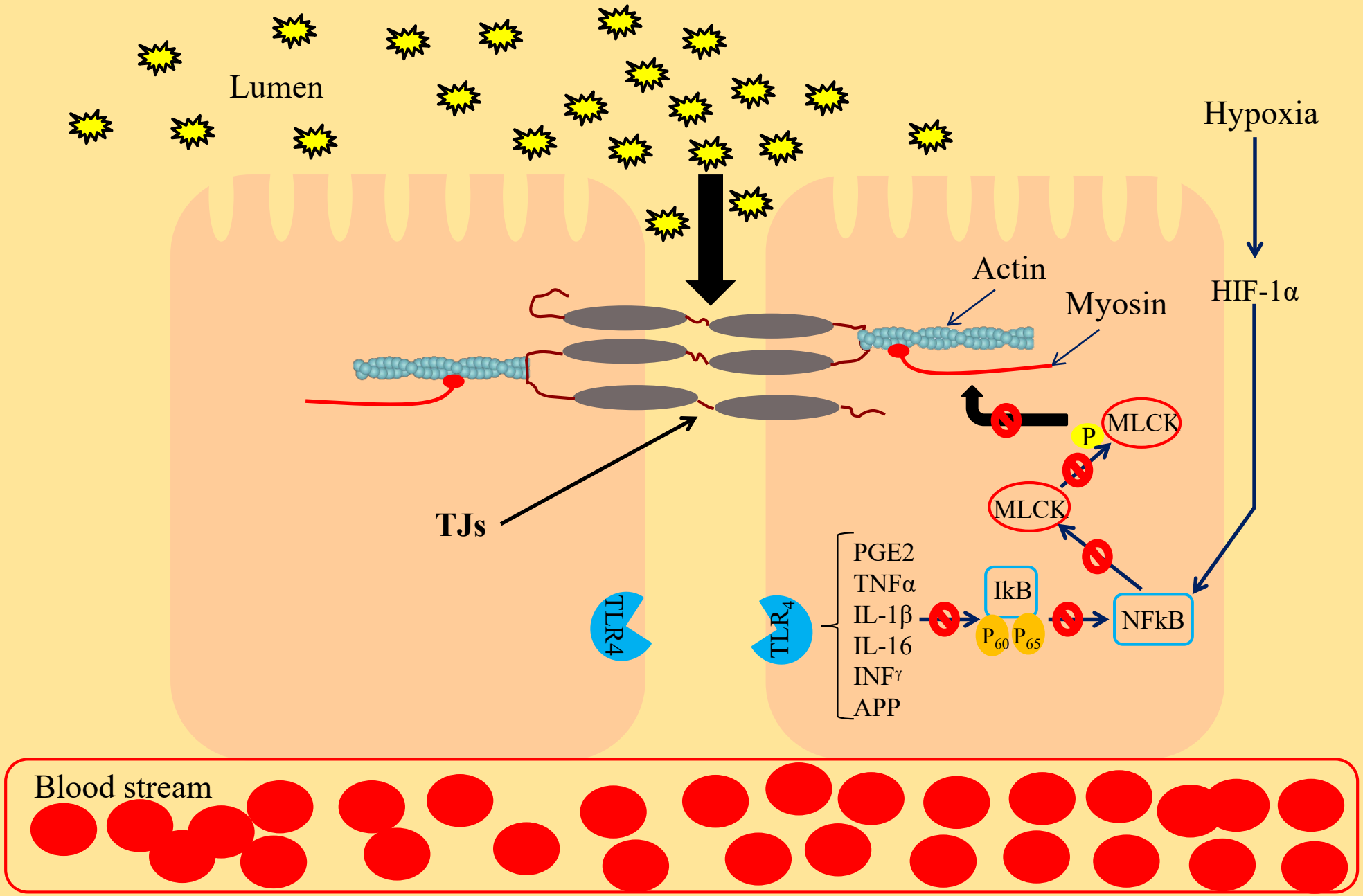
LEAKY GUT

Metabolic Response

Immuno-metabolic Response

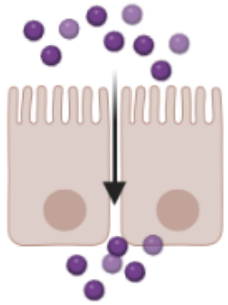
Endocrine Response

↓ Production (Meat, Milk, Eggs, etc.)

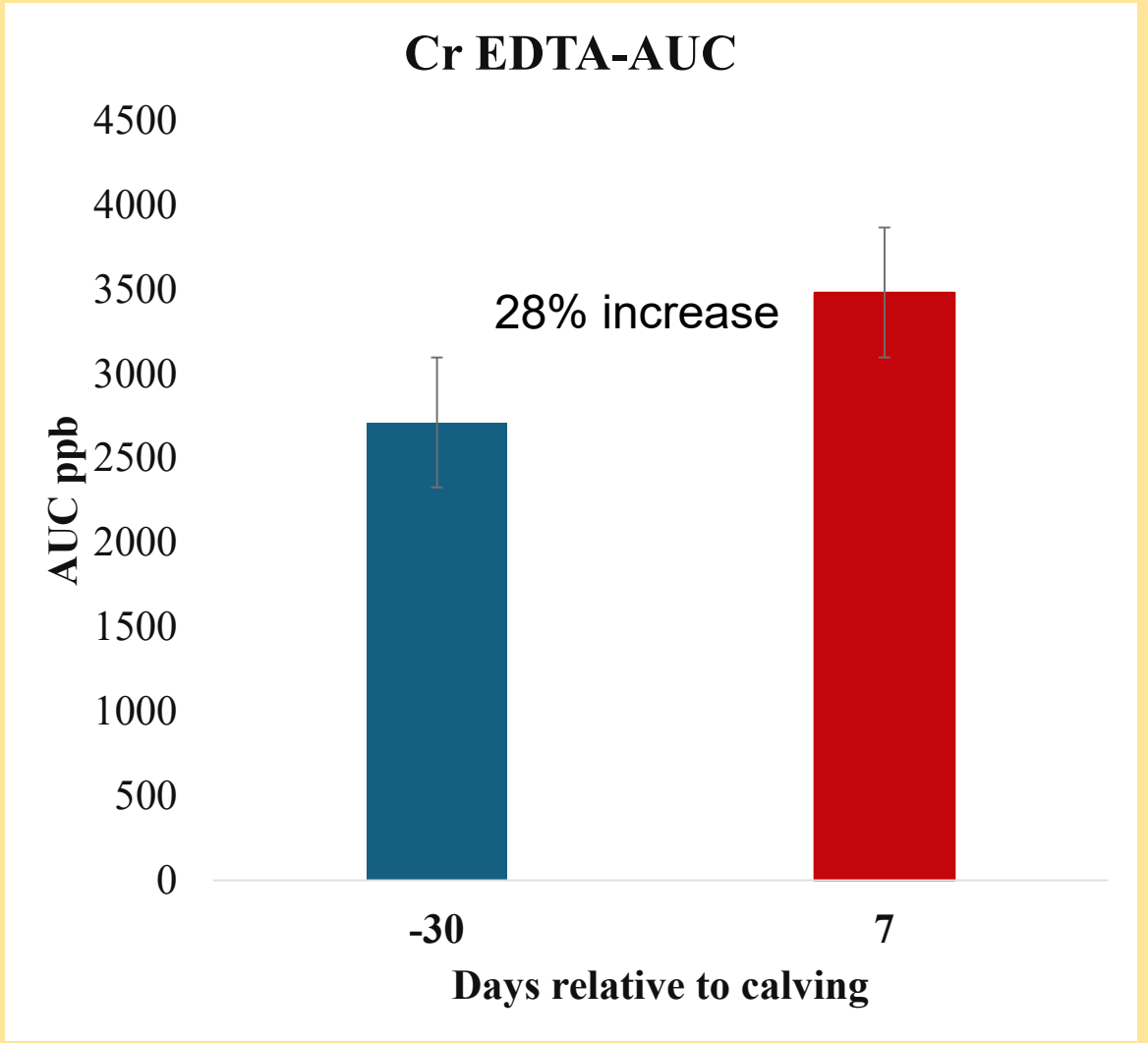

Lumen
Hypoxia
Actin
Myosin
HIF-1α
TJs
MLCK
P
MLCK
TLR4
TLR4
PGE2
TNFα
IL-1β
IL-16
INFγ
APP
IkB
P60 P65
NFkB
Blood stream
Submucosa

GIT Permeability Increases Post Calving

Professor Michael Steele



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

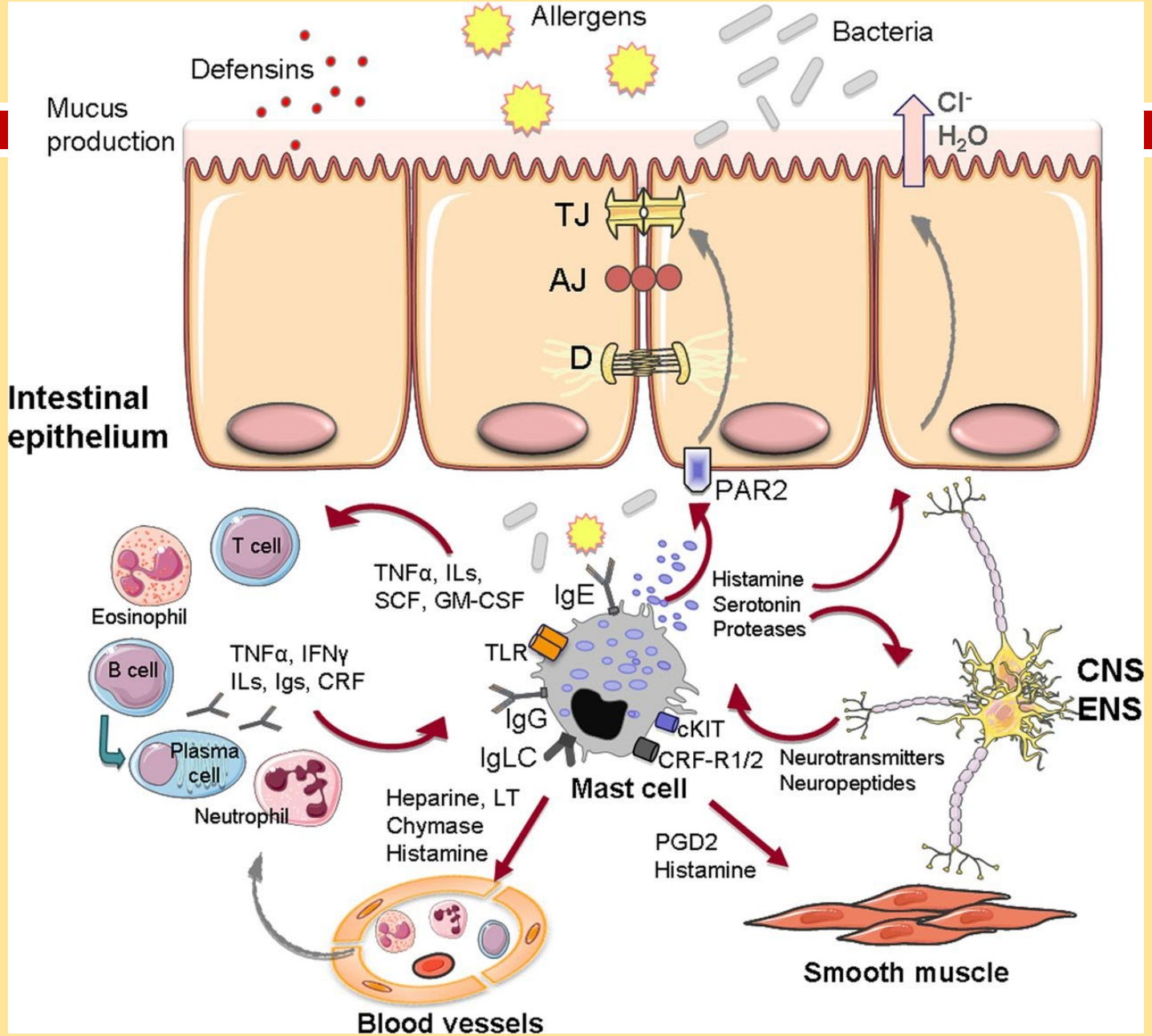


Jantzi et al. (Unpublished data)

Documented Stressors that Cause Leaky Gut

- Heat
- Weaning
- Hunger/feed restriction
- Noise
- Public Speaking
- Cold
- Neonate-Maternal Separation

- How can such different stressors all cause leaky gut???
- They are all psychological



http://gut.bmj.com/content/65/1/155

Stress Increases GIT Pathogens

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Institut Pasteur

Microbes and Infection 17 (2015) 173–183

www.elsevier.com/locate/micinf

Review

How bacterial pathogens colonize their hosts and invade deeper tissues

David Ribet [a,b,c,*], Pascale Cossart [a,b,c,*]

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Received 25 September 2014; accepted 19 January 2015
Available online 29 January 2015

Abstract

Bacterial pathogens have evolved a wide range of strategies to colonize and invade human organs, despite the presence of multiple host defense mechanisms. In this review, we will describe how pathogenic bacteria can adhere and multiply at the surface of host cells, how some bacteria can enter and proliferate inside these cells, and finally how pathogens may cross epithelial or endothelial host barriers and get access to internal tissues, leading to severe diseases in humans.
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Keywords: Bacterial invasion; Bacterial adhesion; Microbiota; Host barrier; Host–pathogen interactions; *Listeria*

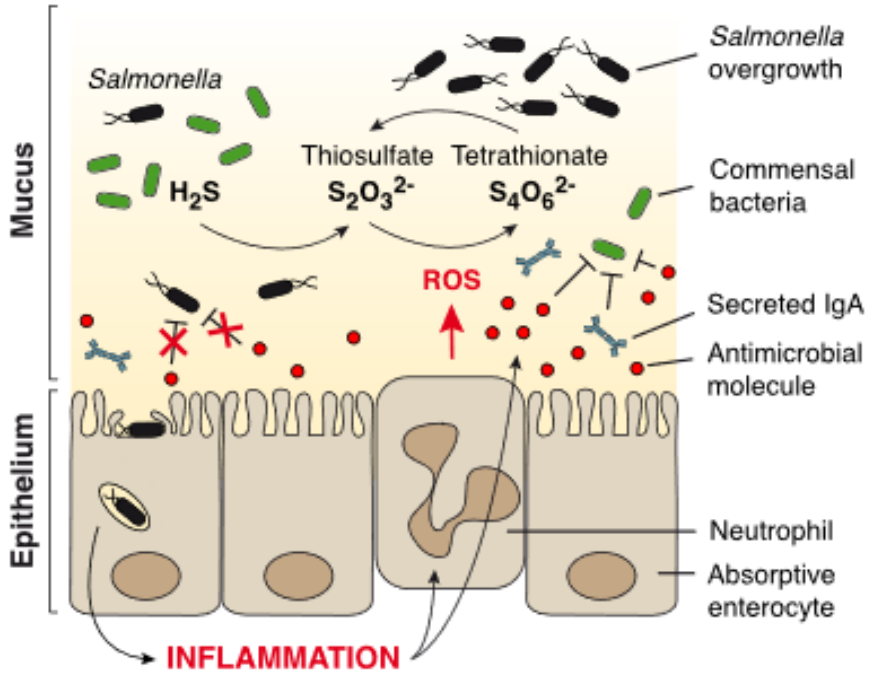

Fig. 2. Schematic representation of events leading to *Salmonella* overgrowth in the intestine. Invasion of intestinal epithelial cells by *Salmonella* triggers an inflammatory response leading to the release of antimicrobial peptides and the production of ROS (*R*eactive *O*xygen *S*pecies) by neutrophils. H_2S, a fermentation end product generated by commensal bacteria, is oxidized into thiosulfate by the colonic epithelium and then into tetrathionate by ROS. In contrast to fermenting bacteria of the microbiota, *Salmonella* can use this tetrathionate as a terminal electron acceptor to support growth in anaerobic conditions. The use of tetrathionate, in addition to *Salmonella* resistance to antimicrobial molecules, allow this pathogen to out-compete commensal bacteria in this inflamed context.

Intestinal epithelium (mainly neutrophils and macrophages) create an oxidative environment (via redox) as a defensive strategy. This kills commensal bacterial….but the pathogens have developed oxidative evasion techniques

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Effect of enzymatically hydrolyzed yeast on health and performance of transition dairy cattle

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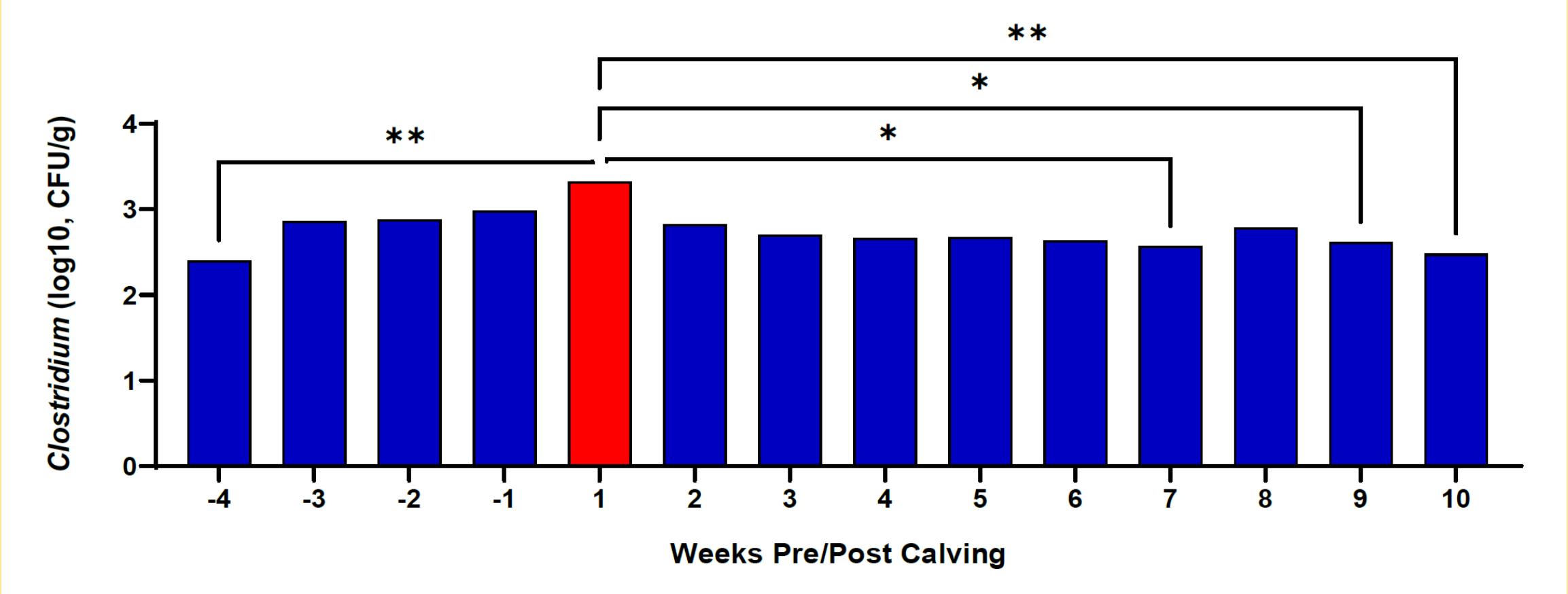
[2]Department of Animal Sciences, Washington State University, Puyallup 98731
[3]Church and Dwight Animal Nutrition, Princeton, NJ 08543

Transition Cow *Clostridia* shedding



Stefenoni et al., 2020; JDS 103: 1541-1552

Practical Strategies: Management, Nutritional and Veterinary

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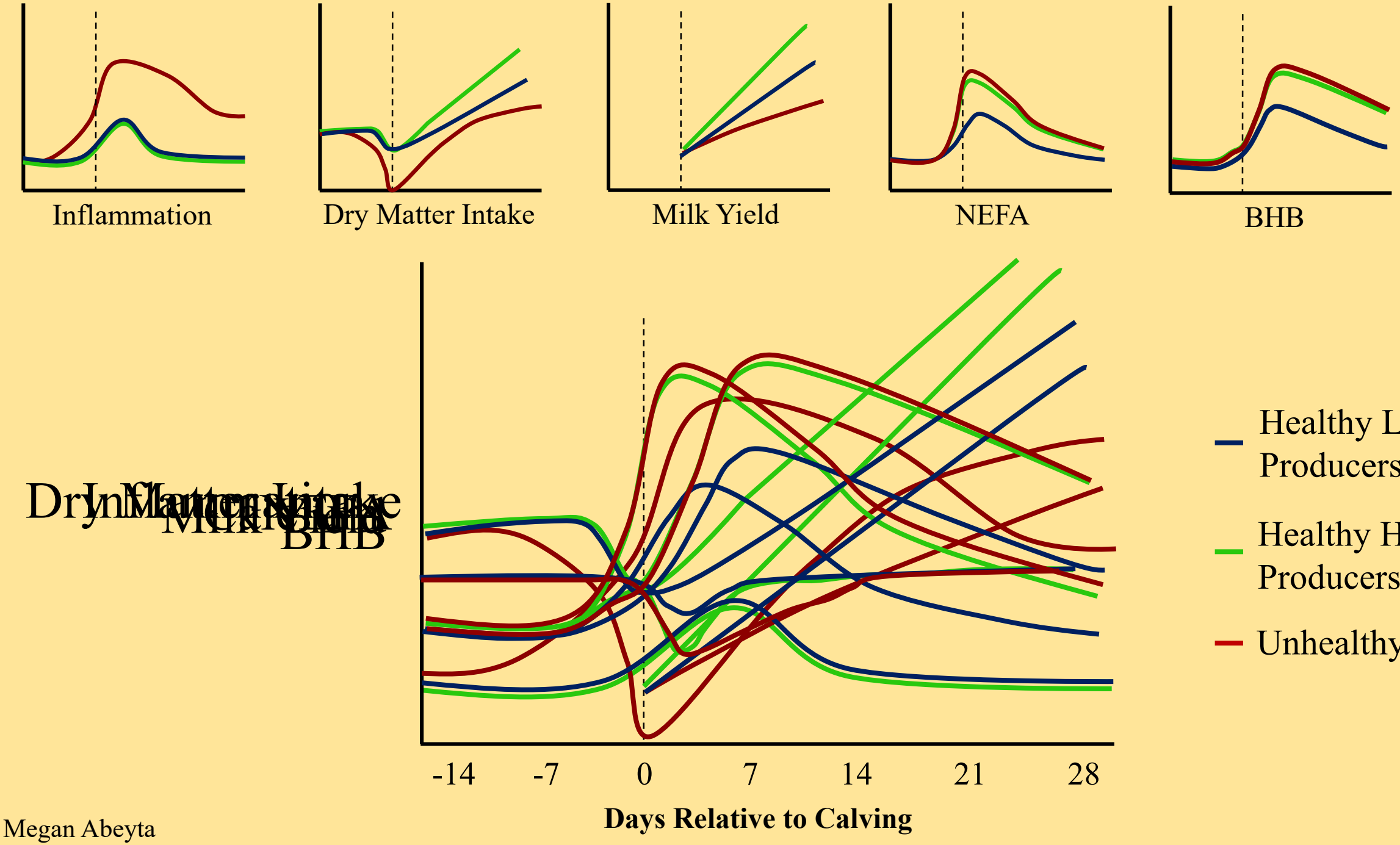
Department of Animal Science



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

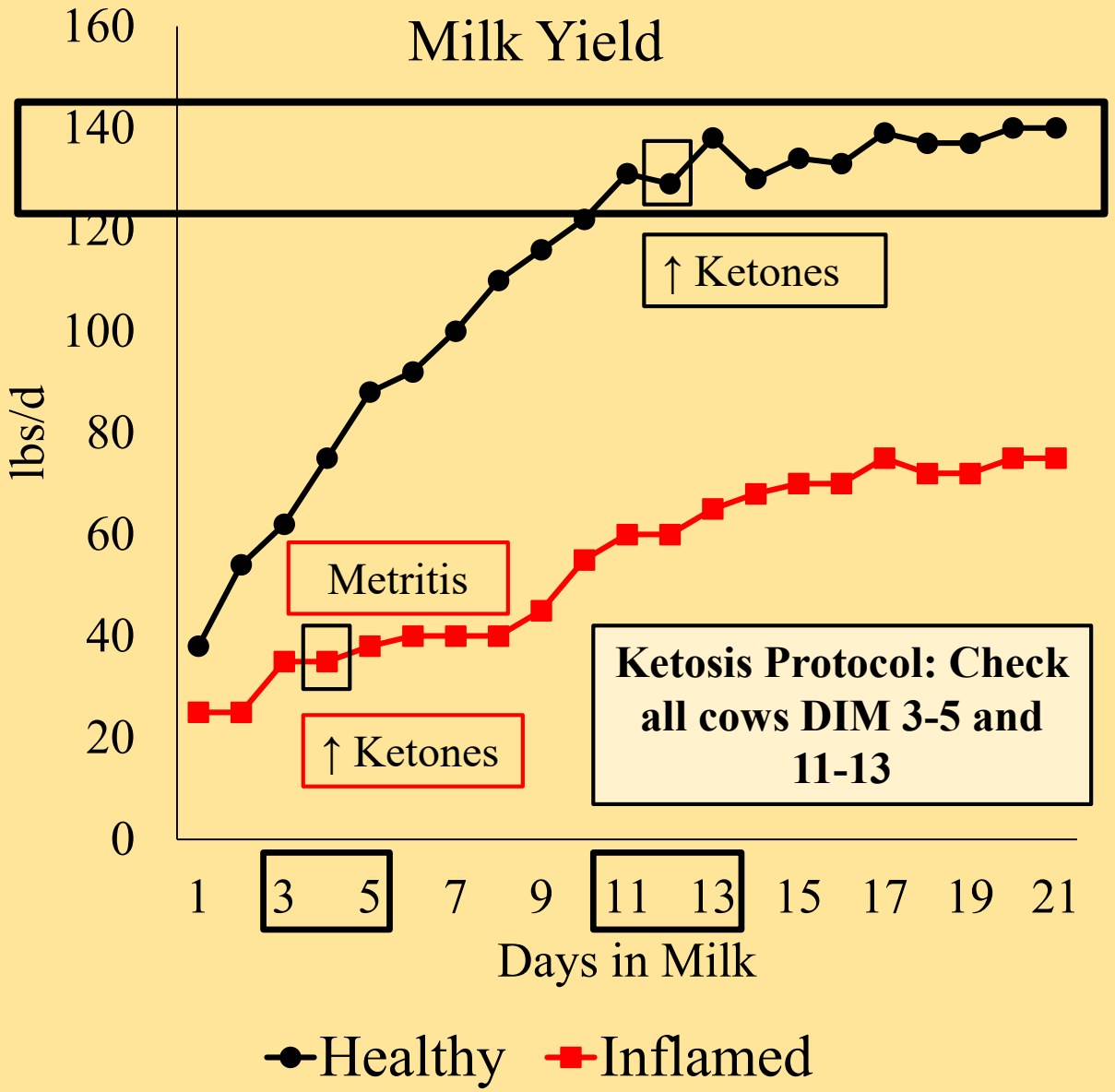
But treating with energy does nothing to address the real problem…..somewhere…..immune-activation is putting the clamp on appetite

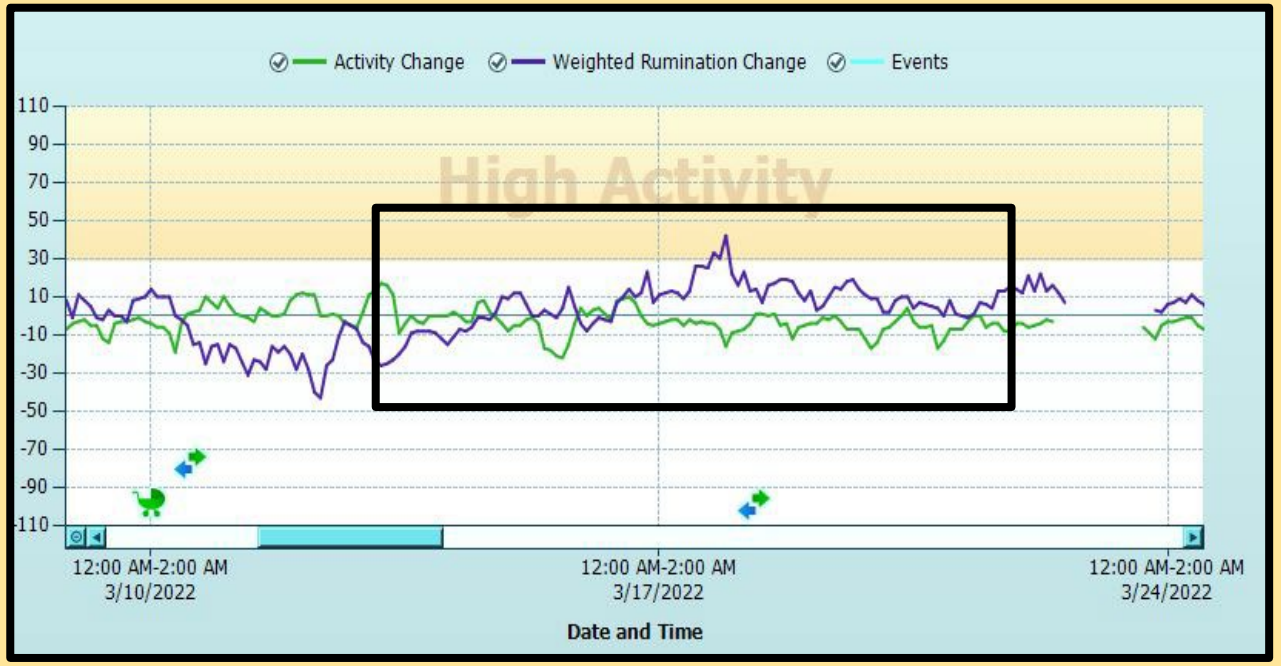
- Don’t mess with
  - High ketones….but she’s eating like a champion
  - Milking like a world-record holder
  - Looks great
  - No fever

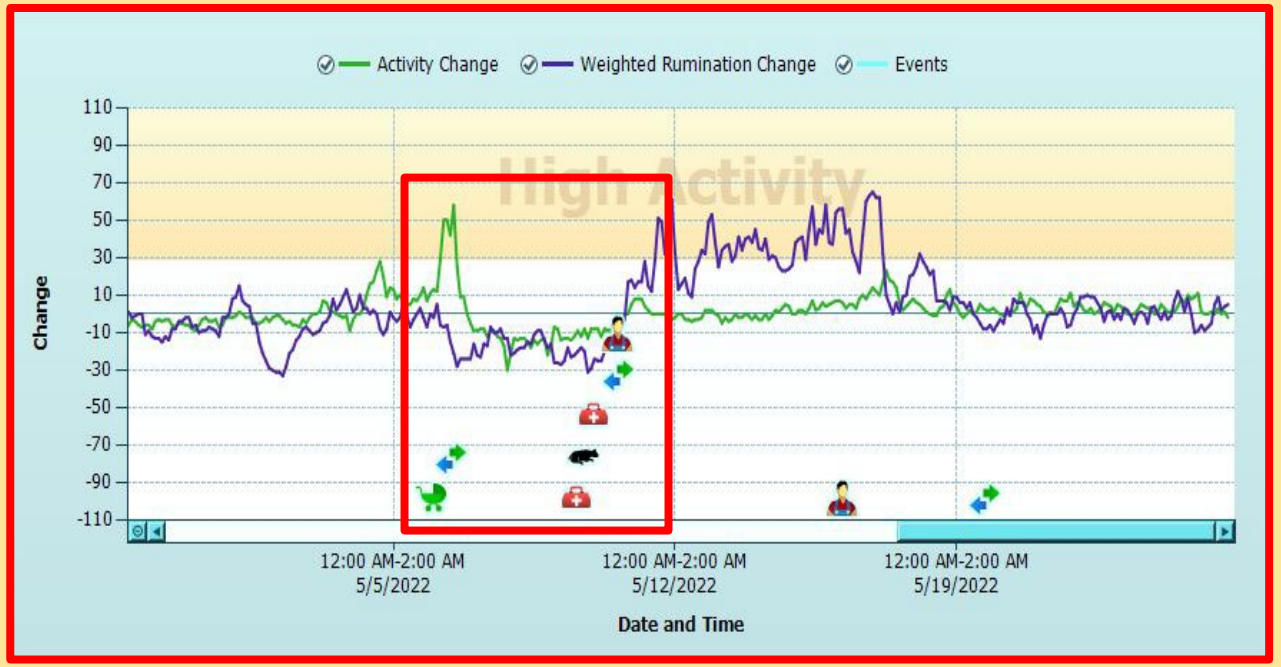
She’s the healthiest cow in the herd

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

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

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

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

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

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

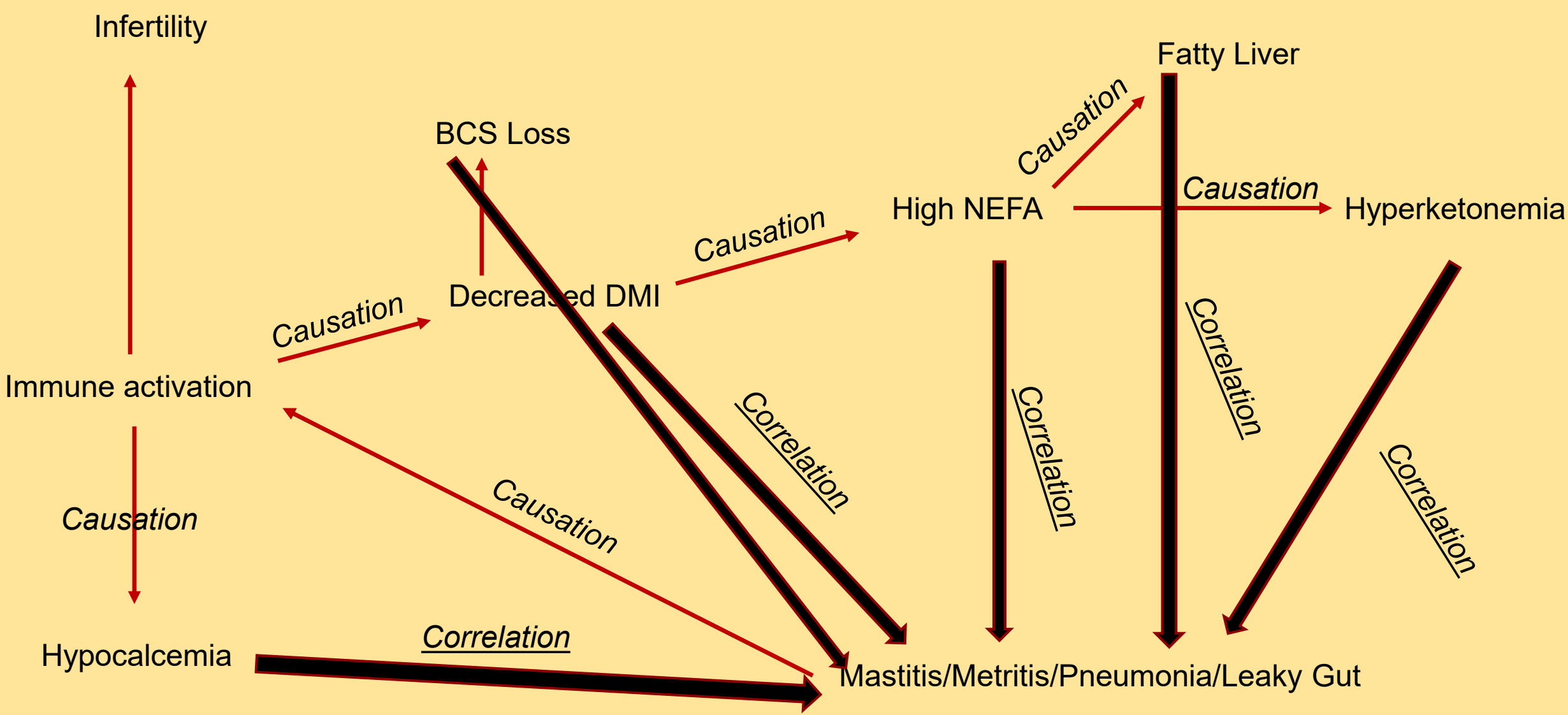
Summary: Inflammation and the Transition Period

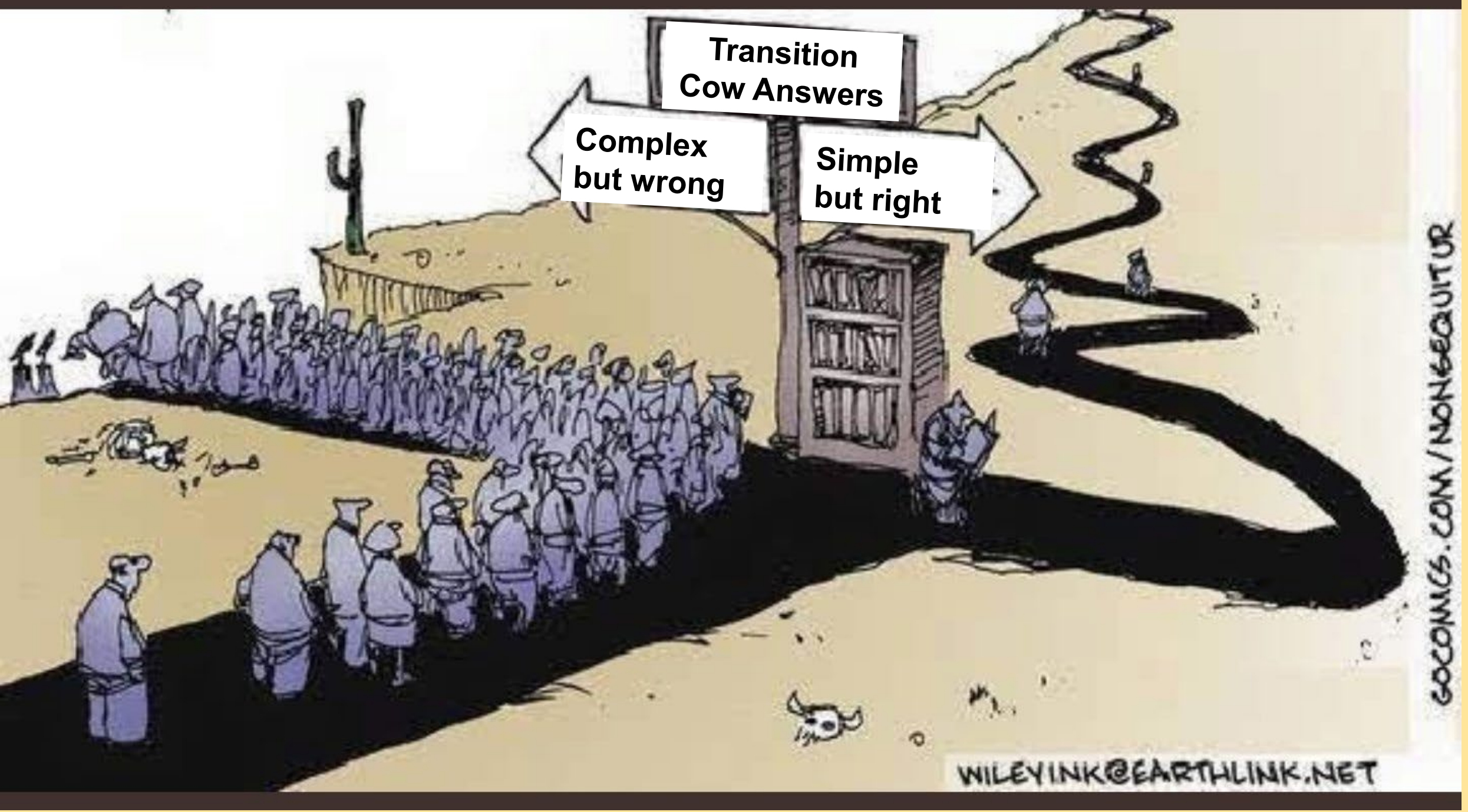
- These metabolic and mineral changes are not “dysfunctional”
- They are required to prioritize survival or required for maximum productivity
  - They aren’t to blame (they’re not the cause) for poor productivity
- Our efforts should be in preventing immune activation in the first place
  - Management
    - 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

Causation vs. Correlation: transition cow perspective




Transition
Cow Answers
Complex
but wrong
Simple
but right
WILEYINK@EARTHLINK.NET
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USDA NIFA United States Department of Agriculture National Institute of Food and Agriculture

- Industry Partners

- ADM
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