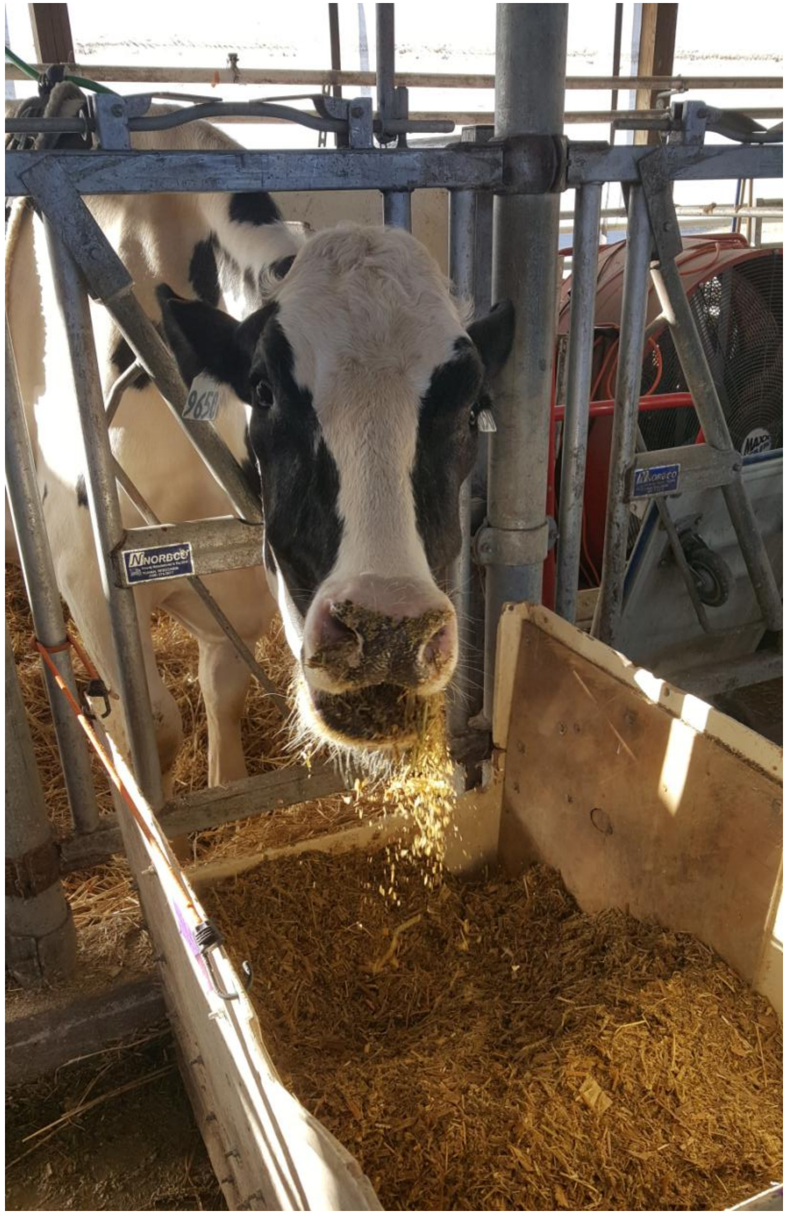
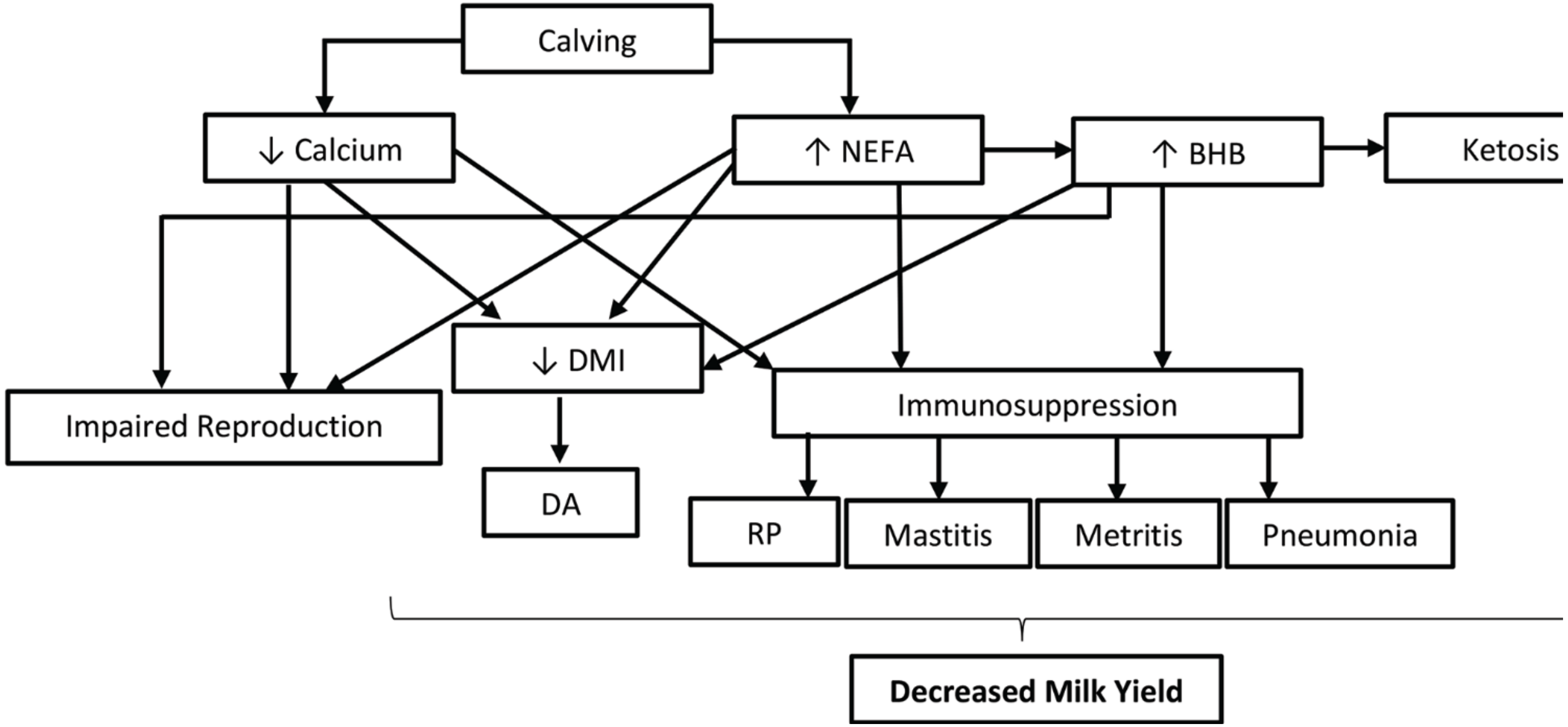




KETOSIS IN DAIRY COWS

DISEASE OR SYMPTOM OF ANOTHER PROBLEM?

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

- Cows with any health disorder around calving produce 7.2 kg (16 lb) less milk per day during the first 20 days in milk[1]

TABLE 1. Mean and range for incidence of selected periparturient health disorders in 61 herds of high producing dairy cows.[1]

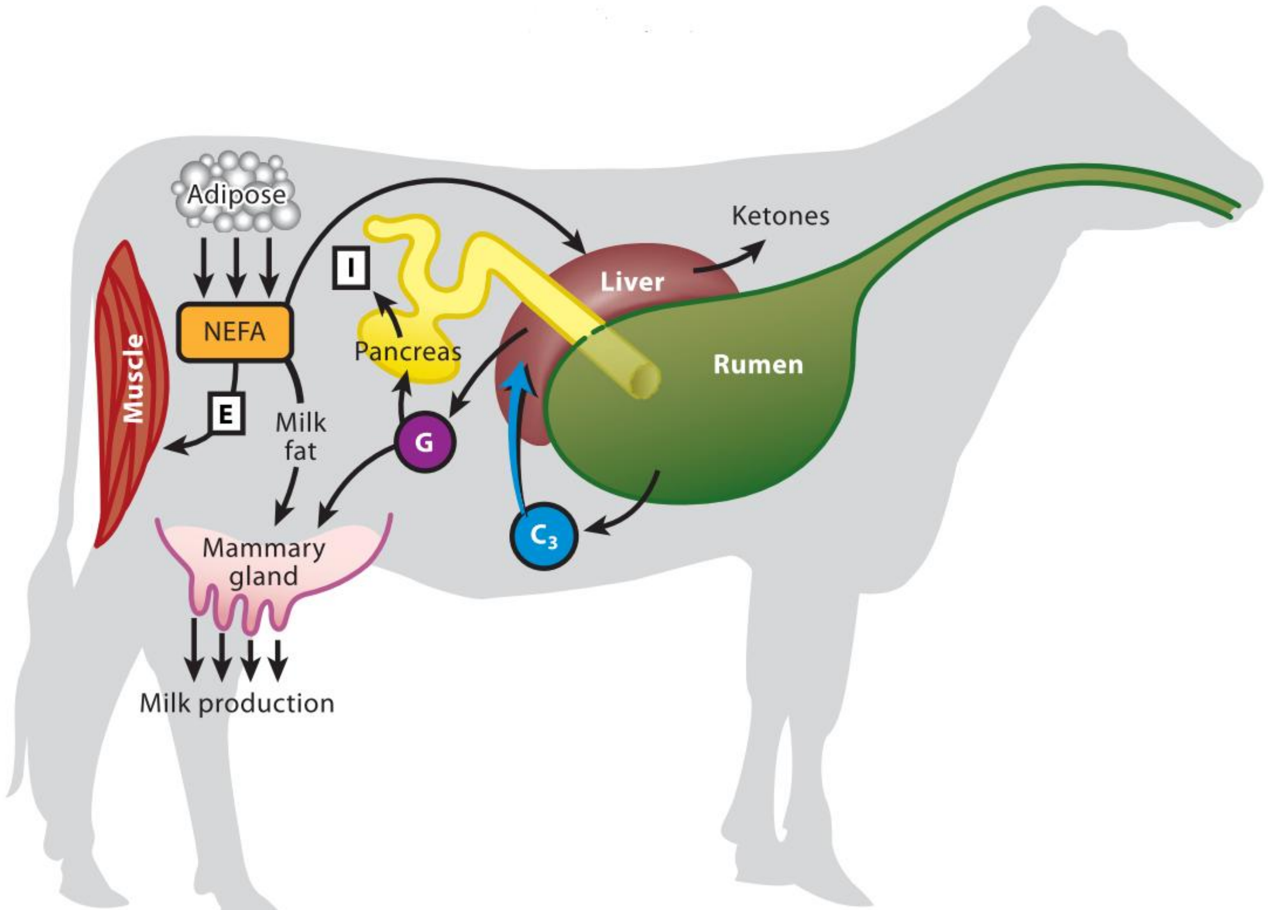
Disorder	Mean (%)	Range (%)
Milk fever	7.2	0 to 44.1
Displaced abomasum	3.3	0 to 14
Ketosis	3.7	0 to 20
Retained fetal membranes	9.0	0 to 22.6
Metritis	12.8	0 to 66

[1]Adapted from Jordan and Fourdraine (57).

Drackley, J.K. 1999. "ADSA foundation scholar award: Biology of dairy cows during the transition period: The final frontier?" J. Dairy Sci. 82.11: 2259–2273.

Homeorhetic Adaptation

- Homeorhesis = orchestrated or coordinated control in metabolism of body tissues necessary to support a physiological state[1]
- Mobilization of adipose tissue and conversion of NEFA into ketones is a normal occurrence in the lactating cow

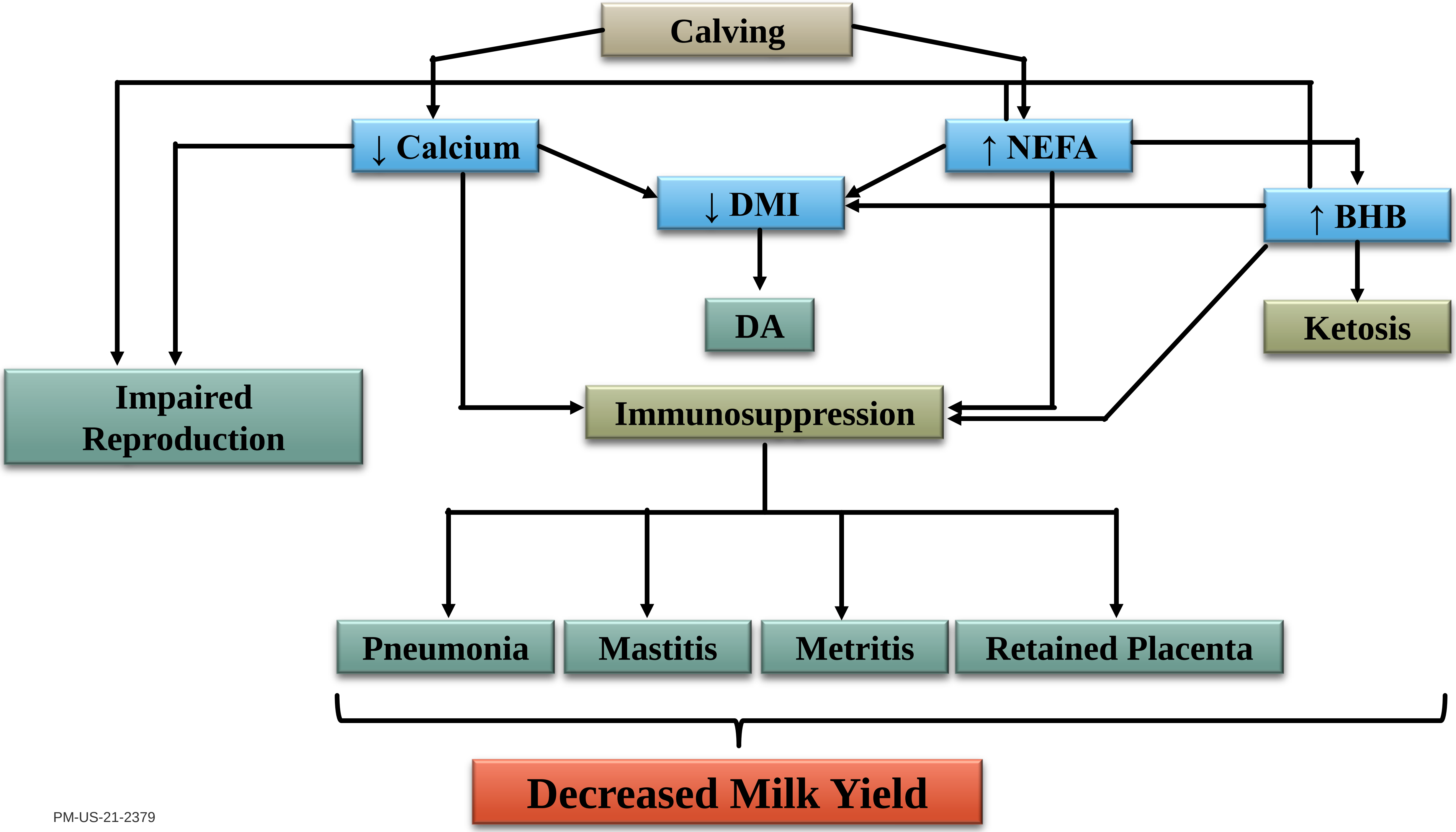


[1]Bauman, D.E. and Currie, B.W. 1980. "Partitioning of nutrients during pregnancy and lactation: a review of mechanisms involving homeostasis and homeorhesis." J. Dairy Sci. 63.9: 1514–1529. Figure from Baumgard, L.H. and Rhoads, R.P. 2013. Effects of heat stress on postabsorptive metabolism and energetics. Annu. Rev. Anim. Biosci. 1.1: 311–337.

Historical Views of Transition Cow Issues

- Many studies **associate** and **correlate** NEFA and BHBA with increased risk of ketosis, decreased milk yield, displaced abomasum, metritis, retained placenta, laminitis, or poor reproduction[1,2,3,4,5]
- **Traditional Belief: Increased NEFA, hyperketonemia, and hypocalcemia cause transition cow health and production problems**
- Increased plasma NEFA following calving occurs in all cows and is an important energy source
  - 15-20% get clinical ketosis…what makes them more susceptible?

[1]Chapinal, N. et al. 2011. "The association of serum metabolites with clinical disease during the transition period." J. Dairy Sci. 94: 4897-4903.
[2]Ospina, P.A. et al. 2010. "Evaluation of nonesterified fatty acids and β-hydroxybutyrate in transition dairy cattle in the northeastern United States: Critical thresholds for prediction of clinical disease." J. Dairy Sci. 93: 546-554.
[3]Huzzey, J.M. et al. 2011. "Associations of prepartum plasma cortisol, haptoglobin, fecal cortisol metabolites, and nonesterified fatty acids with post partum health status in Holstein dairy cows." J. Dairy Sci. 94: 5878-5889.
[4]Duffield et al. 2009. "Impact of hyperketonemia in early lactation dairy cows on health and production." J. Dairy Sci. 92: 571-580.
[5]LeBlanc et al. 2005. "Metabolic predictors of displaced abomasum in dairy cattle." J. Dairy Sci. 88: 159-170.


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

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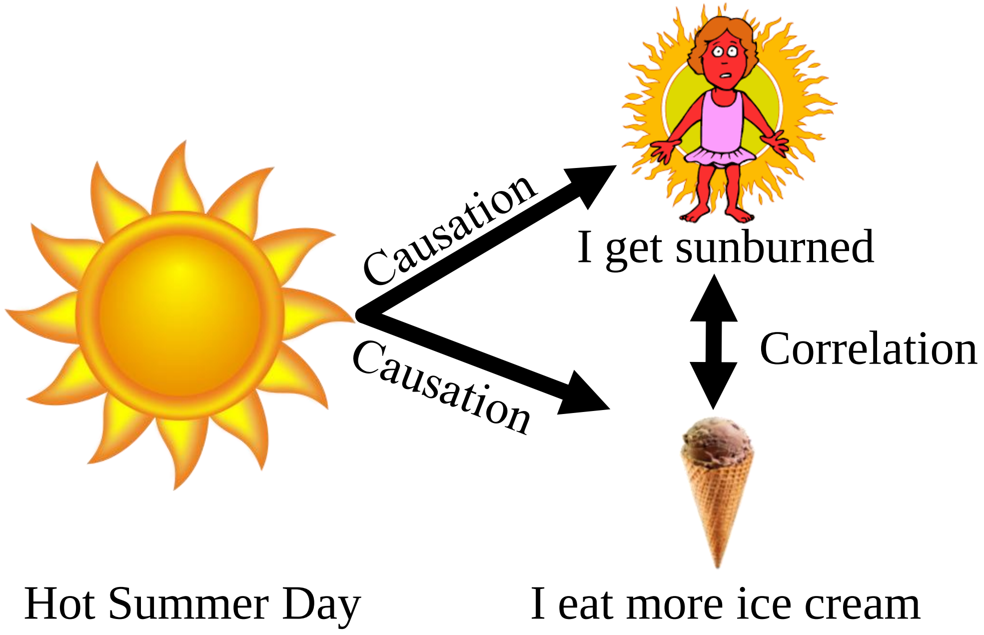
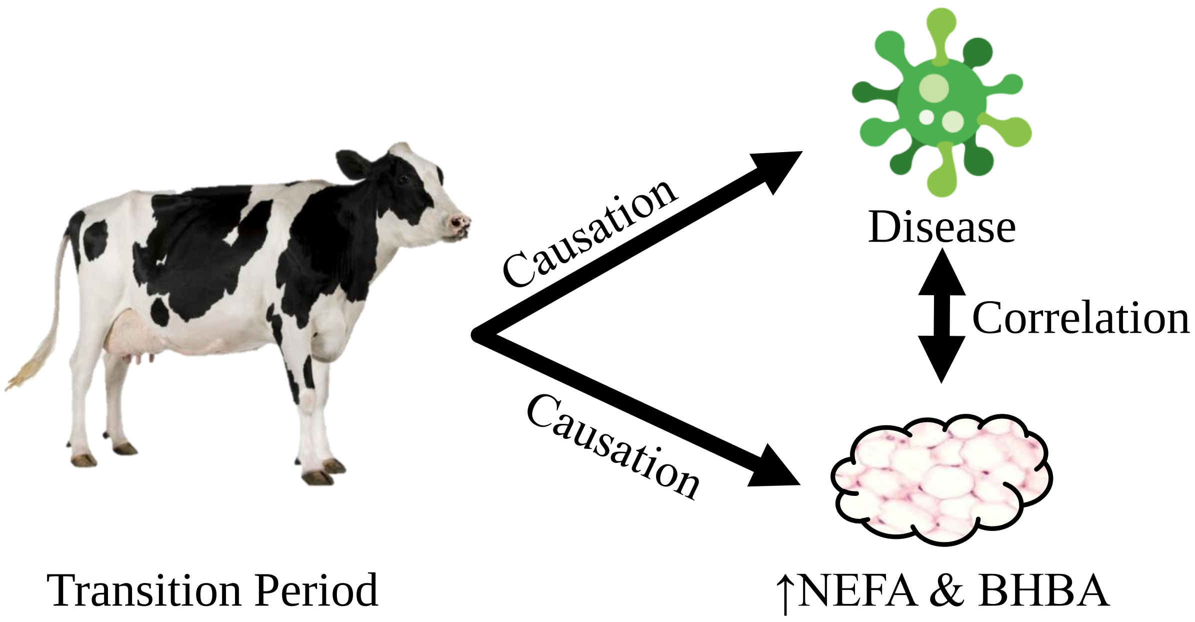
Challenges to the Dogma

1. Correlation ≠ Causation	NEFA and BHBA are correlated with negative outcomes, but this does not mean they are causing the problem
2. Immunosuppresion is Complex	The immune system is in every tissue…are we measuring and extrapolating things correctly?
3. NEBAL and BW Loss During Lactation are Normal	Adipose tissue mobilization to support lactation is a highly conserved response across species.
4. NEFA and BHBA Do Not Directly Inhibit Feed Intake	If NEFA and BHBA mechanistically decreased intake, a starving animal would have no appetite.
5. High-Producing Cows are Hypoinsulinemic	Low insulin levels and insulin resistance at muscle and adipose spare glucose for milk synthesis
6. The Confusing Insulin Status of Ketosis	Despite reduced intake, ketotic cows sometimes have equal or greater circulating insulin compared to healthy controls
7. Inconsistent Success in Treating Ketosis	Propylene glycol treatment has shown both positive and no effect on milk yield

Correlation ≠ Causation

- Observational studies correlate ↑NEFA and BHBA with negative outcomes[1,2], but there are also studies showing no correlation[3,4], or correlation with better milk yield[5,6]

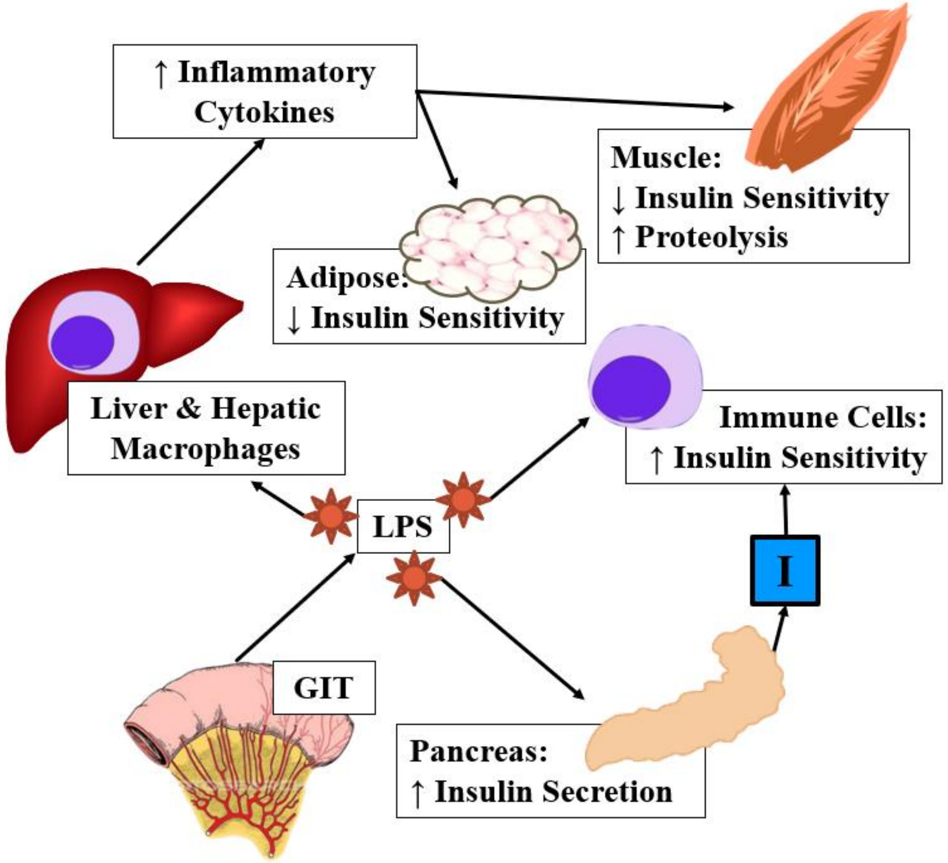




[1]Chapinal, N. et al. 2011. “The association of serum metabolites with clinical disease during the transition period.” J. Dairy Sci. 94: 4897-4903.
[2]Ospina, P.A. et al. 2010. “Evaluation of nonesterified fatty acids and β-hydroxybutyrate in transition dairy cattle in the northeastern United States: Critical thresholds for prediction of clinical disease.” J. Dairy Sci. 93: 546-554.
[3]Abdelli, A. et al. 2017. “Elevated non-esterified fatty acid and β-hydroxybutyrate in transition dairy cows and their association with reproductive performance and disorders: A meta-analysis.” Theriogenology. 93: 99-104
[4]McArt, J.A.A. and Neves, R. C. 2020. “Association of transient persistent, or delayed subclinical hypocalcemia with early lactation disease, removal, and milk yield in Holstein cows.” J. Dairy Sci. 103: 690-701.
[5]Lean, I.J. et al. 1994. “Bovine ketosis and somatotrophin: Risk factors for ketosis and effects of ketosis on health and production.” Res. Vet. Sci. 57: 200-209.
[6]Bach, K.D. et al. 2019. “Association of mid-infrared-predicted milk and blood constituents with early lactation disease, removal, and production outcomes in Holstein cows.” J. Dairy Sci. 102: 10129-10139.

Immunosuppresion is Complex

- Effects of NEFA, BHBA, and Ca on immune cells are inconsistent[1,2]
- Do *in vitro* results translate to whole-animal biology?
- Immune cells in blood vs. immune cells in tissue?
- Is "immunosuppression" partly needed to prevent too much inflammation?



[1]Horst, E.A. et al. 2021. "Invited review: The influence of immune activation on transition cow health and performance—A critical evaluation of traditional dogmas." J. Dairy Sci. 104: 8380-8410.
[2]LeBlanc, S.J. 2020. "Review: Relationships between metabolism and neutrophil function in dairy cows in the peripartum period." Animal. 14: S44–S54.

NEBAL and BW Loss During Lactation are Normal

Bears

- Rely heavily on adipose tissue to meet energy needs during lactation[1]

Whales

- Sustain a 6-month lactation with little food, mobilizing ~33% of their fat stores (equivalent to 16 tons of body weight)[1]

Seals

- >90% of the energy requirements for lactation are powered by lipid stores[2]
- Commonly lose 50% of their body fat reserves[2]

Deer

- Rely on body reserves to support lactation, even during ad libitum feeding[3]

[1]Oftedal, O.T. 2000. "Use of maternal reserves as a lactation strategy in large mammals." Proc Nutr. Soc. 59: 99-206.
[2]Crocker, D.E. et al 2014. "Adiposity and fat metabolism in lactating and fasting northern elephant seals." Adv. Nutr. 5: 57–64.
[3]Sadleir, R.MF.S. 1982. "Energy consumption and subsequent partitioning in lactating black-tailed deer." Can. J. Zool. 60: 382-386.

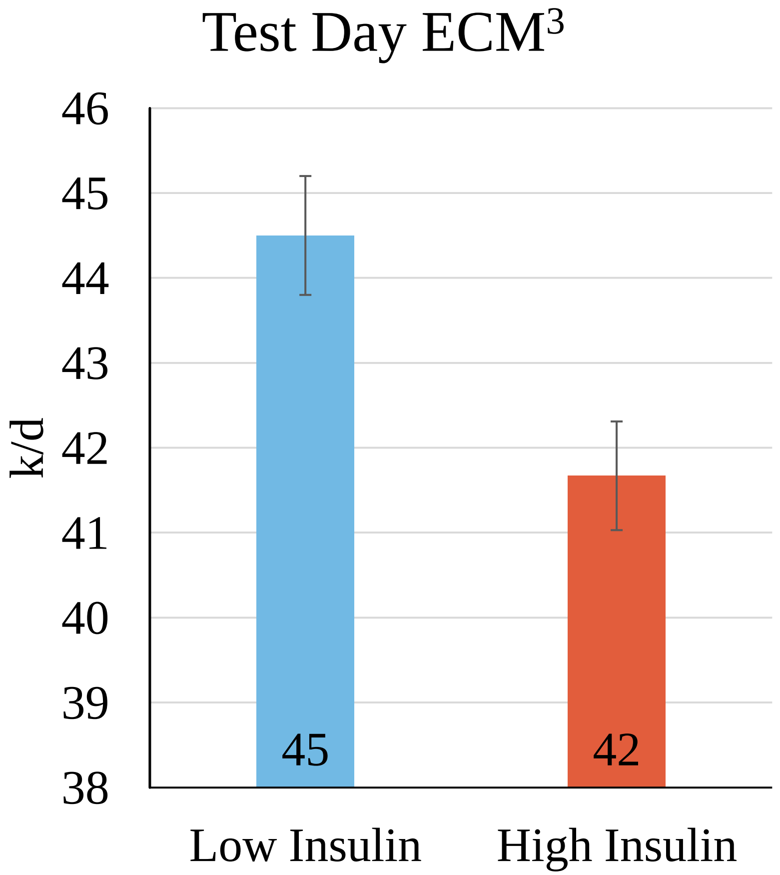
NEFA and BHBA Do Not Directly Inhibit Feed Intake

- The idea that NEFA and BHBA inhibit intake is mostly based on correlation in observational studies
- Inconsistent effects
  - Intravenous BHBA infusion has shown to decrease[1], increase[2], and not affect[3] feed intake
- Appetite regulation is a complex topic
- If NEFA and BHBA decreased intake, a starving animal would have no appetite
- Inflammation consistently decreases intake[4]

[1]Swartz, T.H. et al. 2021. "Connecting metabolism to mastitis: Hyperketonemia impaired mammary gland defense during a *Streptococcus uberis* challenge in dairy cattle." Front Immunol. 12: 1-12.
[2]Carneiro, L. et al. 2016. "Evidence for hypothalamic ketone body sensing: Impact on food intake and peripheral metabolic responses in mice." Am. J. Physiol. Endocrinol. Metab. 310: E103-E115.
[3]Zarrin, M. et al. 2013. "Long-term elevation of β-hydroxybutyrate in dairy cows through infusion: Effects on feed intake, milk production, and metabolism." J. Dairy Sci. 96: 2960-2972.
[4]Bradford, B.J. and Brown, W.E. 2021. "Invited review: Mechanisms of hypophagia during disease." J. Dairy Sci. 104 (In Press).

High-Producing Cows are Hypoinsulinemic

- Low insulin levels spare glucose for milk synthesis via mobilization of adipose tissue[1]
- Higher producing cows are more hypoinsulinemic than low producing cows[2]
- Periparturient insulin concentrations are inversely related to whole lactation performance[3]
- Insulin clearance is increased by genetic selection for milk yield[4]
- Administering insulin decreases milk yield[5]



[1]Bauman, D.E. and Currie, B.W. 1980. "Partitioning of nutrients during pregnancy and lactation: a review of mechanisms involving homeostasis and homeorhesis." J. Dairy Sci. 63.9: 1514–1529.
[2]Hart, I.C. 1979. "Endocrine control of energy metabolism in the cow: Correlations of hormones and metabolites in high and low yielding cows for stages of lactation." J. Dairy Sci. 62: 270-277.
[3]Zinicola, M. and Bicalho, R.C. 2019. "Association of peripartum plasma insulin concentration with milk production, colostrum, insulin levels, and plasma metabolites of Holstein cows." J. Dairy Sci. 102: 1473-1482.
[4]Barnes, M.A. et al. 1985. "Influence of secretion for milk yield on endogenous hormones and metabolites in Holstein heifers and cows." J. Anim. Sci. 60: 271-284.
[5]Kronfeld, D.S. et al. 1963. "Depression of milk secretion during insulin administration." J. Dairy Sci. 46: 559-563.

The Confusing Insulin Status of Ketotic Cows

- Type I Ketosis[1]
  - Underfeeding, glucose shortage
  - **Low insulin**
  - Excellent prognosis
- Type II Ketosis[1]
  - Fat cows
  - **High insulin**
  - Poor prognosis
- Low dry matter intake should result in low insulin
- Ketotic cows with low dry matter intake sometimes have similar[2] or increased[3] levels of insulin compared to healthy herdmates
- Immune activation is also characterized by hyperinsulinemia[4]

[1]Oetzel, G.R. 2007. "Herd-level ketosis – diagnosis and risk factors." Proc. Of 40th Annual AABP Conference. Pages 67-91.
[2]Oikawa, S. et al. 2019. "Peripartum metabolic profiles in a Holstein dairy herd with alarm level prevalence of subclinical ketosis detected in early lactation." Can. J. Vet. Res. 83: 50-56.
[3]Holtenius, P. and Holtenius, K. 1996. "New aspects of ketone bodies in energy metabolism of dairy cows: A review." Zentralbl. Veterinarmed. A. 43: 579-587.
[4]Horst, E.A. et al. 2021. "Invited review: The influence of immune activation on transition cow health and performance—A critical evaluation of traditional dogmas." J. Dairy Sci. 104: 8380-8410.

Inconsistent Success in Treating Ketosis

Propylene Glycol → More Milk

- McArt et al., 2011
  - 2 out of 3 farms had increase milk yield
- Lomander et al., 2012
- Shankare Gowda et al., 2015

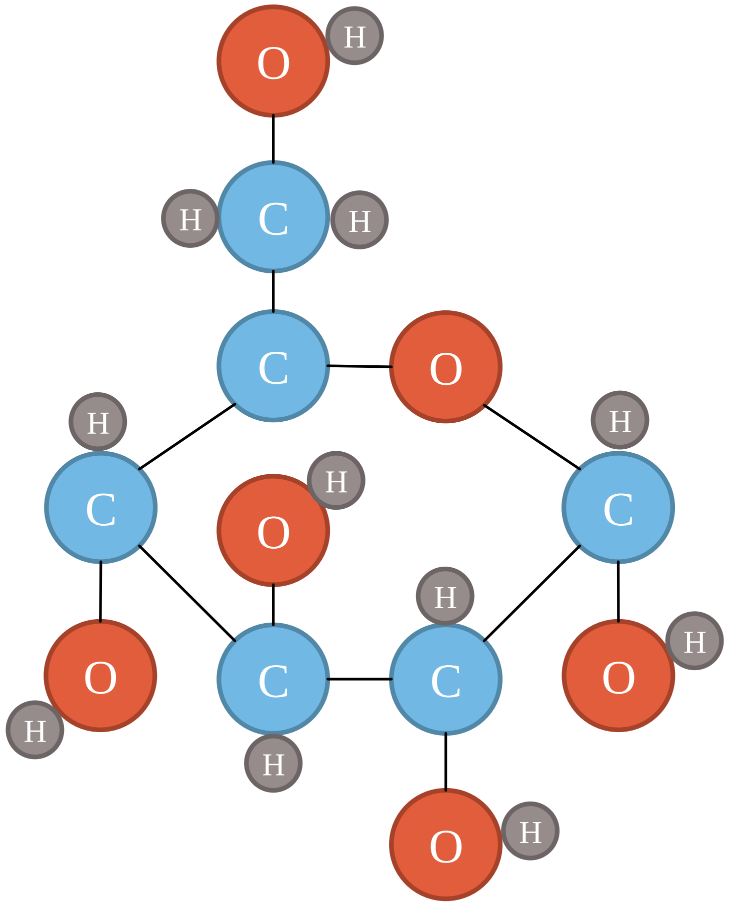
Propylene Glycol → No effect

- Hoedemaker et al., 2004
- Liu et al., 2009
- Bors et al., 2013
- Ostergaard et al., 2020
- Capel et al., 2021

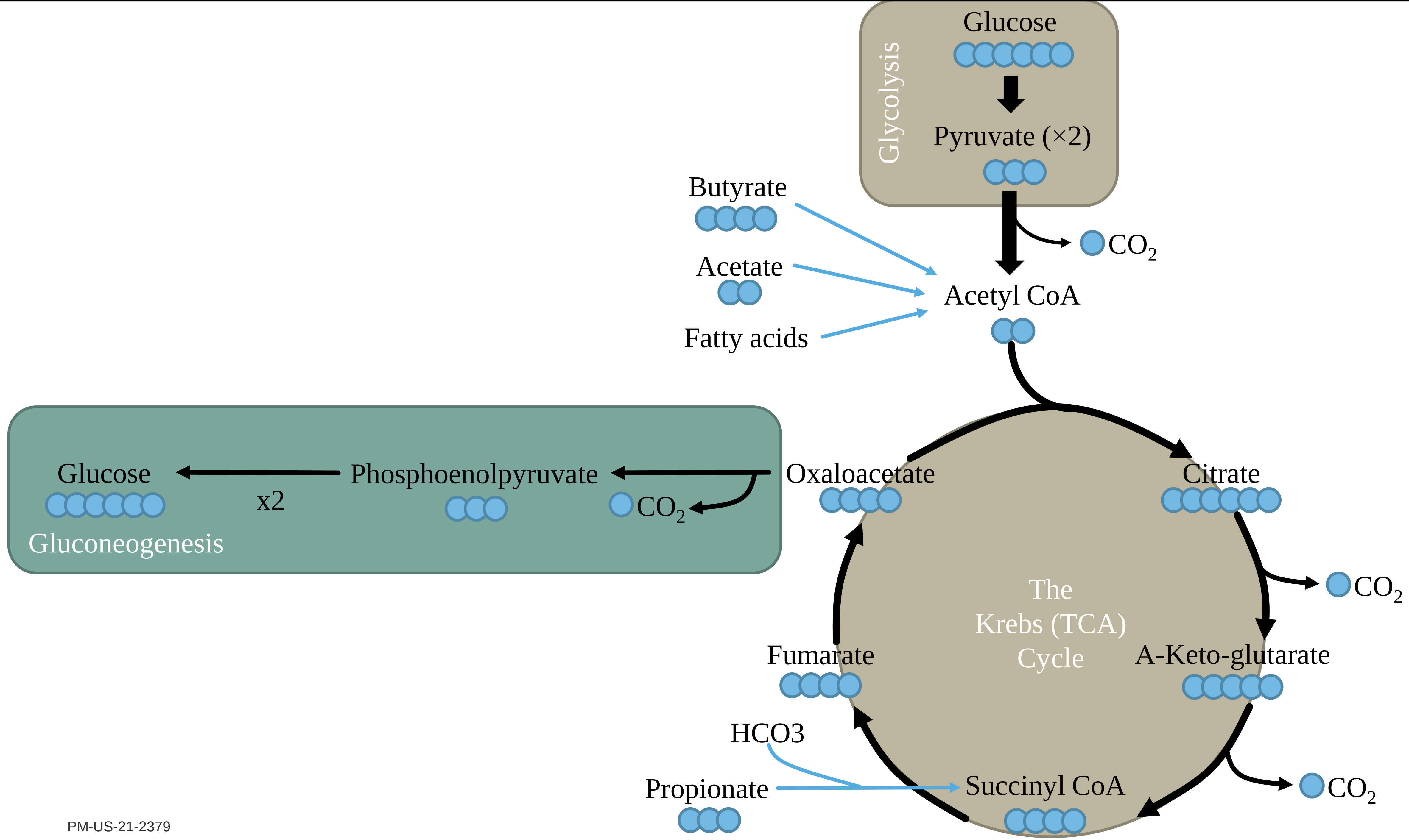
What causes ketosis ?

The Importance of Glucose

- Glucose → Lactose
- Lactose drives milk volume
- For every 1 kg of milk produced, approximately 72 g of glucose is required[1]
- 90% of glucose made by the liver is utilized by the mammary gland in early lactation[2]
- Animals cannot synthesize glucose from fatty acids[3]



[1]Kronfeld, D.S. 1982. "Major metabolic determinants of milk volume, mammary efficiency, and spontaneous ketosis in dairy cows." J. Dairy Sci. 65.11: 2204-2212.
[2]Bell, A.W. 1995. "Regulation of organic nutrient metabolism during transition from late pregnancy to early lactation." J. Anim. Sci. 73.9: 2804-2819.
[3]Berg, J.M. et al. 2007."Fatty Acid Metabolism" Biochemistry 6th Edition. 22: 634.


Glucose
Glycolysis
Pyruvate (×2)
CO_2
Butyrate
Acetate
Fatty acids
Acetyl CoA
Glucose
x2
Phosphoenolpyruvate
CO_2
Oxaloacetate
Citrate
Gluconeogenesis
CO_2
The
Krebs (TCA)
Cycle
Fumarate
A-Keto-glutarate
HCO3
Propionate
Succinyl CoA
CO_2

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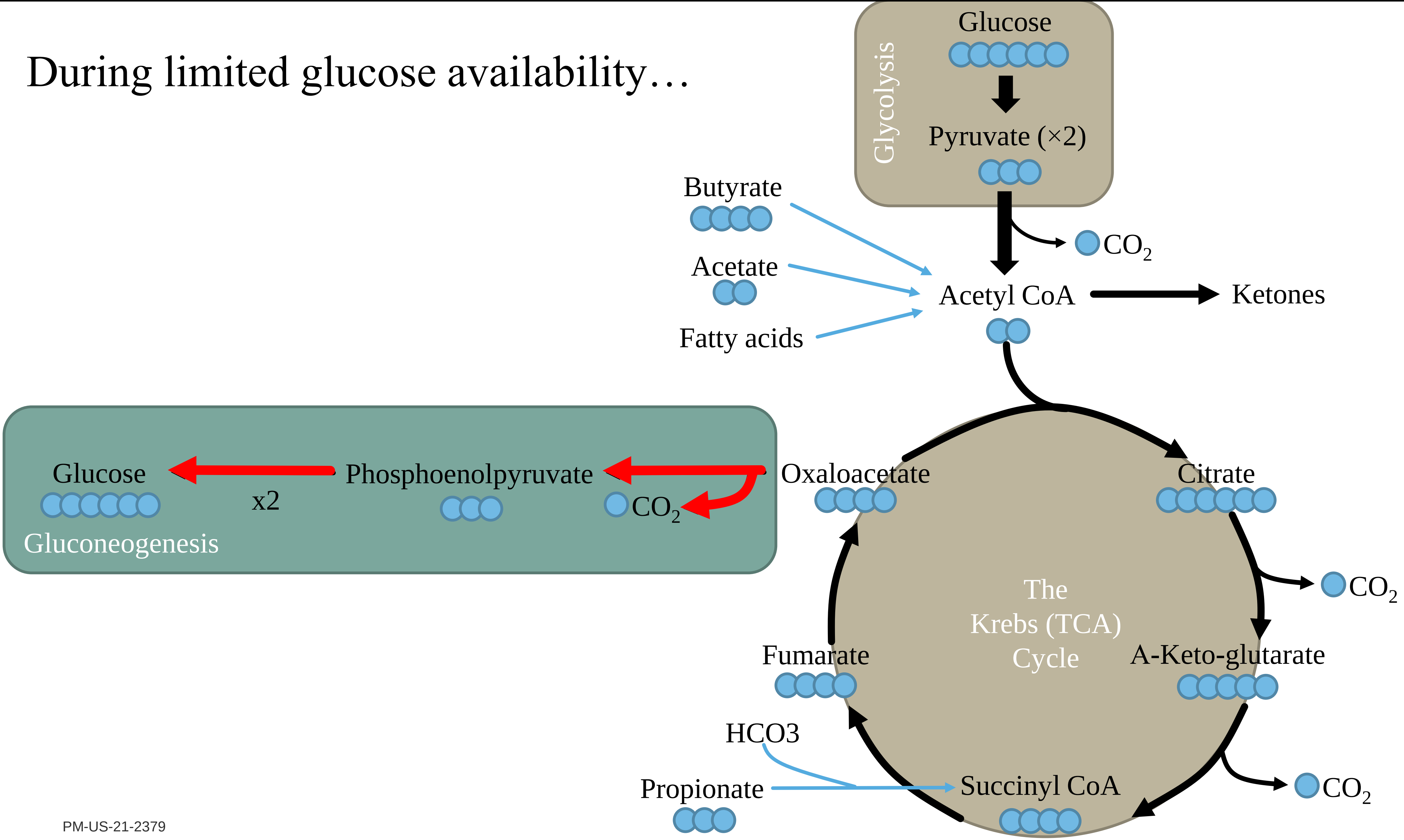
During limited glucose availability…



Hyperketonemia

- Ketogenesis is the coordinated convergence of carbohydrate and lipid metabolism
- Highly conserved amongst almost all mammals
- Ancient strategy that the even the simplest of organisms (i.e., microbes) utilize during energy insufficiency
- Millions of people are on low carbohydrate/ketogenic diet
- Claiming hyperketonemia is a disease is akin to assigning hyperglycemia as the pathological origin of diabetes

THE VETERINARY RECORD

Founded by William Hunting, F.R.C.V.S., in 1888

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Bovine Ketosis

BY

H. A. KREBS

Medical Research Council Unit for Research in Cell Metabolism, Department of Biochemistry, University of Oxford, South Parks Road, Oxford

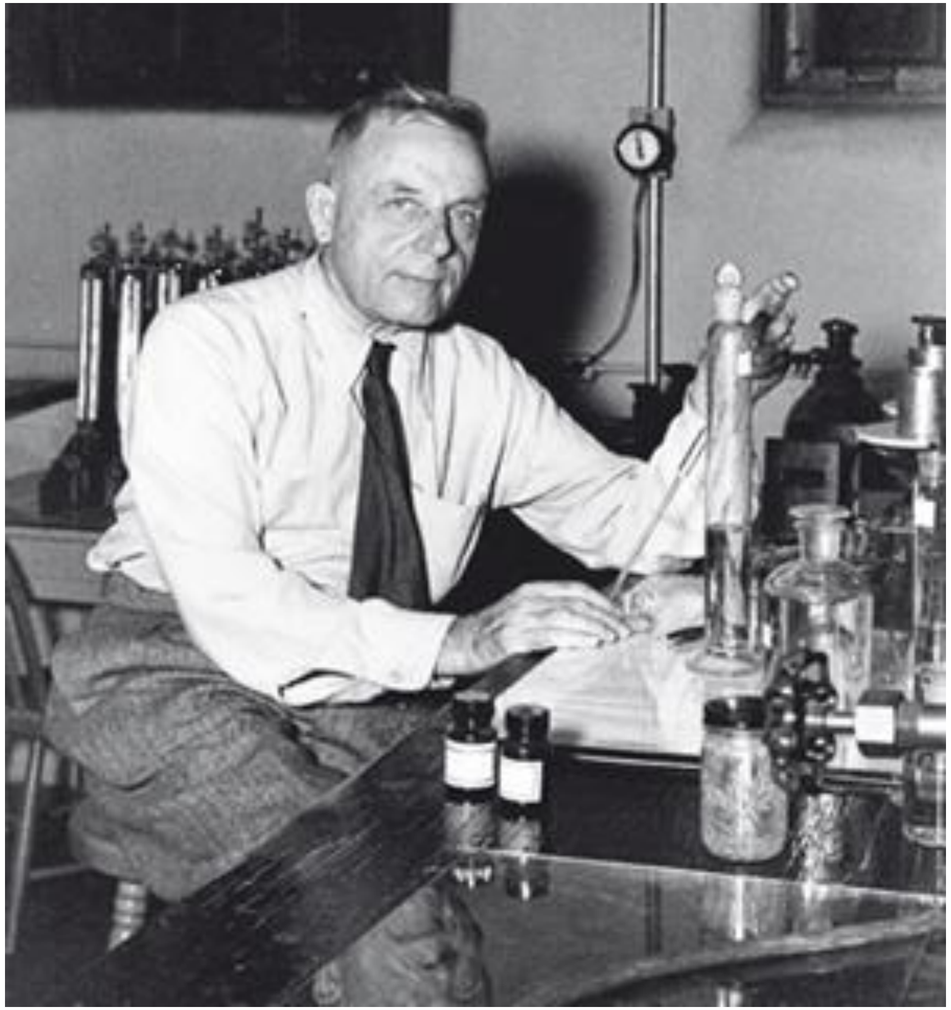
SUMMARY.—The severer forms of ketosis which occur in diabetes mellitus and in the lactating cow are always associated with increased rates of gluconeogenesis. Evidence is discussed which indicates that the high rates of gluconeogenesis in the liver are the direct cause of the high rates of ketone body formation. It follows that the parenteral administration of large doses of glucose is the rational therapy of bovine ketosis because this relieves the need for high rates of gluconeogenesis. The dose must be related to the glucose requirements of milk secretion.

stasis." That animal tissues can oxidise ketone bodies has long been known qualitatively (Snapper & Grünbaum, 1927a, b, 1928; Mirsky & Broh-Kahn, 1937; Wick & Drury, 1941), but the extent to which ketone bodies can be utilised as fuel has become known only recently. Heart muscle, for example, can use acetoacetate preferentially even when glucose and insulin and other substrates are available (Williamson & Krebs, 1961). The living sheep can

Krebs, H.A. 1966. "Bovine ketosis." Vet. Rec. 78:187-92.

Otto Warburg

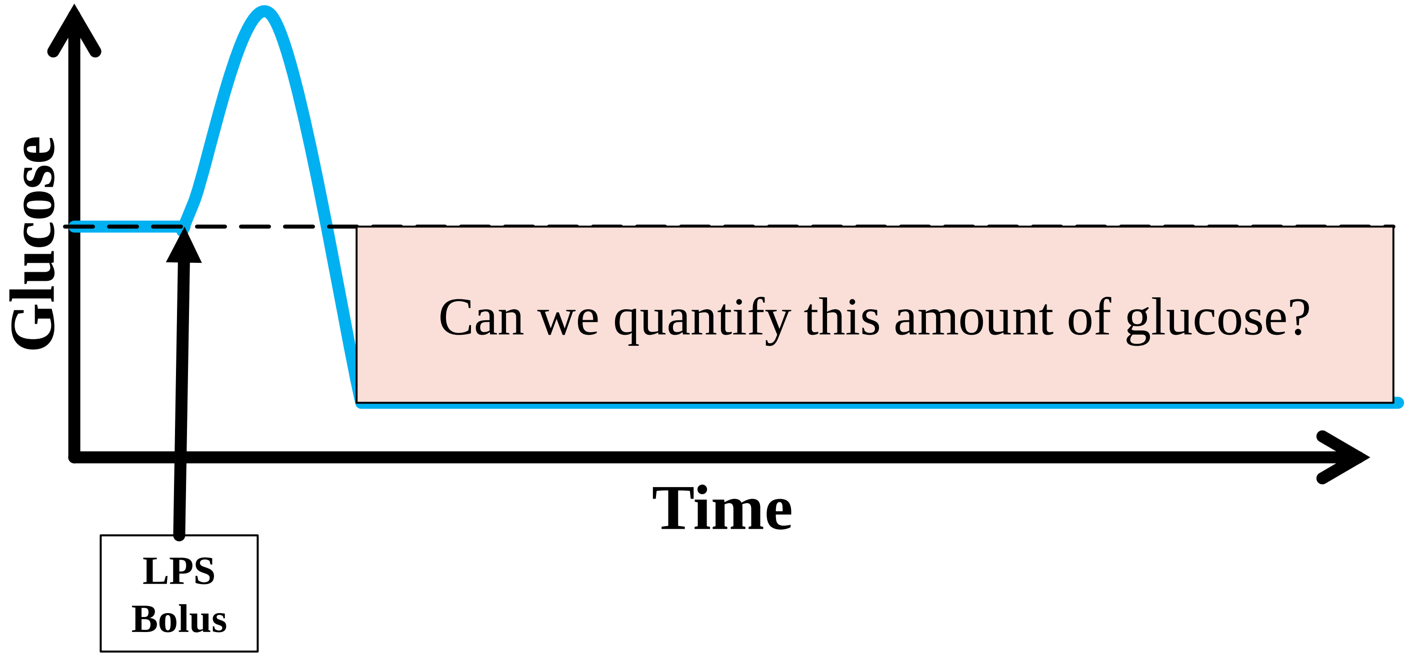
- First recognized the unique metabolism of cancer cells[1] (1927)
  - Large glucose consumers
  - Switch from oxidative phosphorylation → glycolysis
  - Aerobic glycolysis
- **Also observed activated lymphocytes become highly glycolytic[2] (1958)**
- Was a mentor for Hans Krebs
- Family friends with Albert Einstein
- Half-Jewish German during WWII
  - Was allowed to continue research but was not allowed to teach
  - Was offered passage to US, turned it down
  - Moved lab to outskirts of Berlin to avoid air attacks



[1]Warburg, O. et al. 1927. "The metabolism of tumors in the body." J. of Gen. Phys. 8.6: 519–530.
[2]Warburg, O. et al. 1958. "Metabolism of white blood cells." J. Chem. Sci. 13.B: 515-516.

Energy Demand of Infection

- When activated, immune cells demand large quantities of glucose
- Often, sick animals become hypoglycemic



Kvidera, S.K. et al. 2017. “Glucose requirements of an activated immune system in lactating Holstein cows.” J. Dairy Sci. 100.3: 2360–2374.

Energy Equivalence to Fuel an Immune Response

- 1,092 g in 12 hours[1]
- 2,184 g glucose (~4.8 lbs) in 24 hours
- **= 8.7 Mcal per day**
  - 4 kcal/g glucose
- **= 30 kg (~65 lbs) milk per day**
  - 72 g glucose → 1 kg milk[2]

[1]Kvidera, S.K. et al. 2017. "Glucose requirements of an activated immune system in lactating Holstein cows." J. Dairy Sci. 100.3: 2360–2374.
[2]Kronfeld, D.S. 1982. "Major metabolic determinants of milk volume, mammary efficiency, and spontaneous ketosis in dairy cows." J. Dairy Sci. 65.11: 2204-2212.

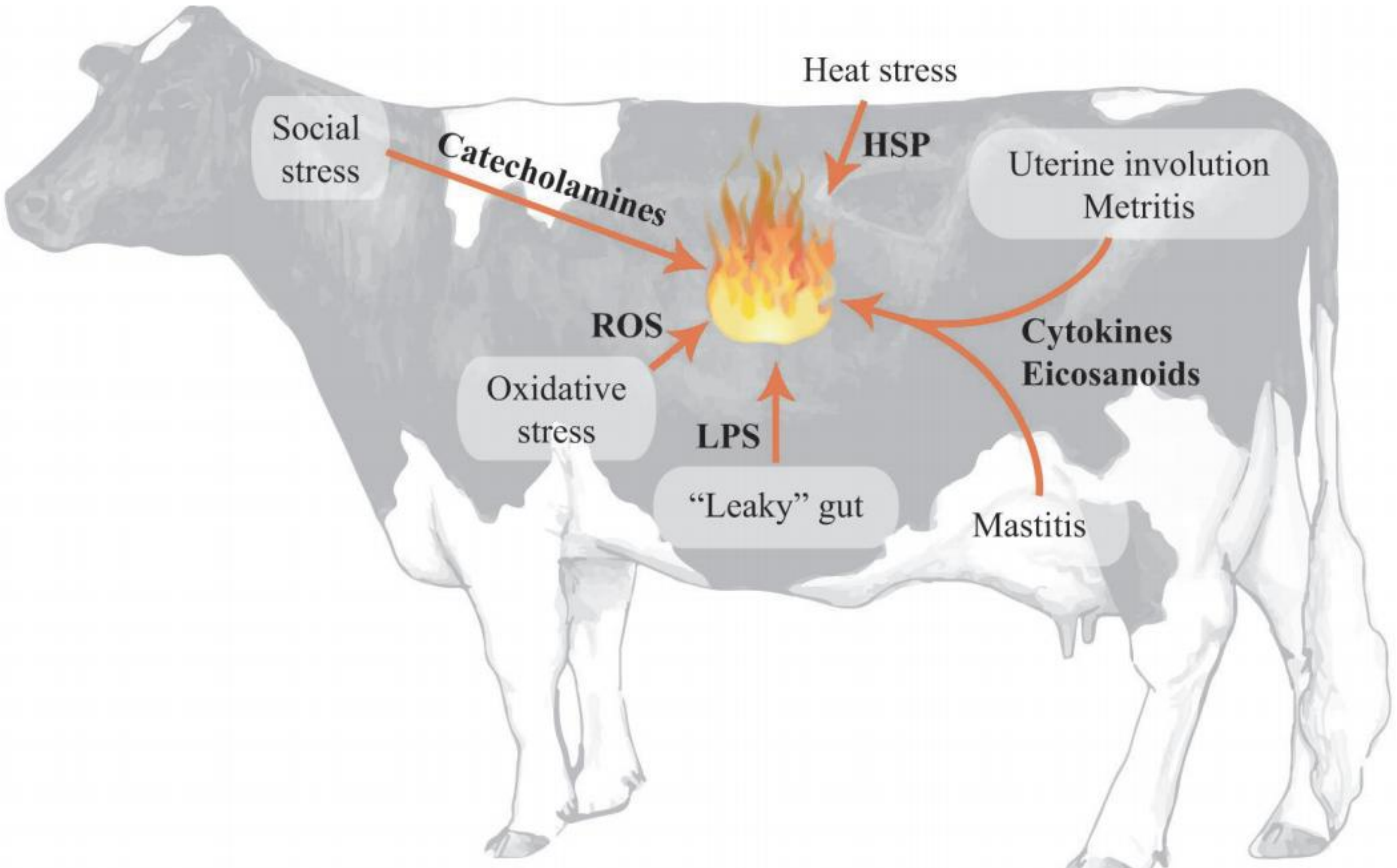
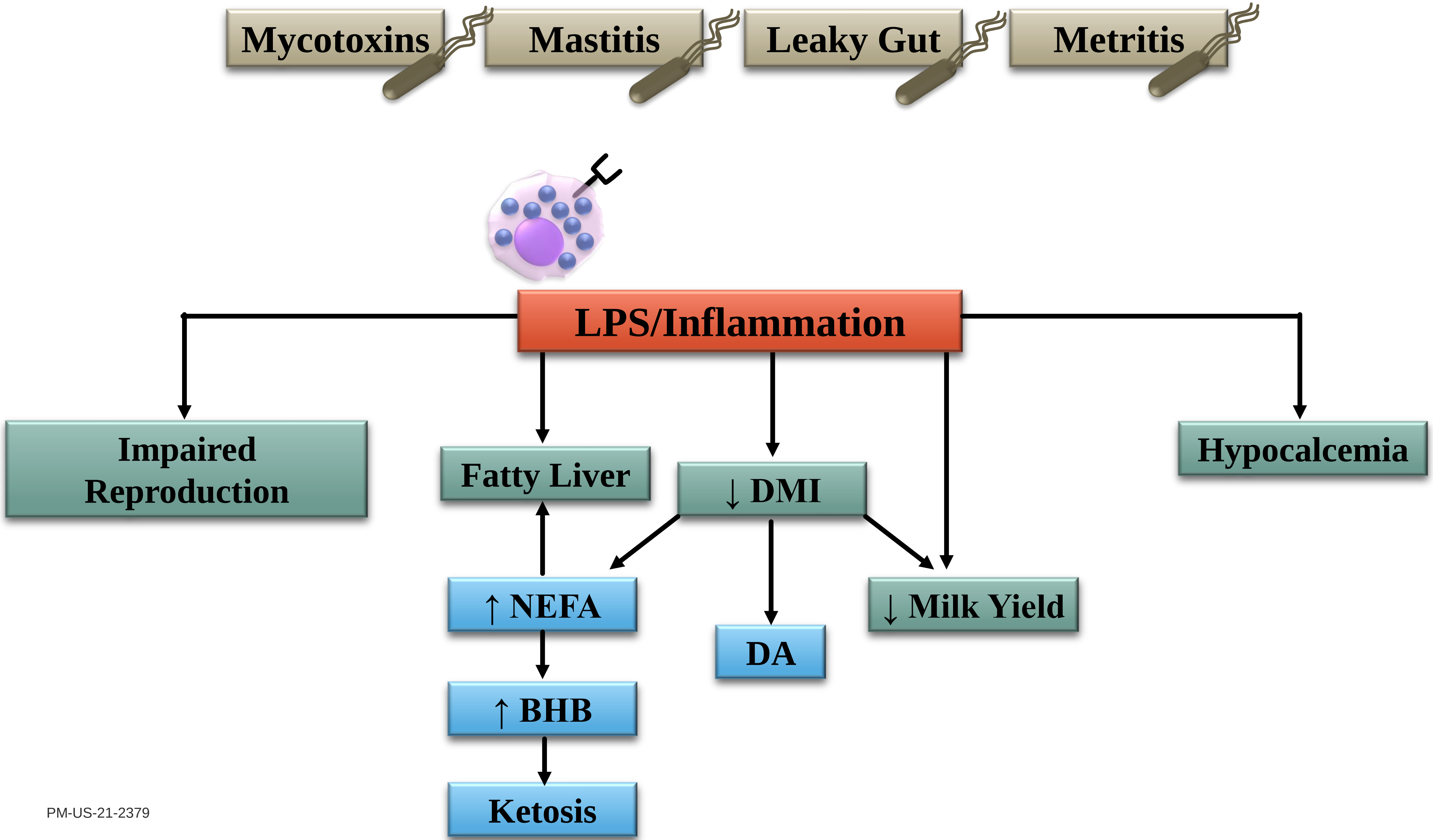


Figure from Bradford, B.J. et al. 2015. "Invited review: Inflammation during the transition to lactation: New adventures with an old flame." J. Dairy Sci. 98: 6631-6650.


Mycotoxins
Mastitis
Leaky Gut
Metritis
LPS/Inflammation
Impaired Reproduction
Fatty Liver
↓ DMI
Hypocalcemia
↑ NEFA
DA
↓ Milk Yield
↑ BHB
Ketosis

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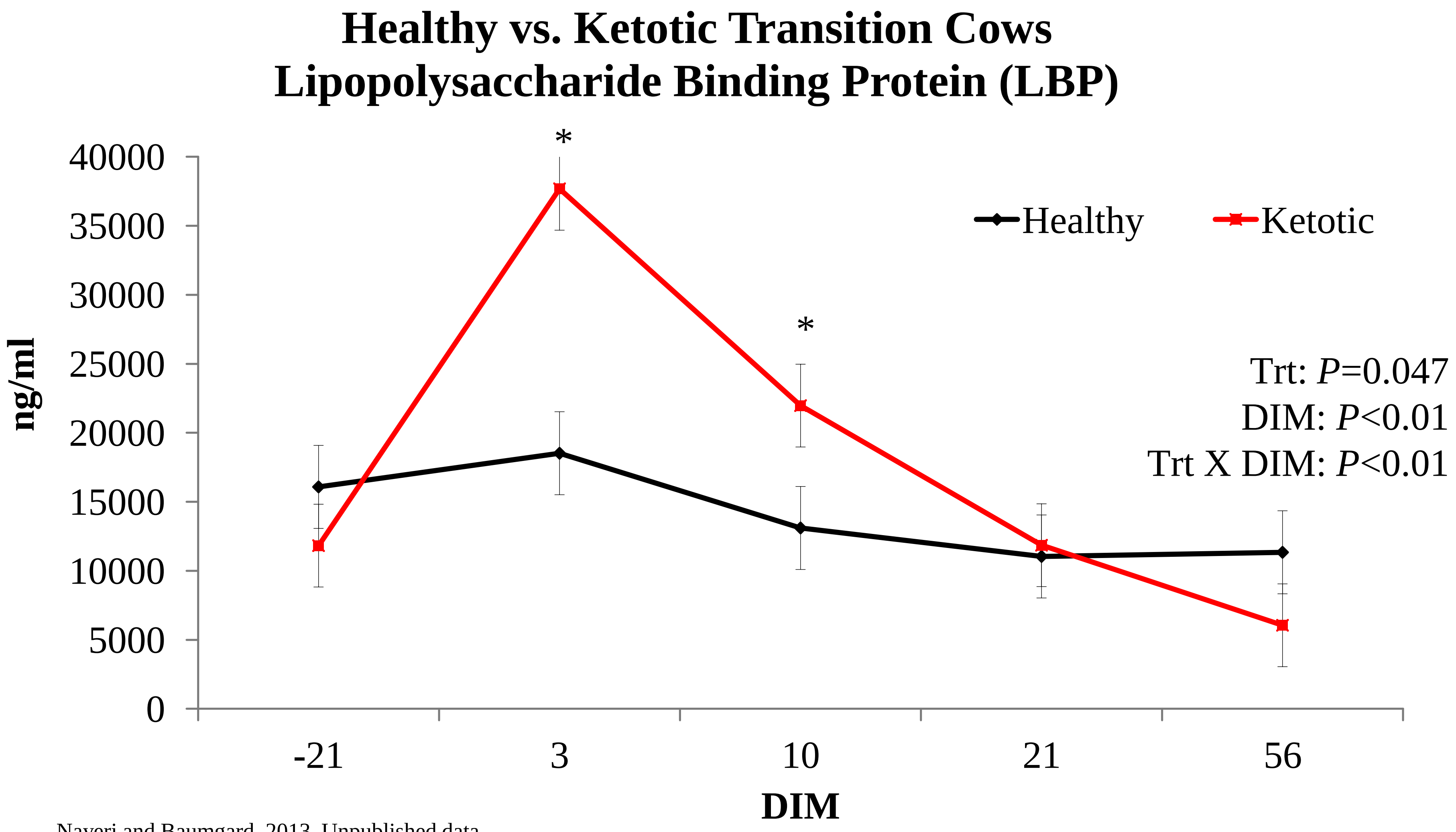
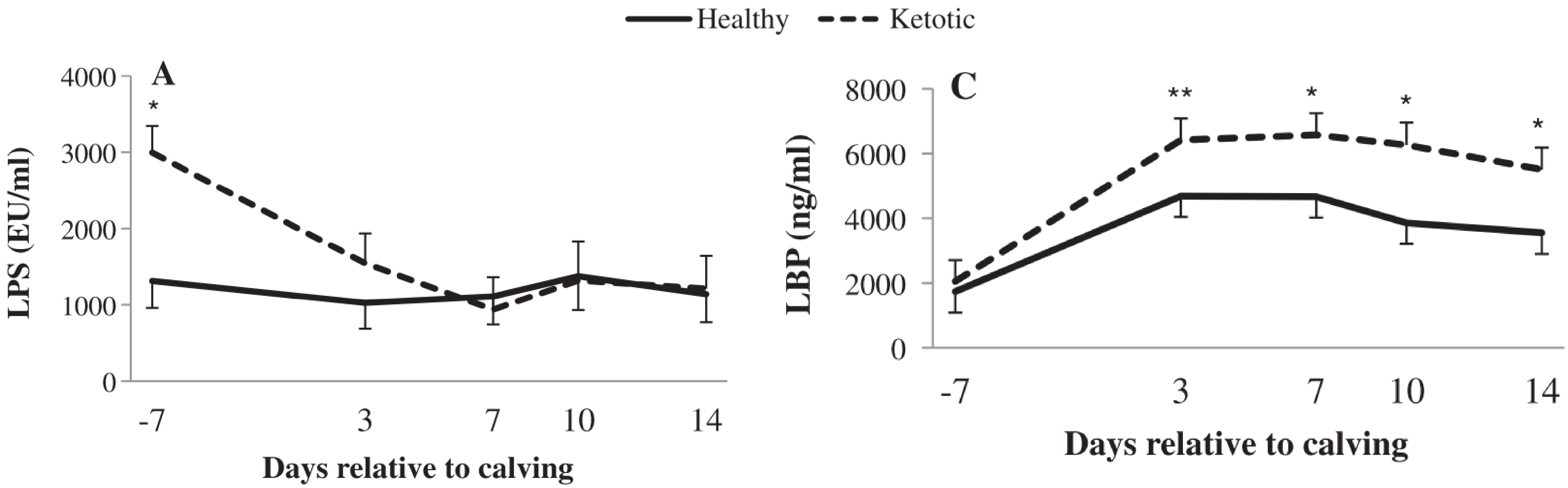
Increased Inflammation in Ketotic Cows



Nayeri and Baumgard, 2013. Unpublished data.

Increased Inflammation in Ketotic Cows



Abuajamieh, M. et al. 2016. “Inflammatory biomarkers are associated with ketosis in periparturient Holstein cows.” Res. Vet. Sci. 109: 81–85.

Increased Inflammation in Ketotic Cows

- “The occurrence of subclinical ketosis was preceded by a preeclampsia-like status during the dry period.”
  - Oxidative stress
  - High levels of pro-inflammatory cytokines and nitrates
  - Reduced renal function
  - Liver damage
  - Reduced blood mineral concentrations
  - Activated immune system

J. Dairy Sci. 102:9241–9258
https://doi.org/10.3168/jds.2019-16497

The role of altered immune function during the dry period in promoting the development of subclinical ketosis in early lactation

M. Mezzetti,[1] A. Minuti,[1] F. Piccioli-Cappelli,[1] M. Amadori,[2] M. Bionaz,[3] and E. Trevisi[1]*
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[2]Istituto Zooprofilattico Sperimentale della Lombardia e dell'Emilia-Romagna, Laboratory of Cellular Immunology, 25124 Brescia, Italy
[3]Department of Animal and Rangeland Sciences, Oregon State University, Corvallis 97331

Mezzetti, M. et al. 2019. “The role of altered immune function during the dry period in promoting the development of subclinical ketosis in early lactation.” J. Dairy Sci. 102: 9241–9258.

Ketosis: When (or if) to intervene?

The Olympic Athlete

- High ketones
- Eating well
- Milking great
- Looks great
- No fever

Leave her alone!

The Damsel in Distress

- High ketones
- No appetite
- Not milking well
- Lethargic
- Fever

Treat her. But realize giving her more energy probably doesn’t fix the underlying problem. Somewhere, immune activation is putting the brakes on appetite.

Target Mitigation Strategies

Dairy Producer Responsibility

- Prevent infection – keep a clean environment
- Minimize stresses – feed restriction, weaning, shipping, overcrowding, unpalatable feed, pen moves, etc.

Nutritionist & Producer Responsibility

- Prevent rumen acidosis
- Maximize digestion prior to large intestine

Nutritionist Responsibility

- Ensure adequate energy and nutrients
- Use feed additives that have a positive effect on gut health
- Explore immunomodulatory strategies

Summary and Conclusions

- Inflammation is energetically costly.
  - Inflammation steals energy resources from concurrent infections or productivity.
  - The cost can be up to 1 kg of glucose (4 Mcal) in a 12-hr period.
  - Preventing inflammation saves money.
- Ketosis is defined by high circulating ketone bodies.
  - Ketosis is a result of a glucose deficit.
  - If using ketones as a red flag, what's causing high ketone bodies needs to be investigated further by the herdsman, nutritionist, and veterinarian.
- Glucose is an extremely important molecule in a lactating cow.
  - Supporting her glucose needs will help her be a healthy and productive cow.