The Intestinal, Metabolic, Inflammatory and Production Consequences of Heat Stress

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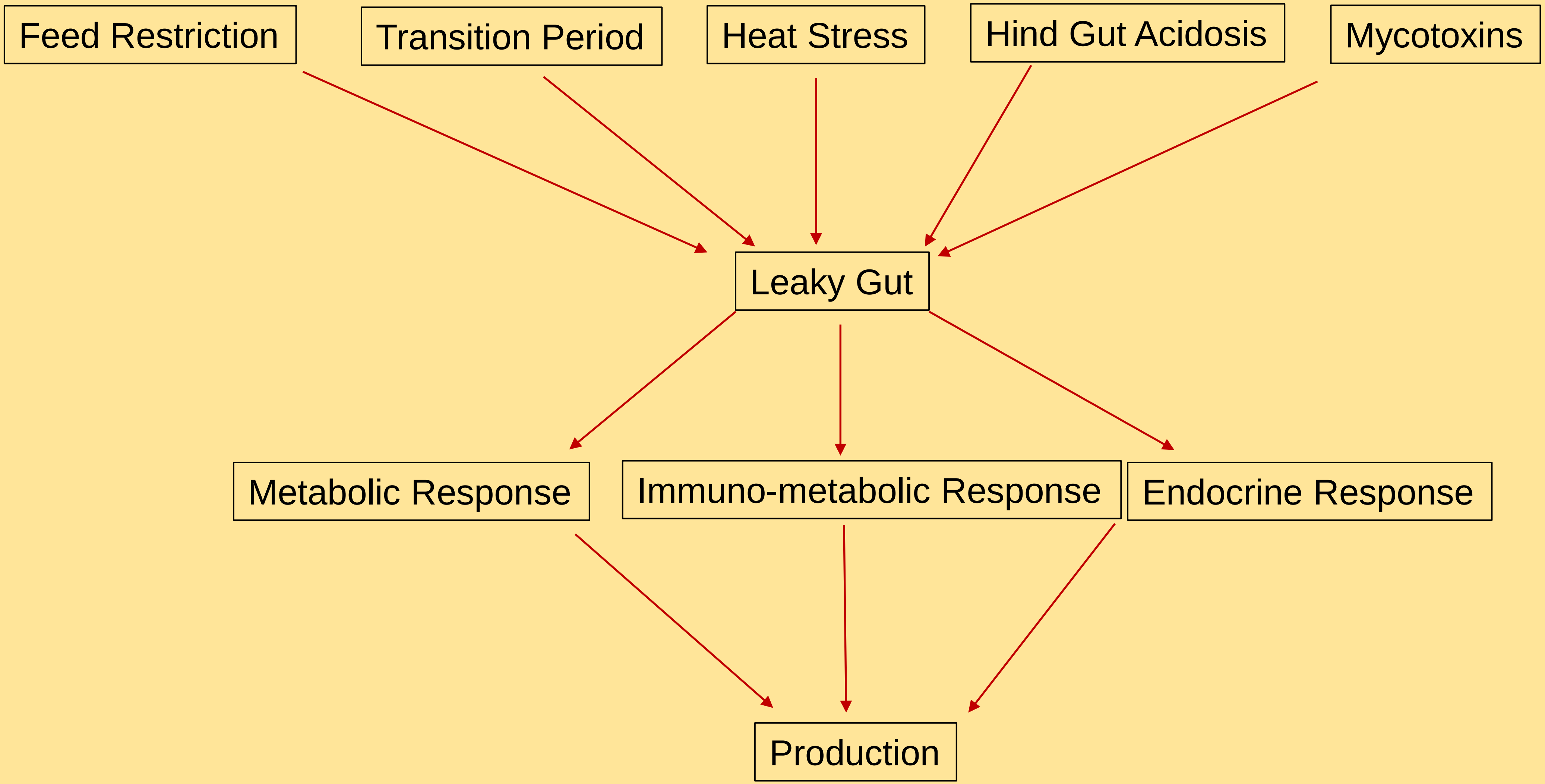
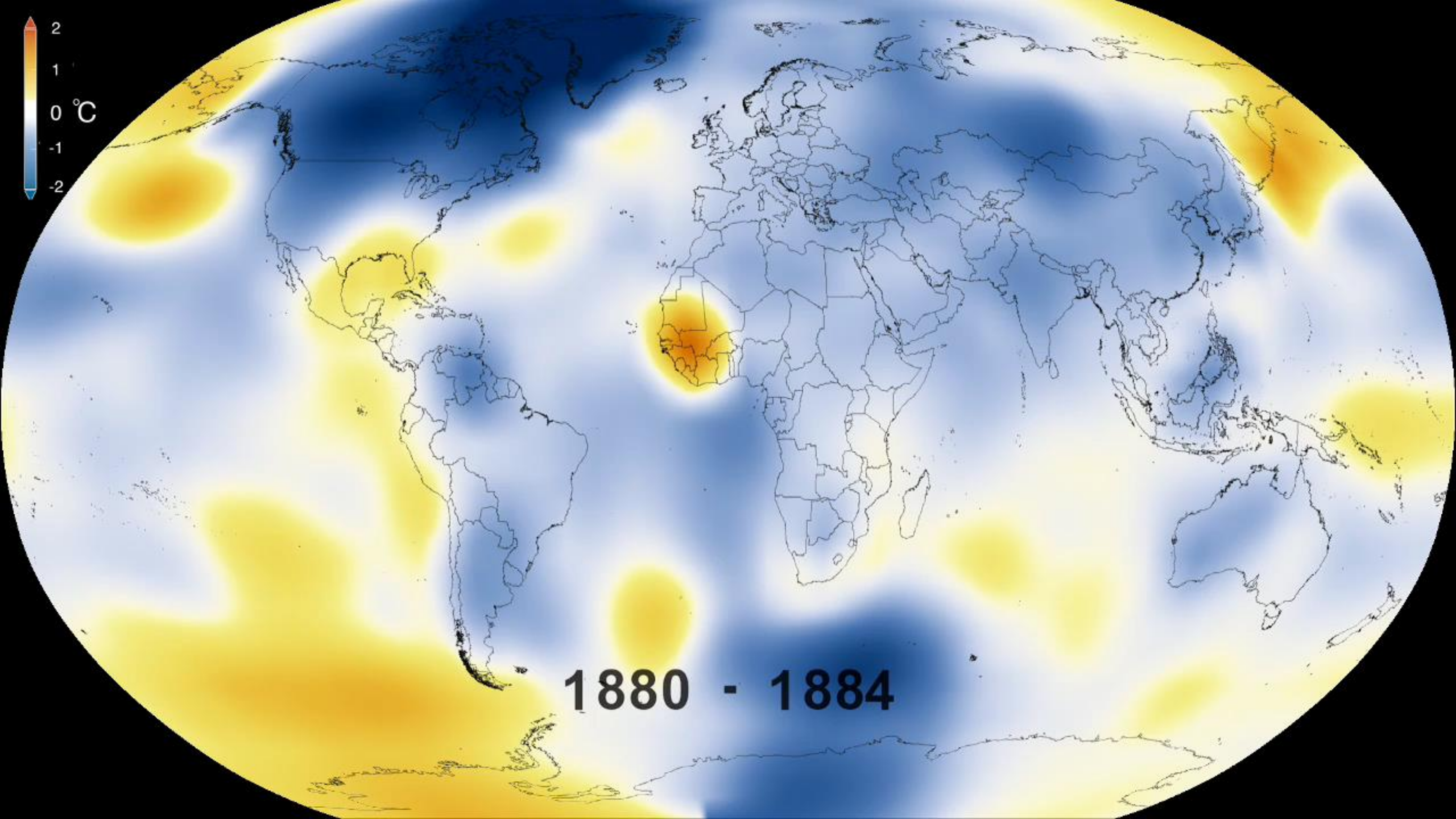
Baumgard Research Group Priorities: Ruminants and Pigs



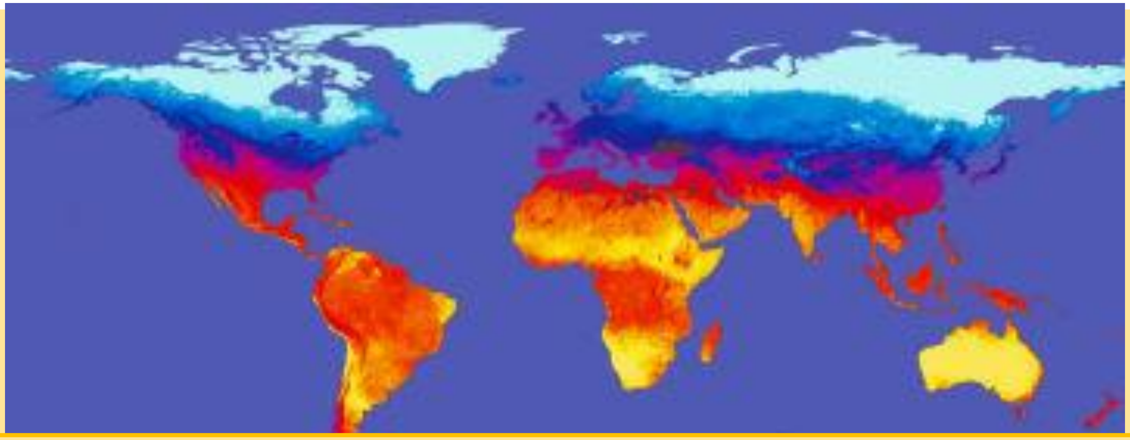
Farm Animal Productivity and Environment

- Production (growth, milk, eggs etc.) is maximized within a narrow thermal range (thermal neutral zone)
  - When temperatures are above are below the thermal neutral zone, productivity is decreased and feed efficiency is reduced

- Unfavorable environment is already the largest impediment preventing animals from reaching their genetic potential
  - Economic and food security issue


2
1
0 ℃
-1
-2
1880 - 1884

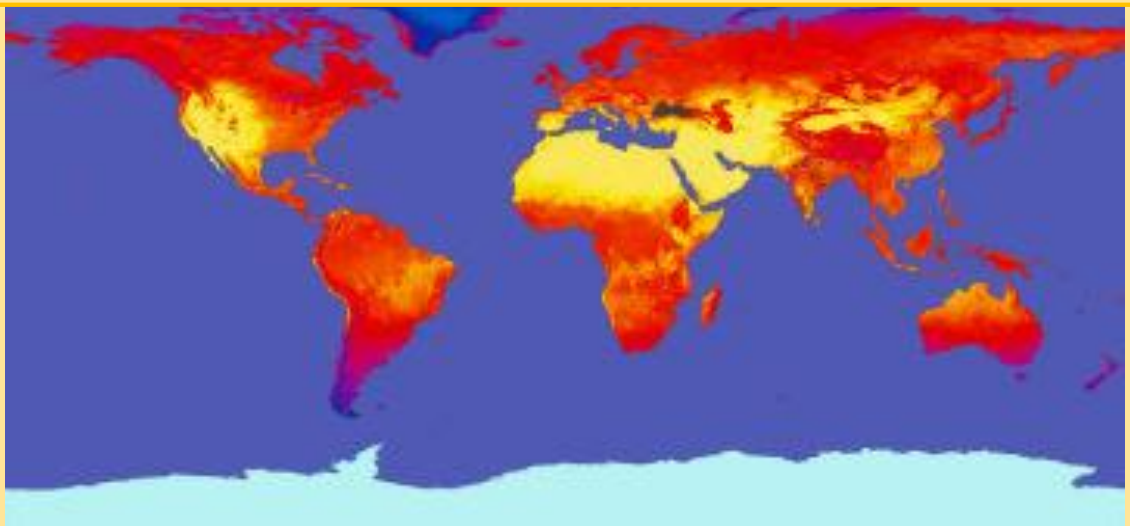
Heat Stress is a Global Problem



January 2003, NASA

40% of W. Canadian summer days THI > 72

Ominski et al., 2002



July 2003, NASA

Heat Stress and Industry Issues

Beef and Pigs

- Don’t “finish”
- Increased variability in market weight
- Fatter carcass
- Packing issues with “seam fat”/“flimsy fat”/”watery fat”
  - Dark Cutters/PSE
- Seasonal infertility
  - Especially in non-spring programs
- Mortality
  - Heavy/fat and black cattle
  - Especially early spring
- Decreased Efficiency
  - Feed
  - Production/Facility

Dairy

- Decreased milk yield
- Decreased milk fat and protein content
- Decreased reproduction
- Increased health care
  - Mastitis and fatty liver
- Increased mortality
- Decreased efficiency
  - Feed
  - Production/Facility
- Increased energy costs
- Increased water use
- Cost of getting rid of spent water

Heat Stress: Economics and Food Security

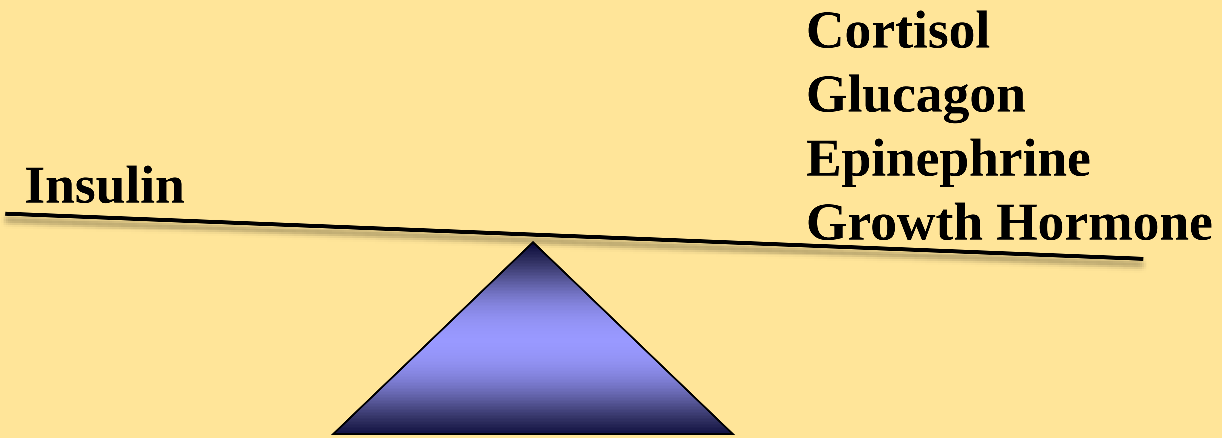
- Cost: (lost productivity, mortality, product quality, health care etc.)
  - American Agriculture: > $4 billion/year
    - $1.7 billion in dairy industry
  - Global Agriculture: > $500 billion/year

- It will get worse in the future if:
  - Climate change continues as predicted
  - Genetic selection continues to emphasize milk synthesis, lean tissue accretion, piglets/sow etc..
    - Heat producing processes

St. Pierre et al., 2003; Baumgard and Rhoads, 2013

"Normal" Metabolism Review

- Ad Libitum Intake
  - ↑ Insulin
  - ↓ NEFA
  - ↓ catabolic hormones
- Suboptimal Intake
  - ↓ Insulin
  - ↑ NEFA
  - ↑ catabolic hormones



Heat Stress and Gross Metabolism

- Decreased appetite
- Loss of body weight (negative energy balance)
- Hyperventilation
- Systemic acidosis
- Diarrhea
- Death

- Catabolic….even “hypercatabolic” phenotypes

Heat Stress Increases Lipid and Decreases Carcass Lean Content

- Pigs
  - Close et al., 1971; Verstegen et al., 1978; Stahly et al., 1979; Heath, 1983, 1989; Bridges et al., 1998; Collin et al., 2001
- Chickens
  - Geraert et al., 1996; Yunianto et al., 1997
- Rodents
  - Schmidt and Widdowson, 1967; Katsumata et al., 1990

- But, normally growing animals on a restricted-diet <u>prioritize lean tissue accretion and deemphasize fat synthesis</u> (Le Dividich et al., 1980; Oresanya et al., 2008)

- Heat Stress alters the nutrient partitioning hierarchy

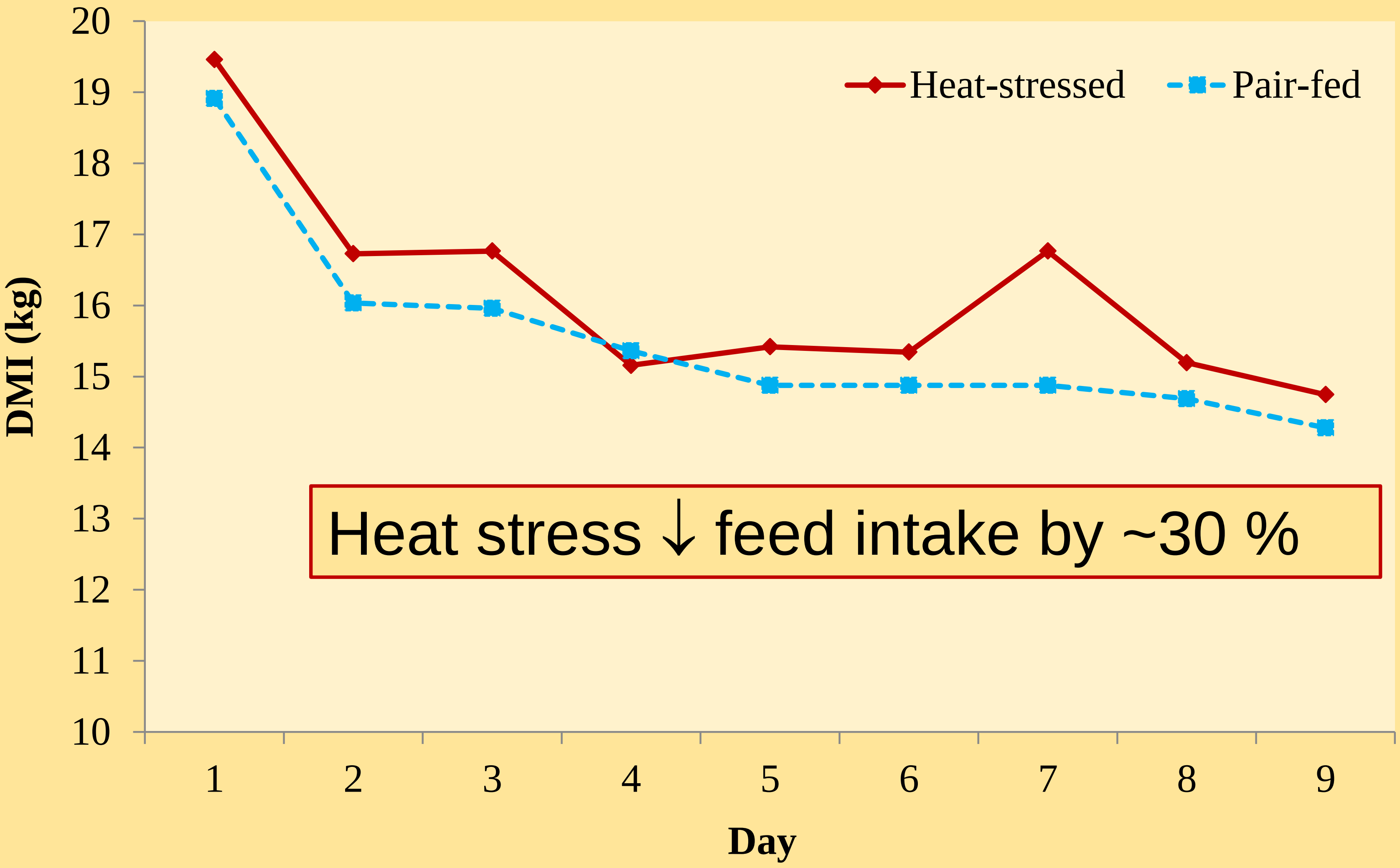
Heat Stress Questions??

- Does the decrease in feed intake explain reduced productivity during heat stress?

Indirect vs. direct effects of heat

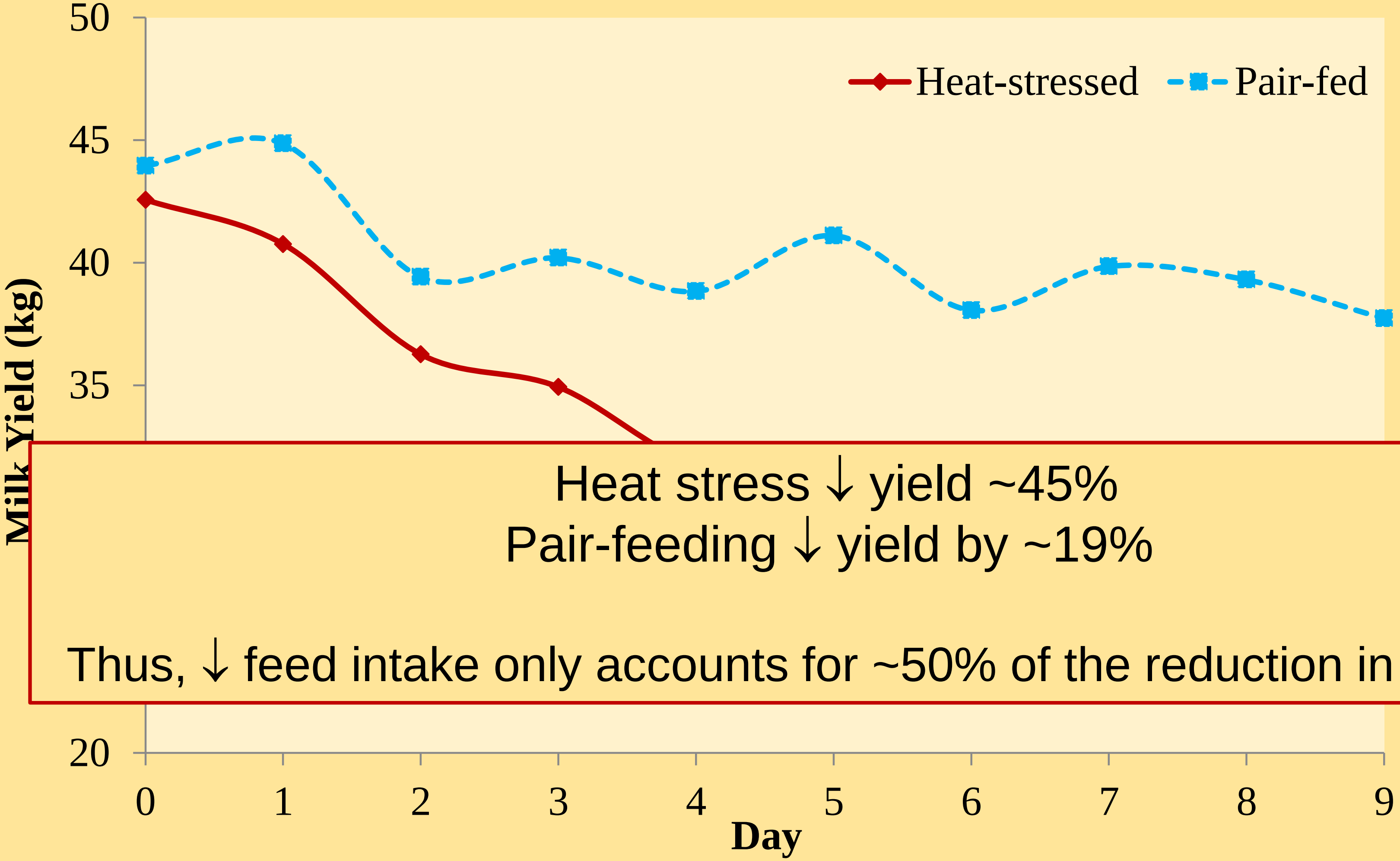
- If we have a better understanding of the biological reasons WHY heat stress reduces production, we'll have a better idea of how to alleviate it.

Effects of HS on Feed Intake



Rhoads et al., 2009

Effects of HS on Milk Yield

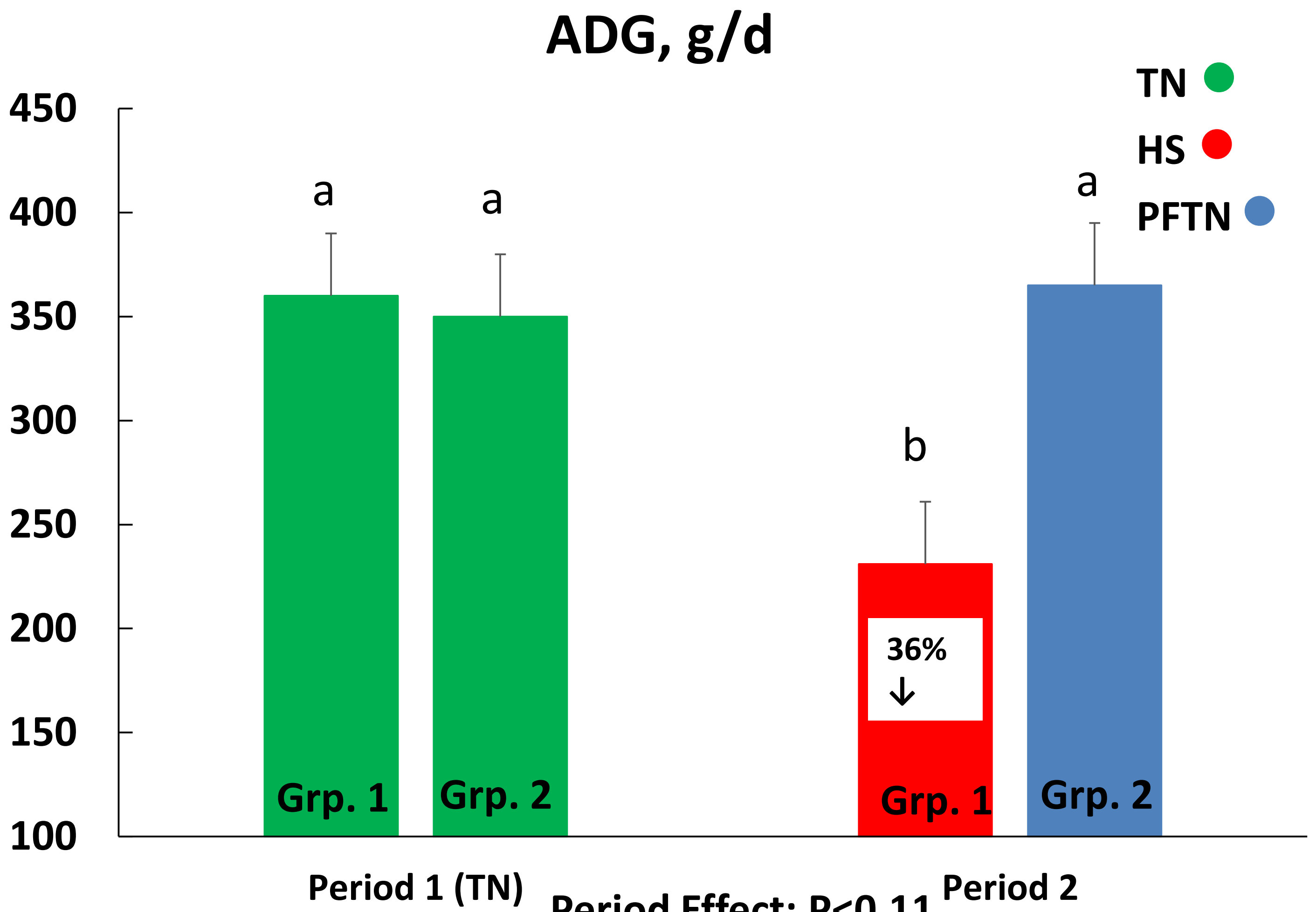


Heat stress ↓ yield ~45%
Pair-feeding ↓ yield by ~19%

Thus, ↓ feed intake only accounts for ~50% of the reduction in milk yield

Rhoads et al., 2009

Mild Heat-Stress Lambs

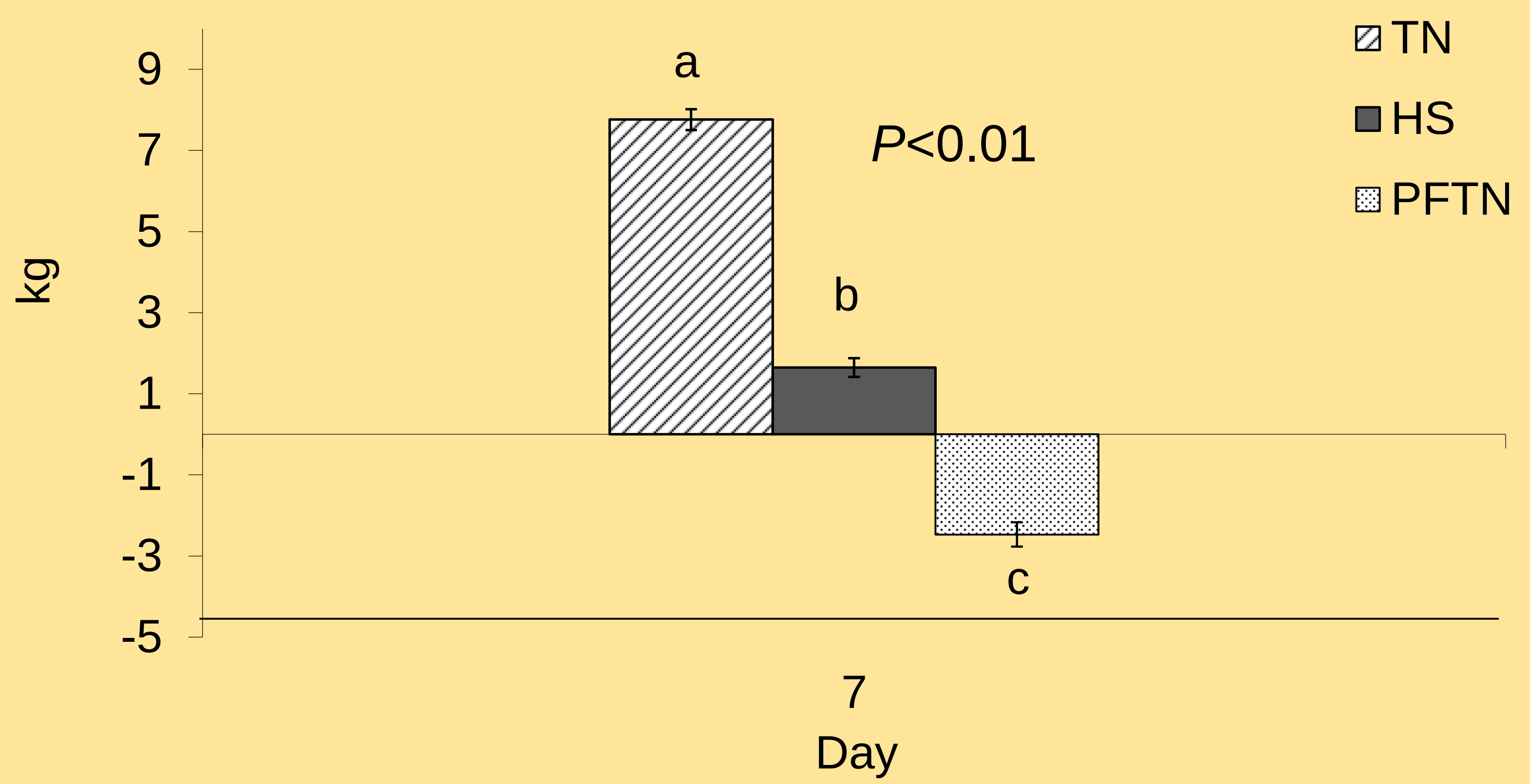


Period Effect: P<0.11
Environment Effect: P<0.01
Interaction: P<0.05

[a, b]Means statistical difference among groups.

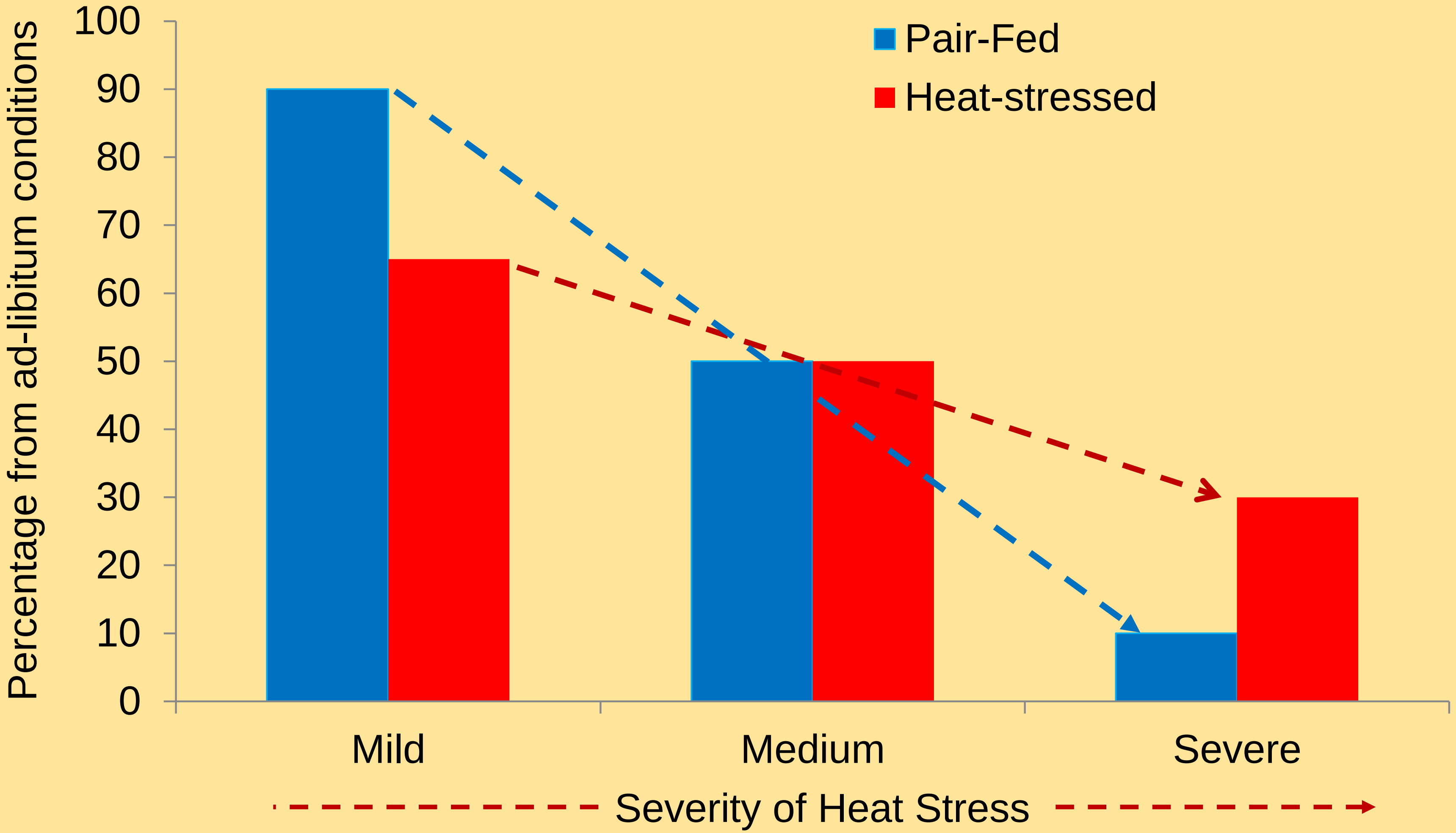
Mahjoubi and Baumgard, 2014

Severe Heat Stress: Pigs Body Weight



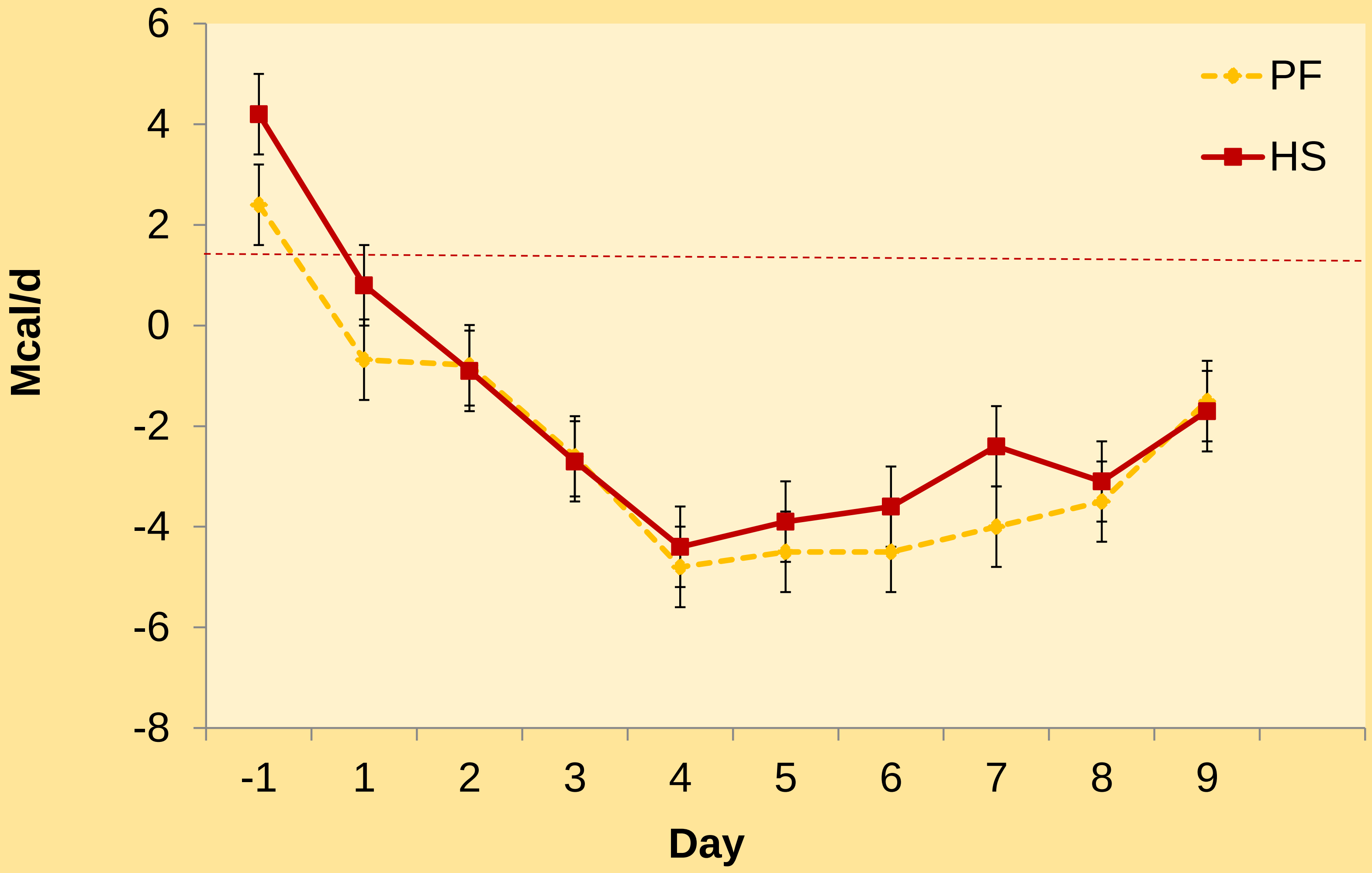
Pearce et al., 2013

HS and Growth Performance: Depends Upon the Feed Intake Response



Baumgard et al., 2015

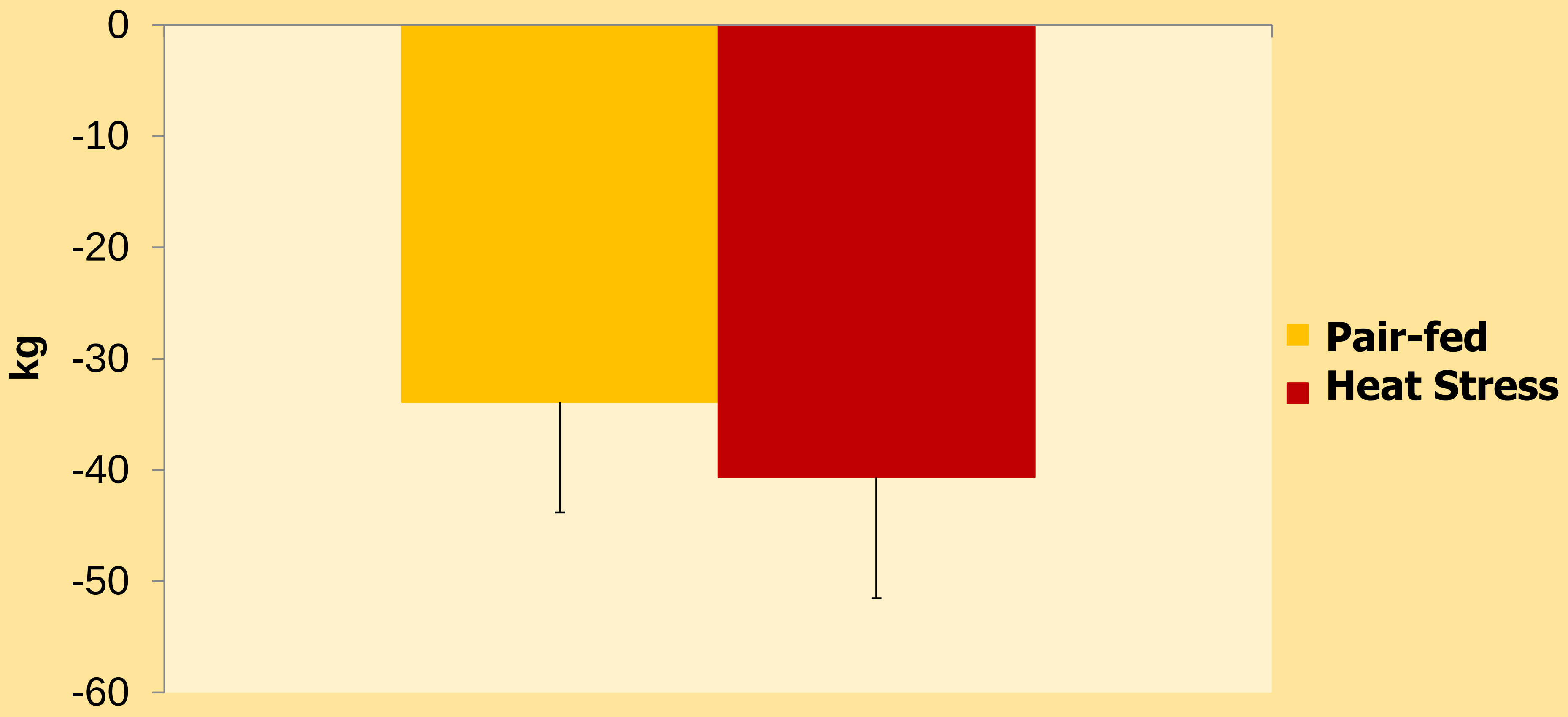
Calculated Energy Balance



Maintenance cost ↑ 25%: 1989 NRC

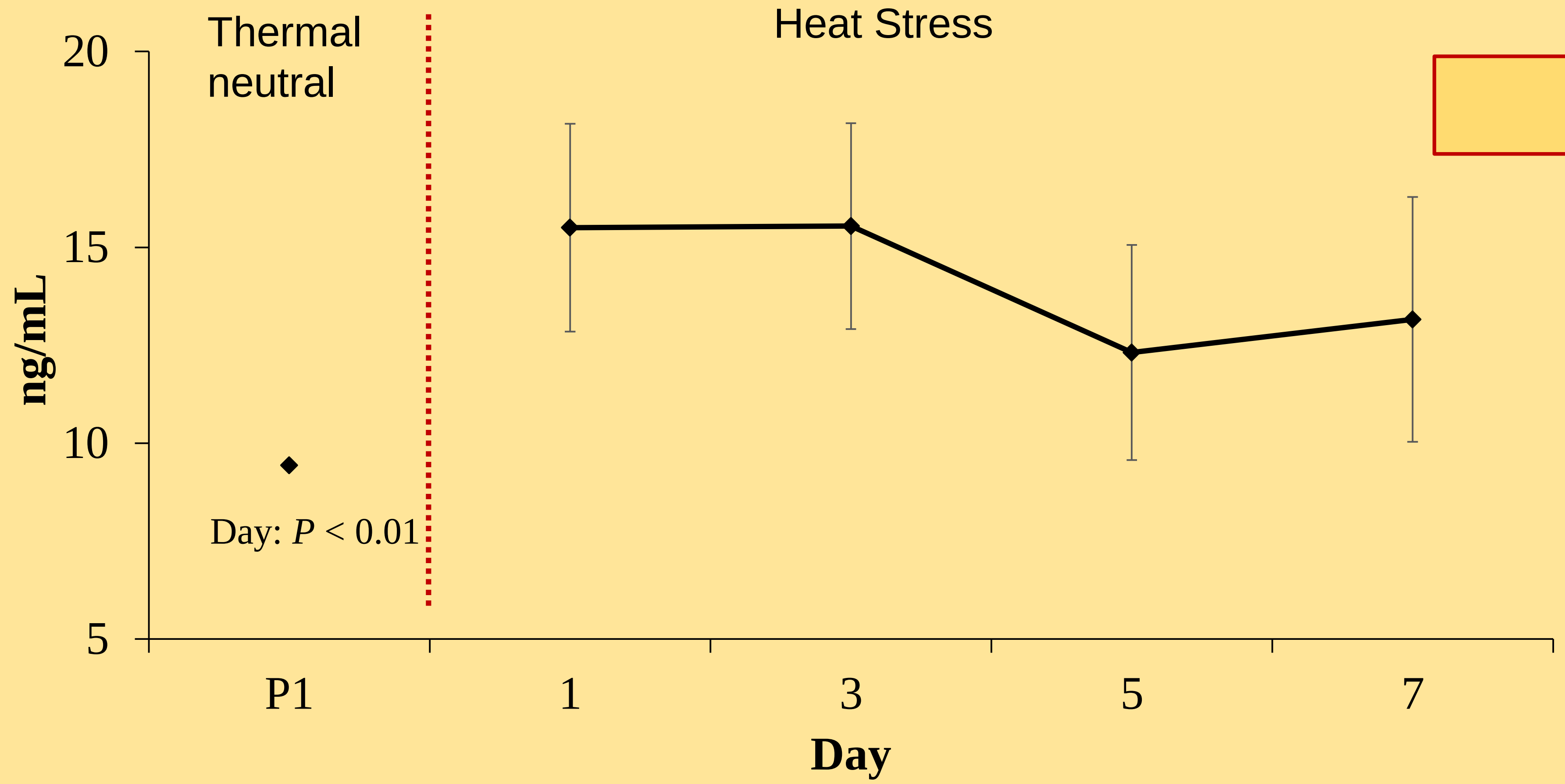
Rhoads et al., 2009

Body Weight Loss During 9 days



Rhoads et al., 2009

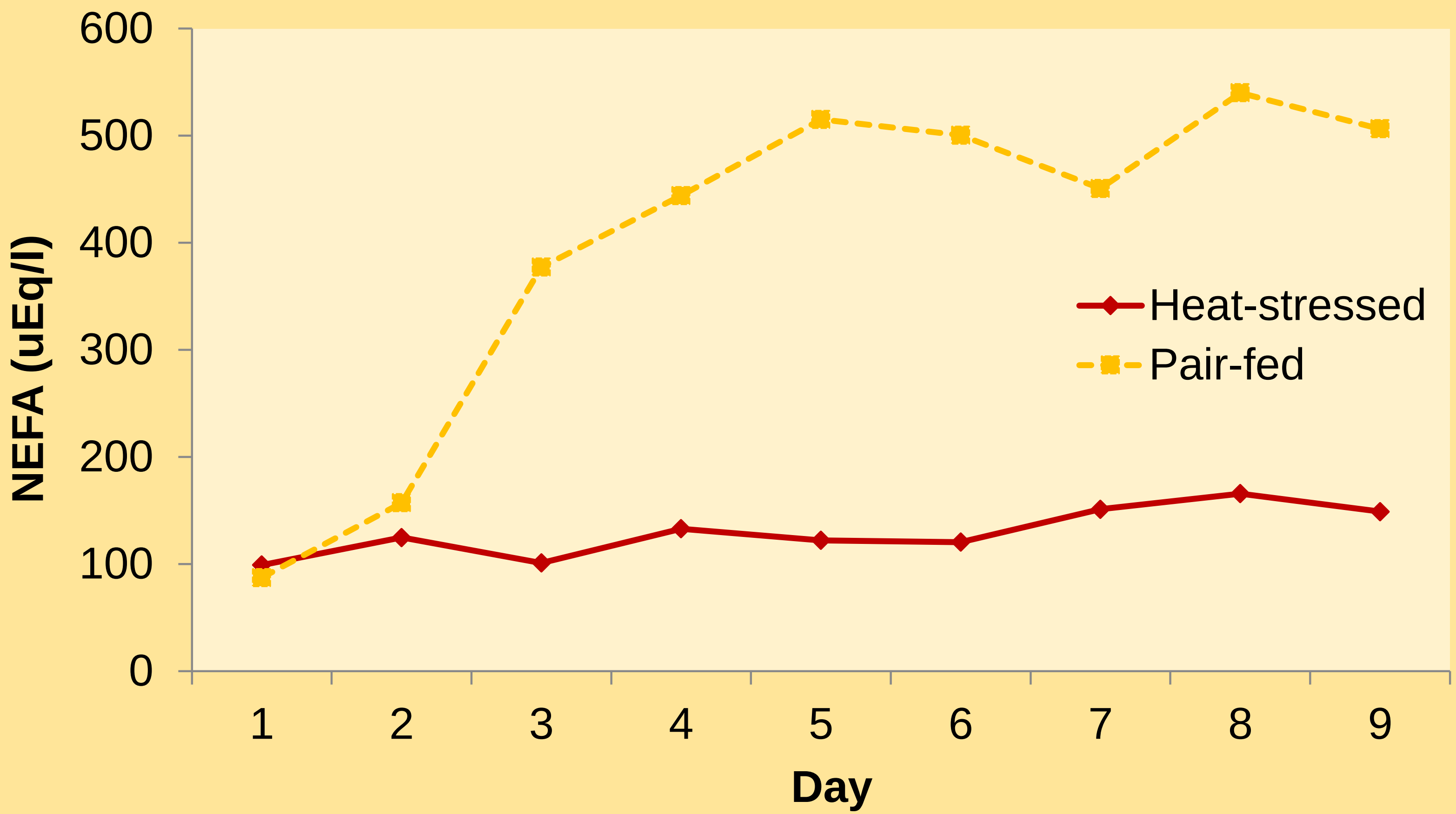
Cortisol



Thermal
neutral
Heat Stress
20
15
10
5
ng/mL
Day: P < 0.01
P1
1
3
5
7
Day

↑ 58%

Effects of Heat Stress on Adipose Tissue Mobilization: Cattle



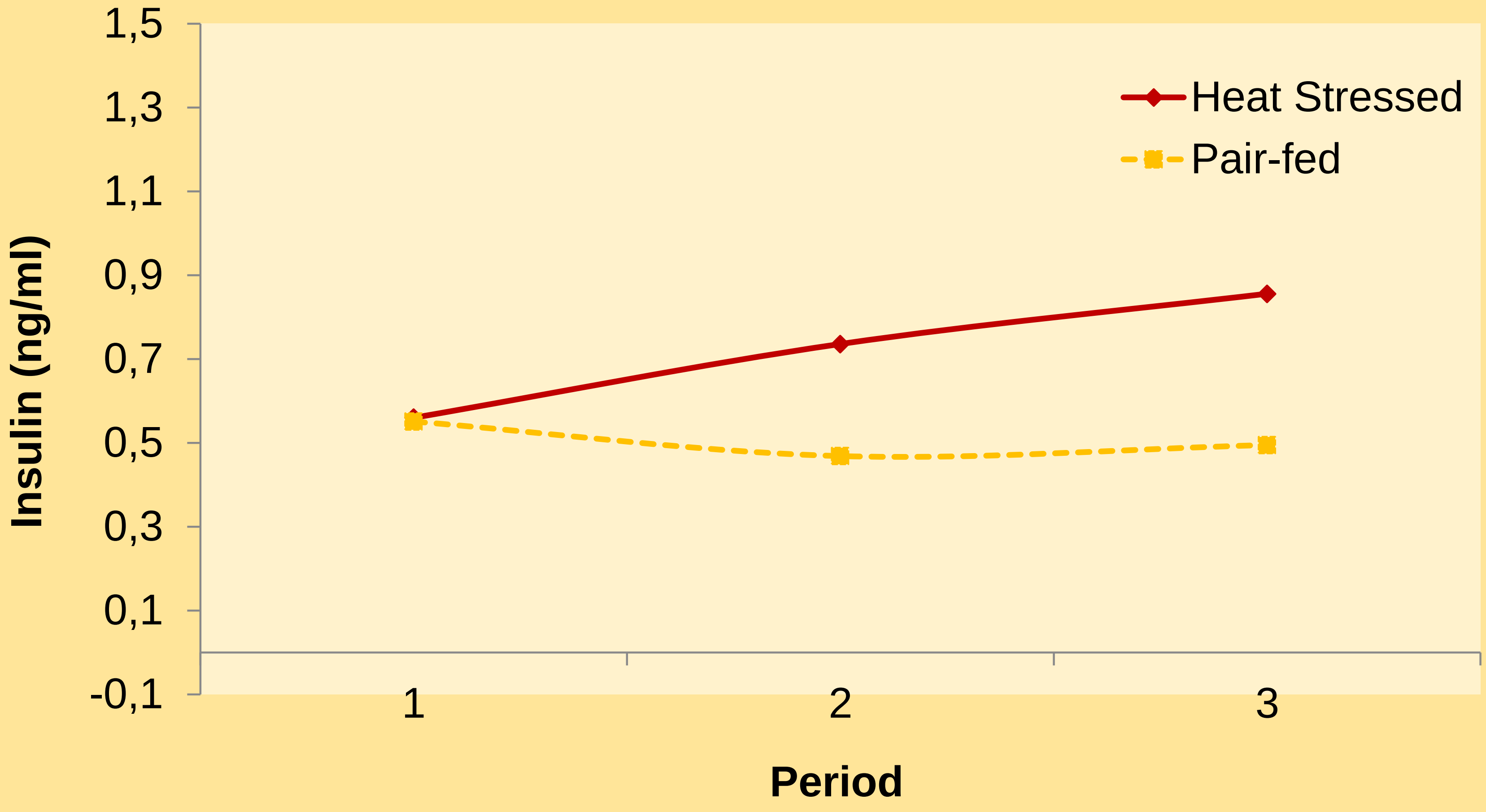
Rhoads et al., 2009

Lipid Metabolism

- Basal and stimulated (epinephrine) lipolysis is blunted during heat stress in multiple species
  - Ruminants
  - Pigs
  - Chickens
  - Rodents

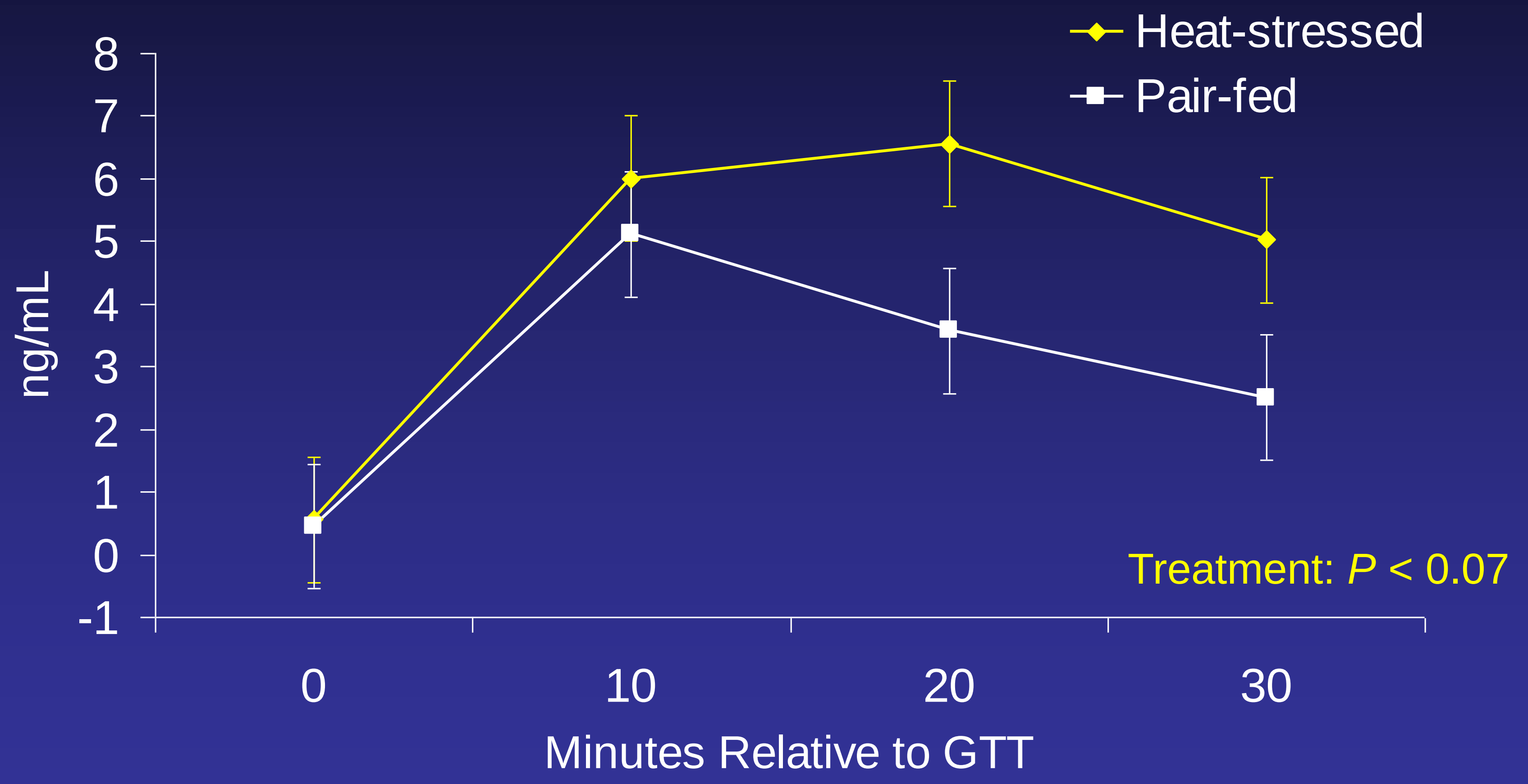
- What is preventing lipid mobilization?
- What’s the purpose of preventing lipid metabolism during a hyper-catabolic state?

Circulating Insulin in Cattle



Wheelock et al., 2010

Insulin Response to a GTT

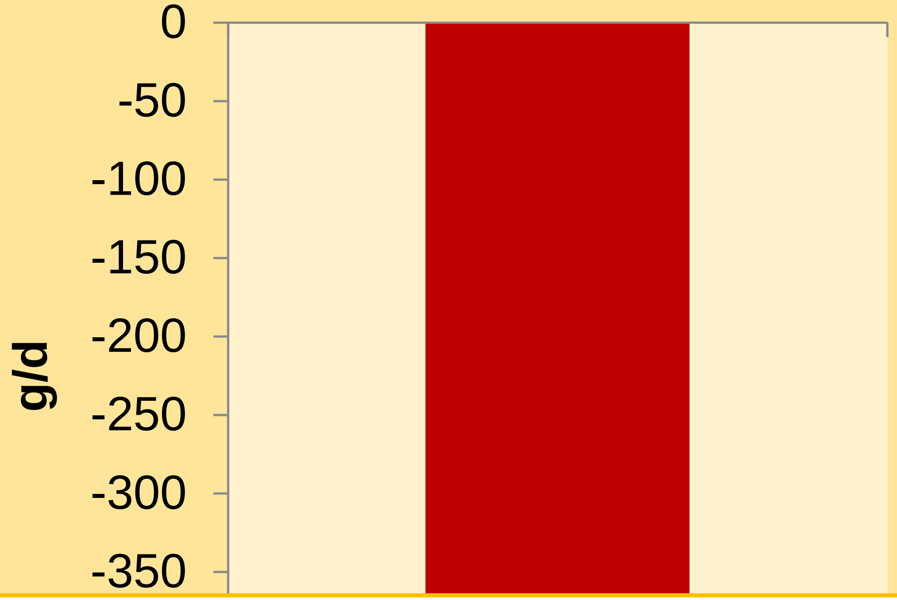


O'Brien et al., 2010

HS and Hyperinsulinemia

- Basal and stimulated (GTT) increases conserved across species
- Especially when compared to pair-fed thermal neutral controls
  - Dairy
  - Beef
  - Pigs
  - Rodents
  - Rabbits
  - Snakes
  - Human

Milk Sugar Output

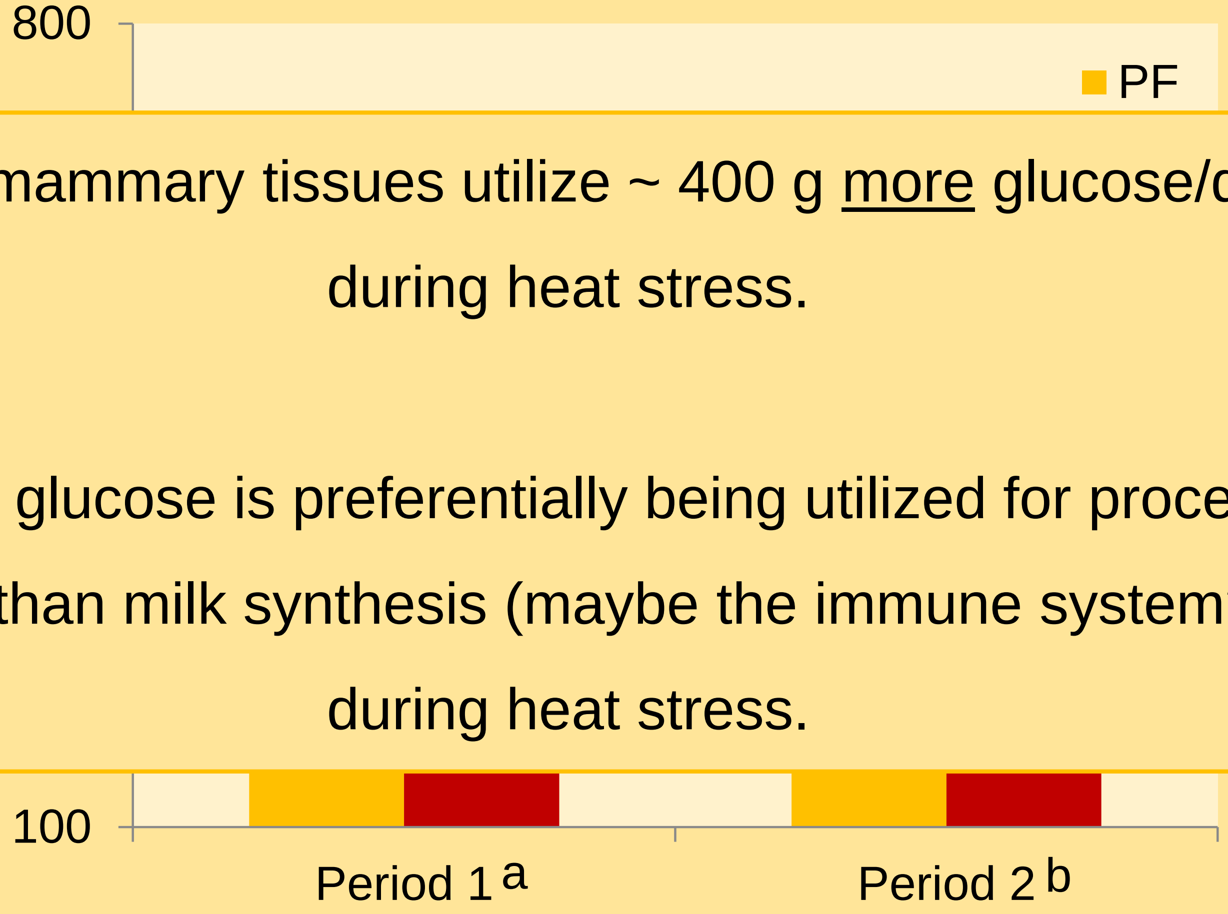


Heat Stress Cows Secrete ~400 g <u>less</u> lactose/day than Pair-Fed Thermal Neutral Controls

Is the liver producing ~ 400 g less glucose/day??
or is extra-mammary tissues utilizing ~400 g more/day?

Rhoads et al., 2009
Wheelock et al., 2010

Whole Body Glucose Production



Extra mammary tissues utilize ~ 400 g more glucose/day during heat stress.

Indicates glucose is preferentially being utilized for processes other than milk synthesis (maybe the immune system?) during heat stress.

Period: $P < 0.05$

Baumgard et al., 2011

Heat Stress Metabolism Review

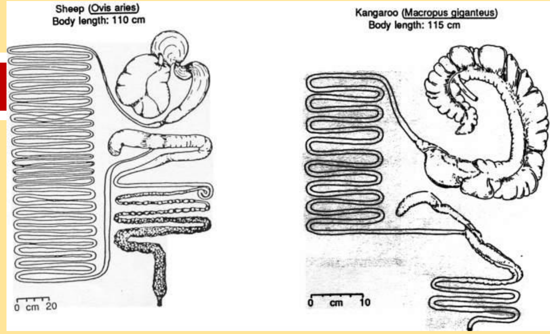
- <u>Expected</u>
  - ↑ catabolic hormones
  - ↓ insulin
  - ↑ adipose lipolysis
  - ↑ fatty acid oxidation
  - ↓ glucose oxidation
- <u>What Actually Occurs</u>
  - ↑ catabolic hormones
  - ↑ insulin
  - ↓ adipose lipolysis
  - ↓ fatty acid oxidation
  - ↑ glucose oxidation

Heat stress prevents “glucose sparing” that would normally be employed to prioritize muscle and milk synthesis.

What Explains the Other 50% of Decreased Productivity??

Gastro-Intestinal Tract Review

Reminder: Intestinal Functions



- GIT is a tube running from the mouth to the anus
  - Everything inside of the tube is technically “outside” of the body
- Digest and absorb nutrients
  - GIT lumen is a inhospitable environment
- Prevent parasites, pathogens, enzymes, acids, toxins etc.. From infiltrating “self”
  - Barrier function

Human GIT Surface Area:

That's an enormous amount of area to "defend"!

No wonder 70% of the immune system resides in GIT

Biology of Heat Stress Symptoms

Heat Stress and Gut Health

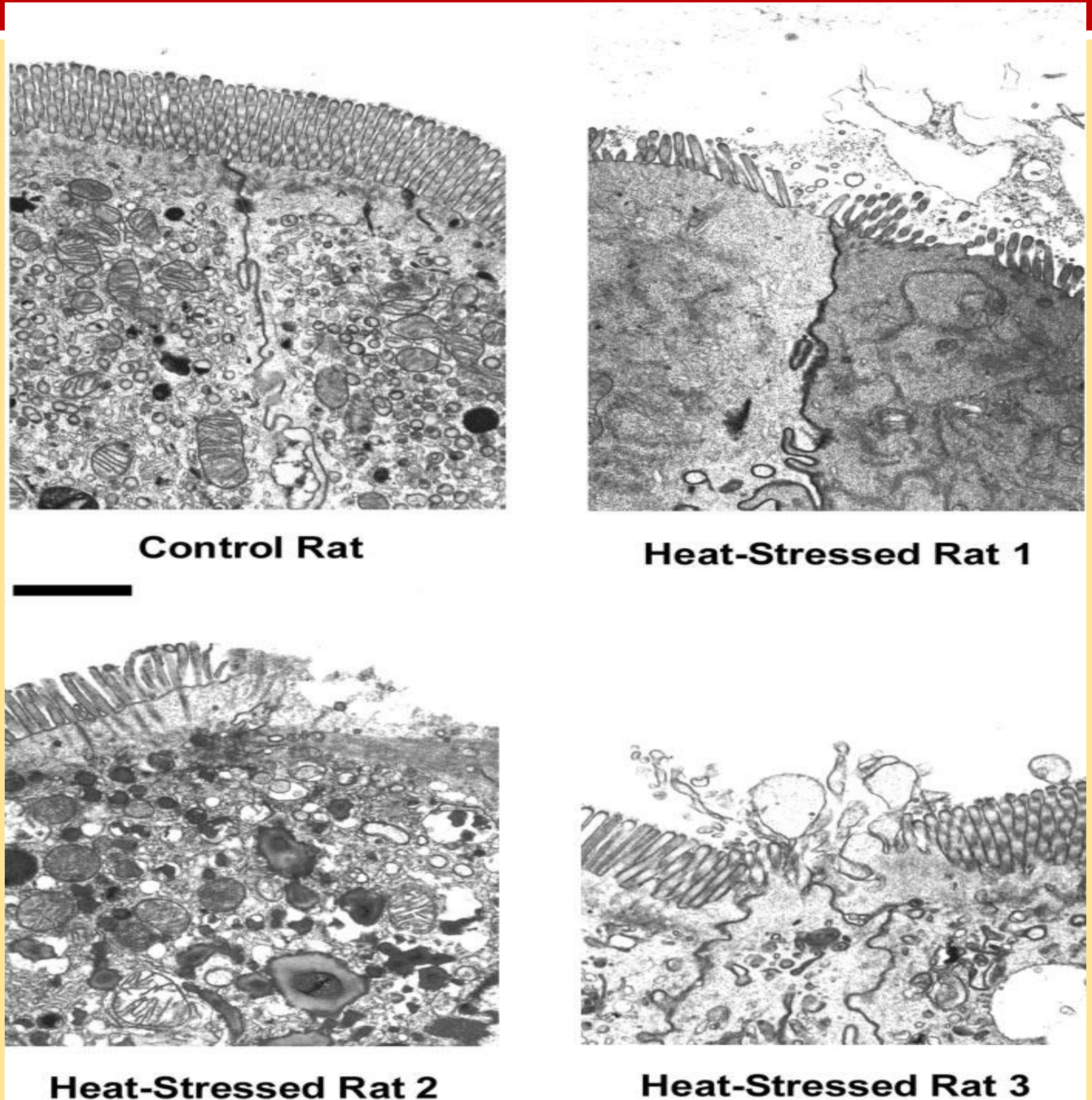
- Diversion of blood flow to skin and extremities
  - Attempting to maximize radiant heat dissipation

- Coordinated vasoconstriction in intestinal tissues
  - Reduced nutrient and oxygen delivery to enterocytes
  - Hypoxia increases reactive oxygen species (ROS)

- Reduced nutrient uptake increases rumen and intestinal osmolarity in the intestinal lumen
  - Multiple reasons for increased osmotic stress

Baumgard and Rhoads, 2013

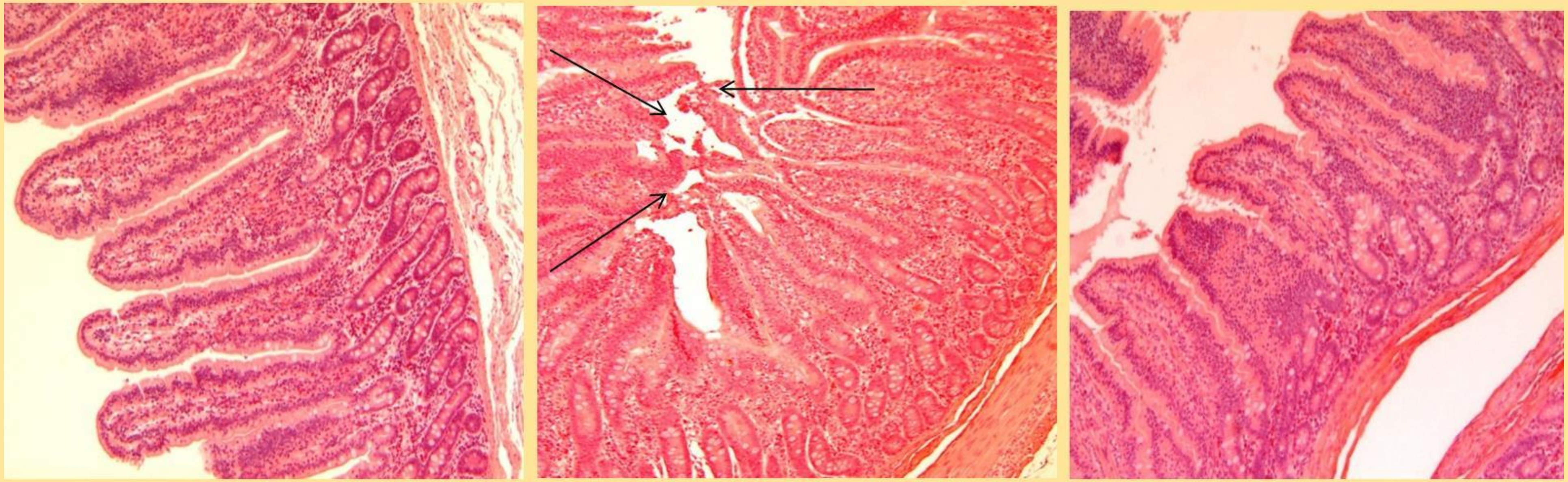
Gut Health and Heat Stress



Damage to the microvilli in rats 1 and 2 and cell membrane in rat 3

(Lambert, 2002)

Intestinal Morphology



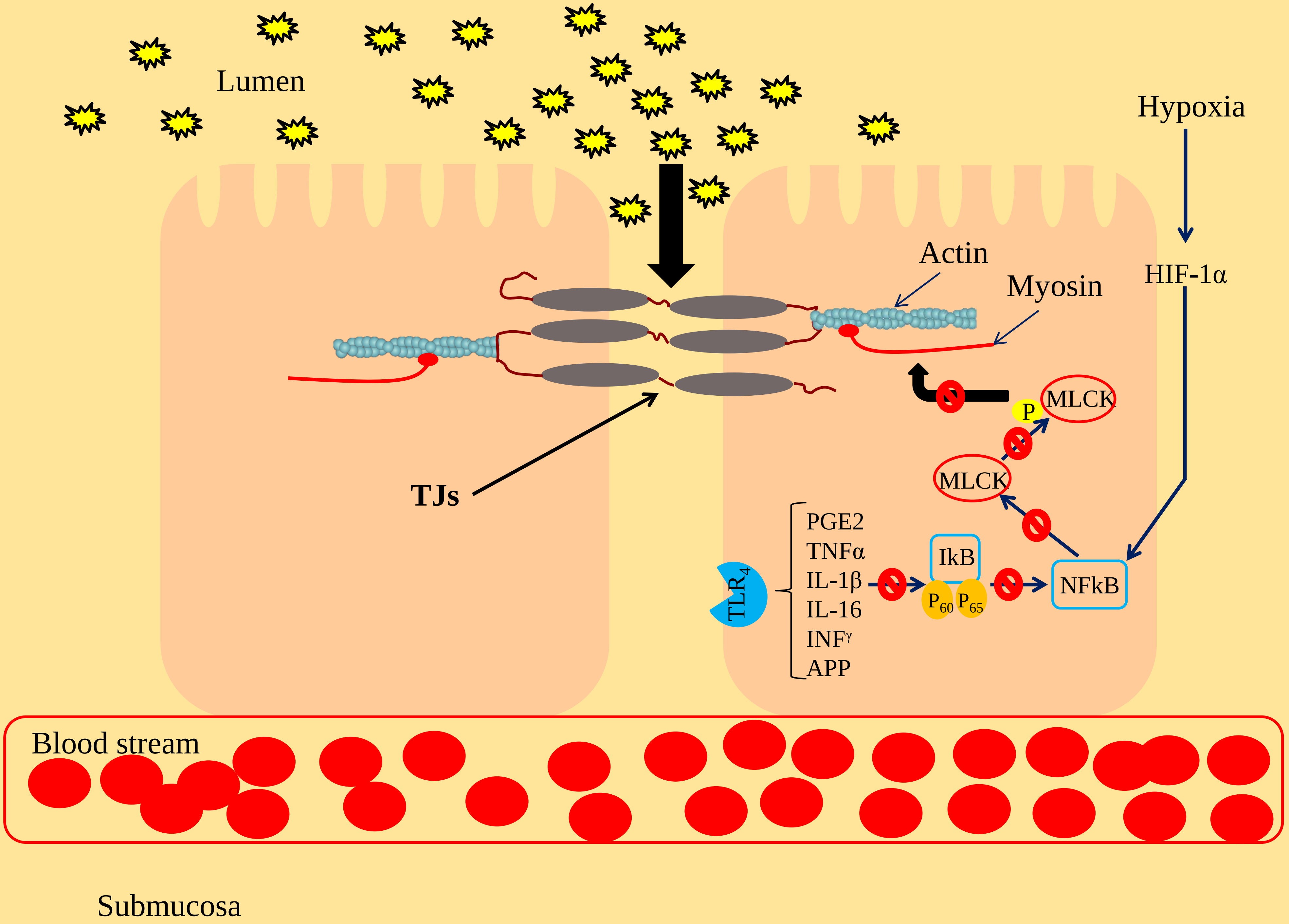
Thermal Neutral — Heat Stress — Pair-fed

Pearce et al., 2011

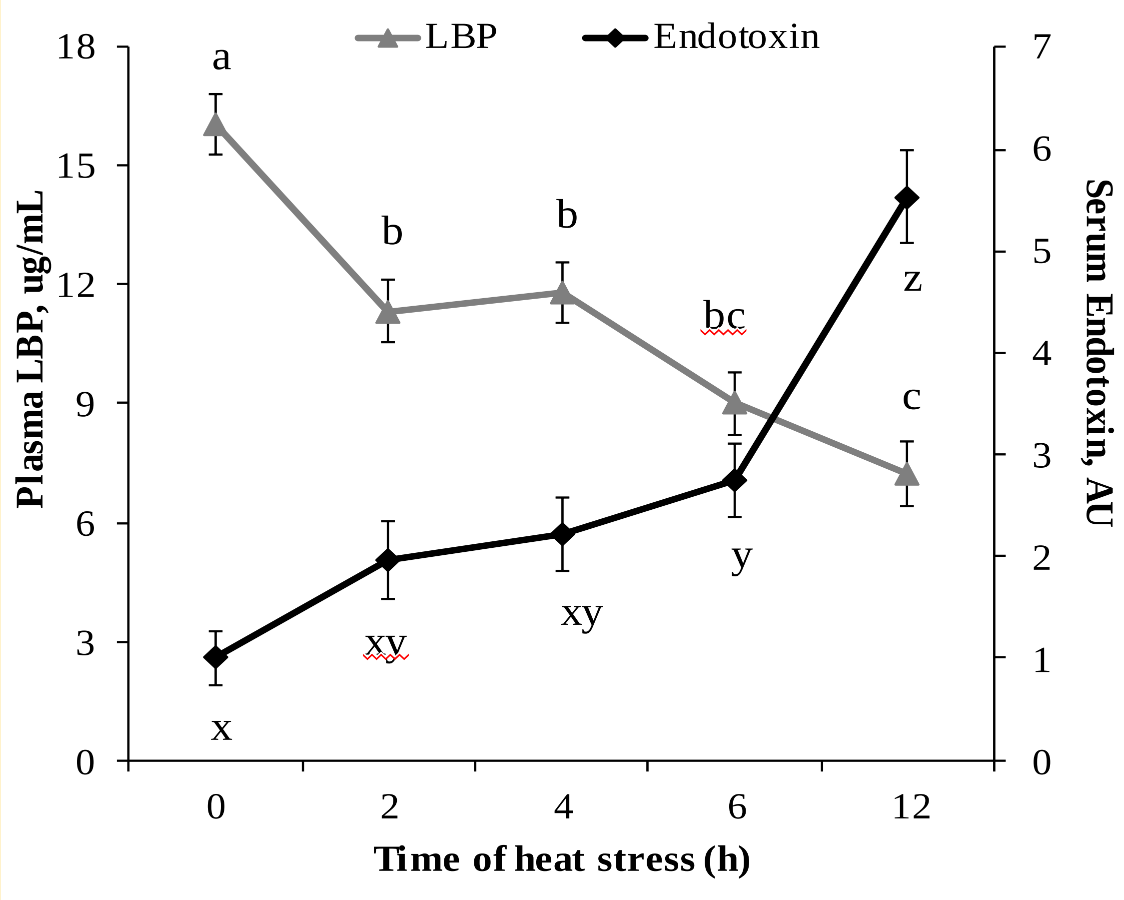
Heat Stress and Gut Health

- Lipopolysaccharide (LPS) stimulates the immune system

- LPS promotes inflammation production….catabolic condition
  - TNFα, IL-1 etc..
    - Reduced appetite
    - Stimulates fever
    - Causes muscle breakdown
    - Induces lethargy
    - ....reduces productivity

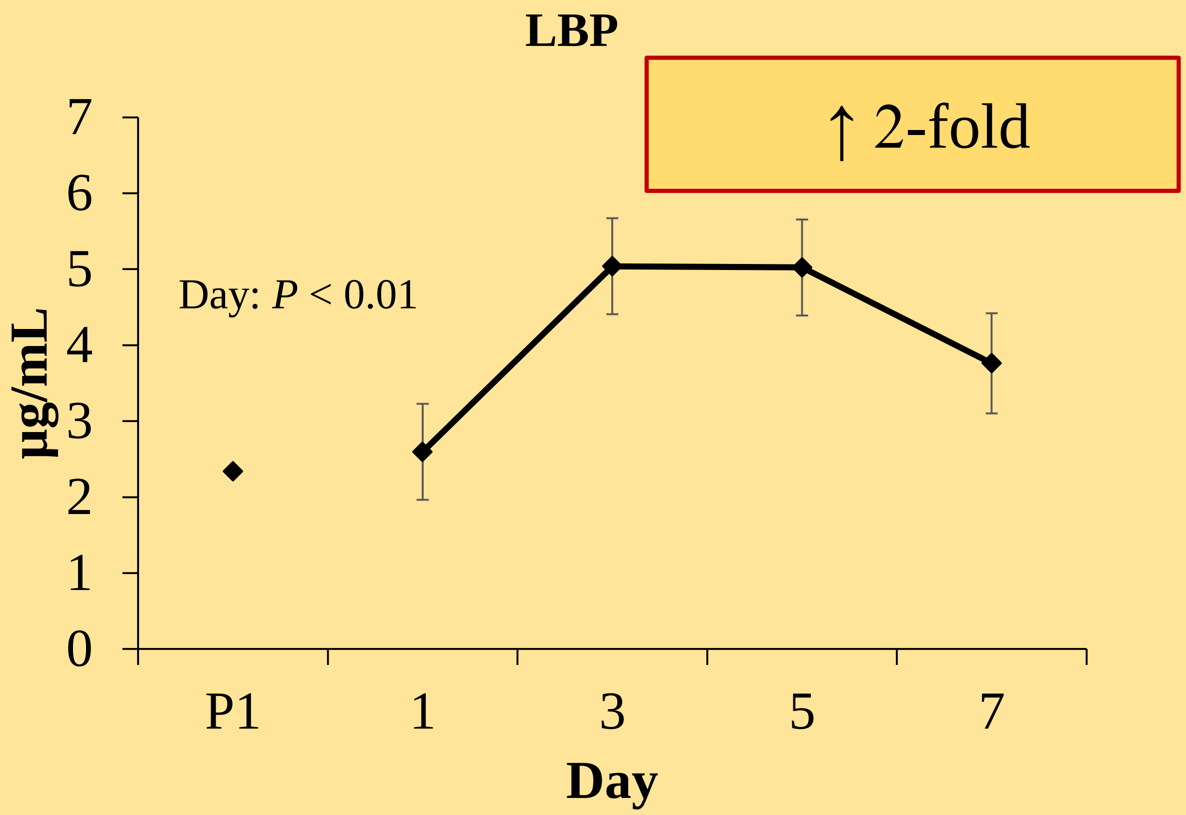

Lumen
Hypoxia
HIF-1α
Actin
Myosin
TJs
MLCK
P
MLCK
PGE2
TNFα
IL-1β
IL-16
INFγ
APP
TLR4
IkB
P60 P65
NFkB
Blood stream
Submucosa

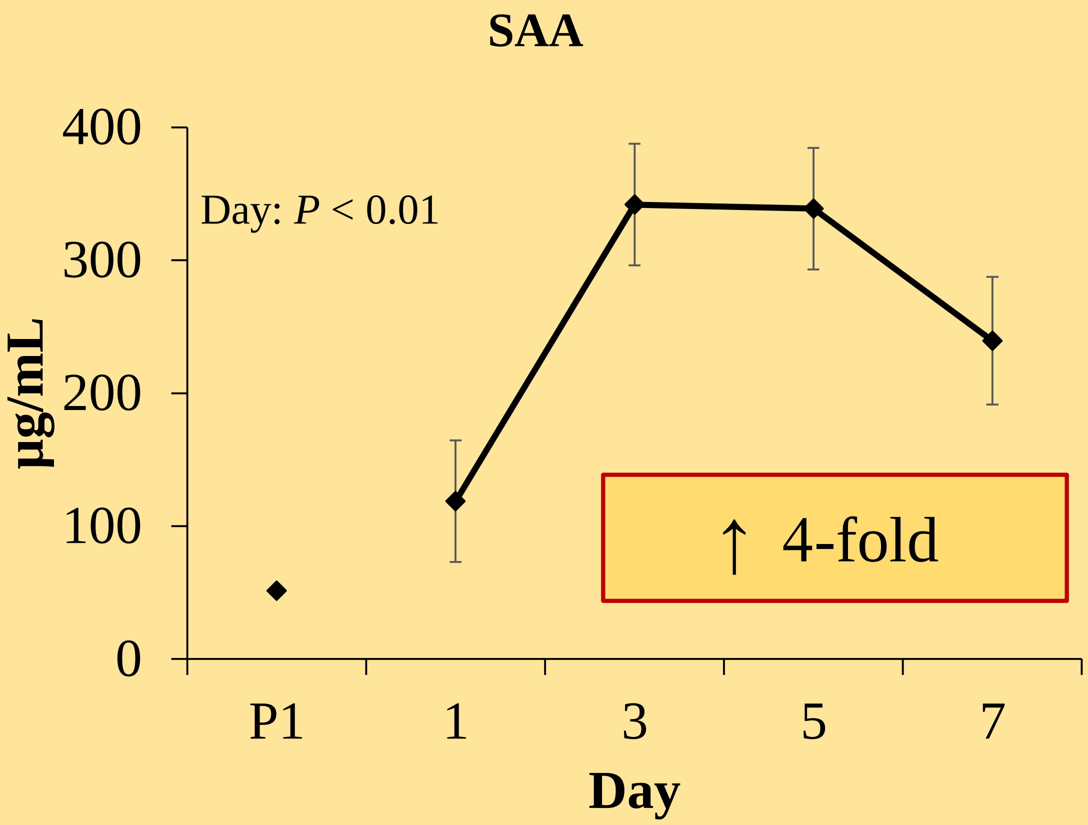
The effects of HS are rapid!



Pearce et al., 2015

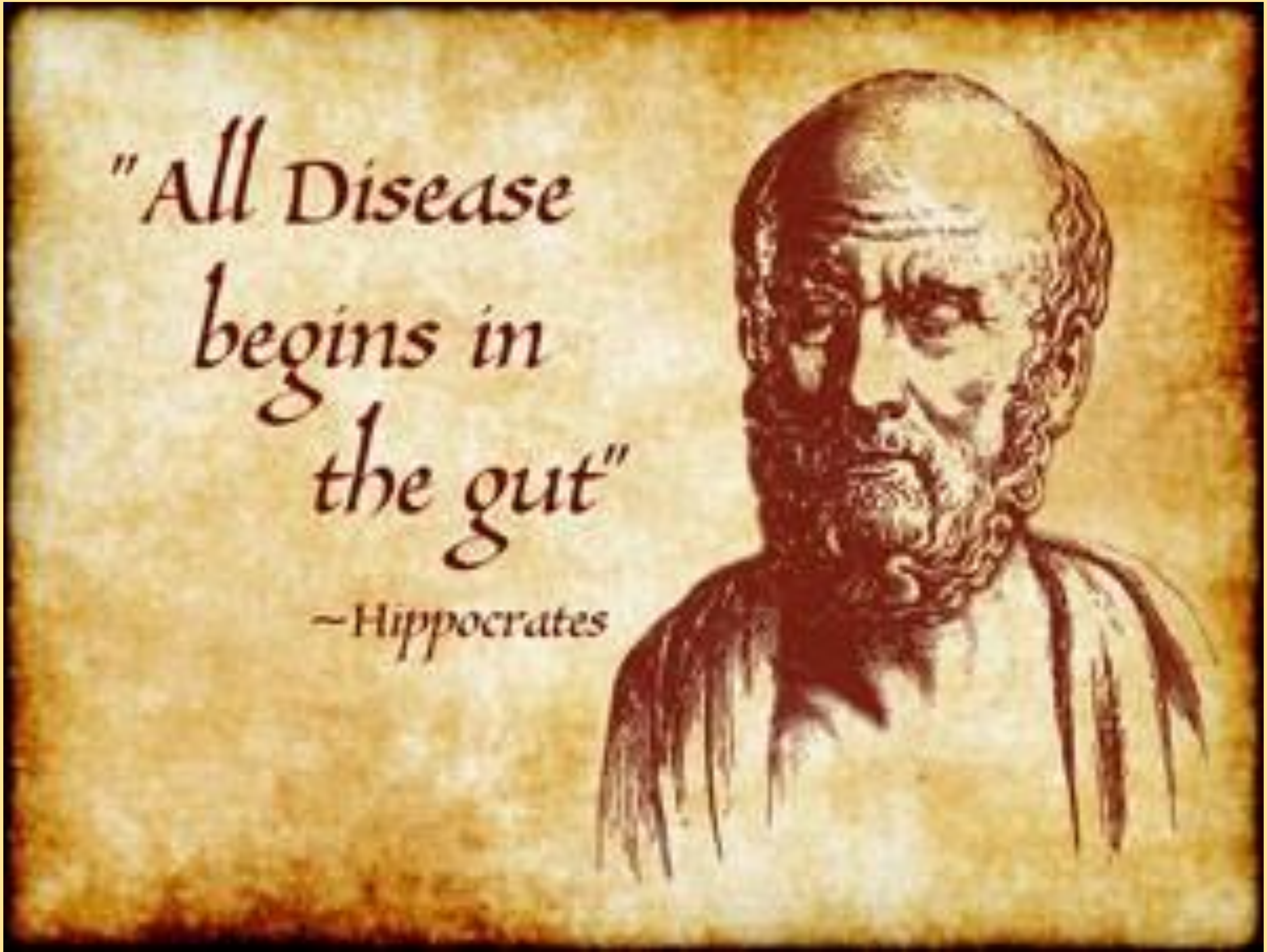
Acute Phase Proteins





Heat Stress is Essentially an Immune Activation Event

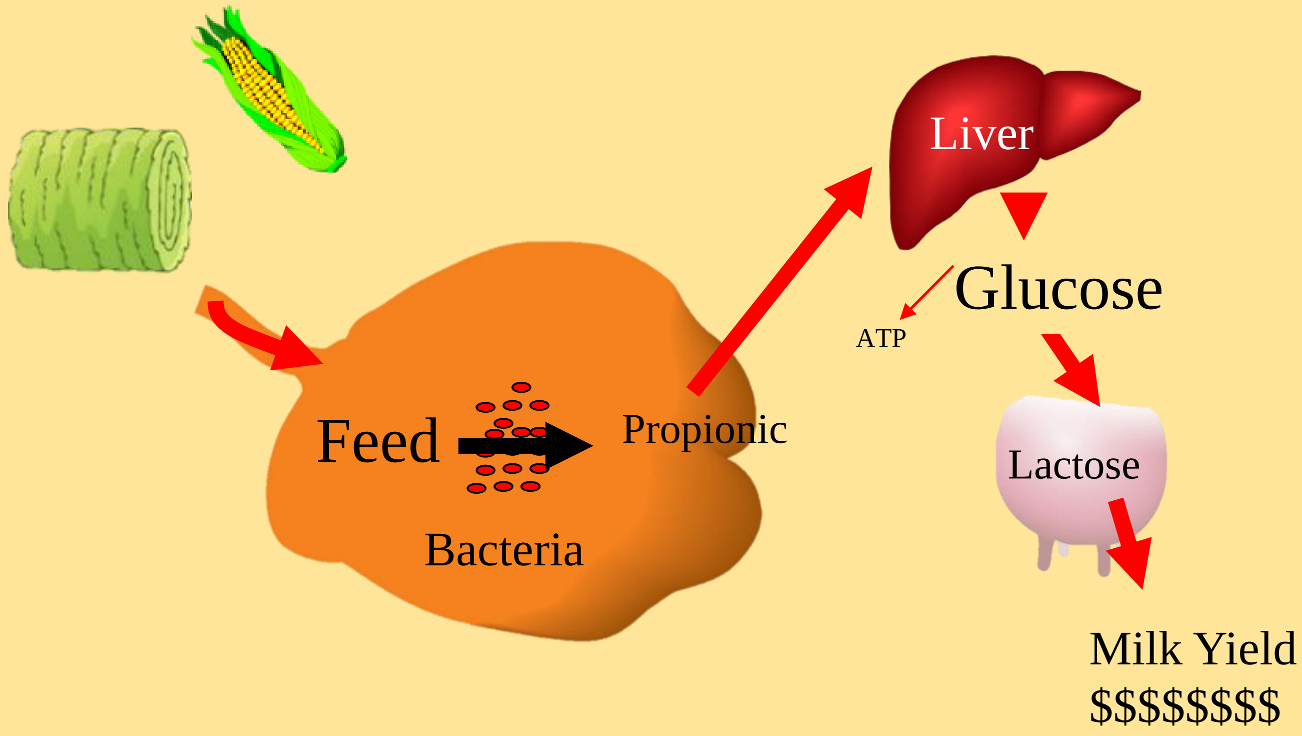
Similar to Other Infections


"All Disease
begins in
the gut"
~Hippocrates

So the Gut Becomes Leaky….the Immune System is Activated…….who Cares?

Friendly Reminder of Glucose's Importance

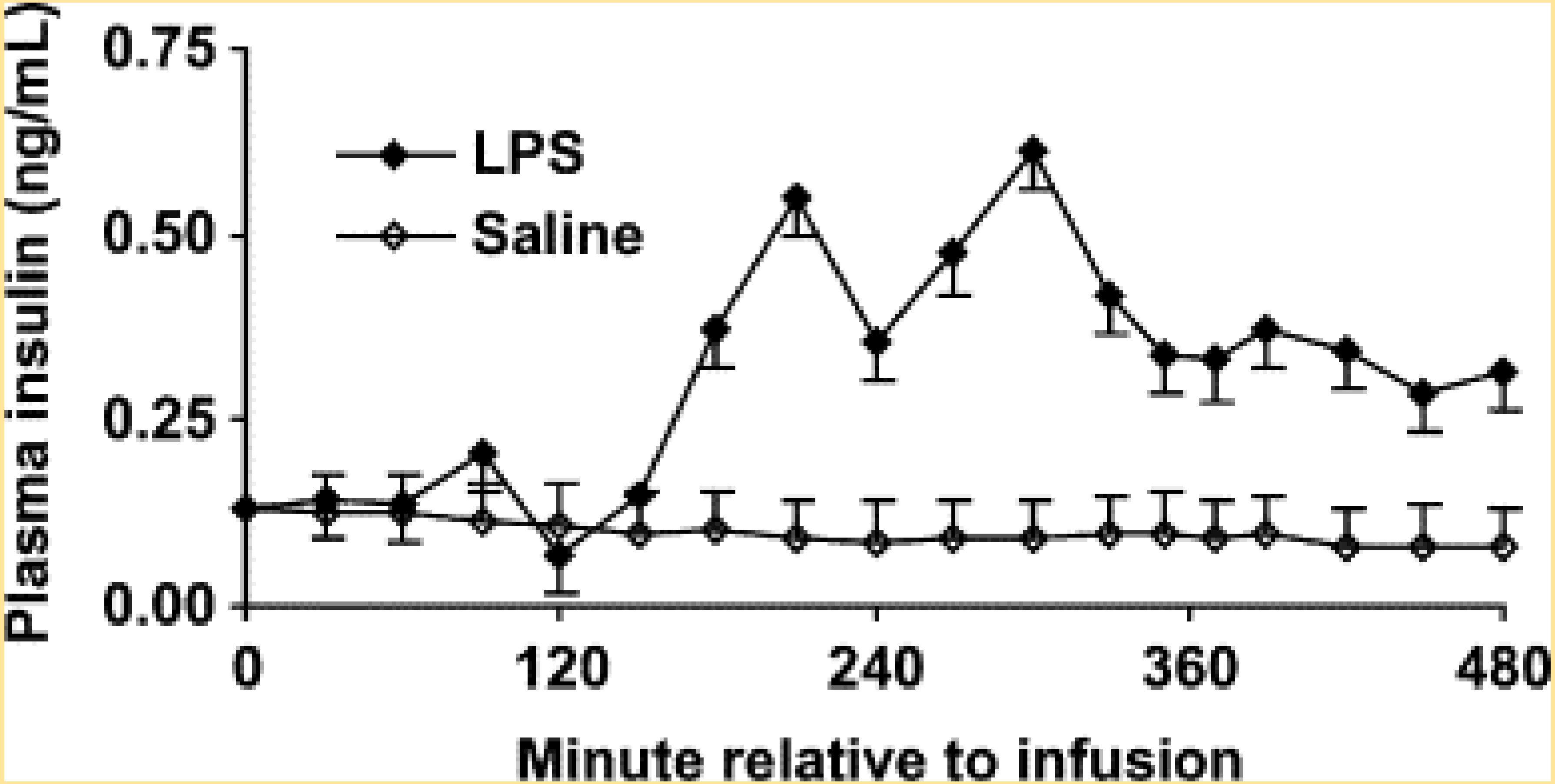
Glucose is primarily made from propionate
Lactose is made from glucose
72 g of glucose/ 1 kg of milk
<u>Milk yield</u> is primarily determined by the amount of synthesized lactose



Insulin??

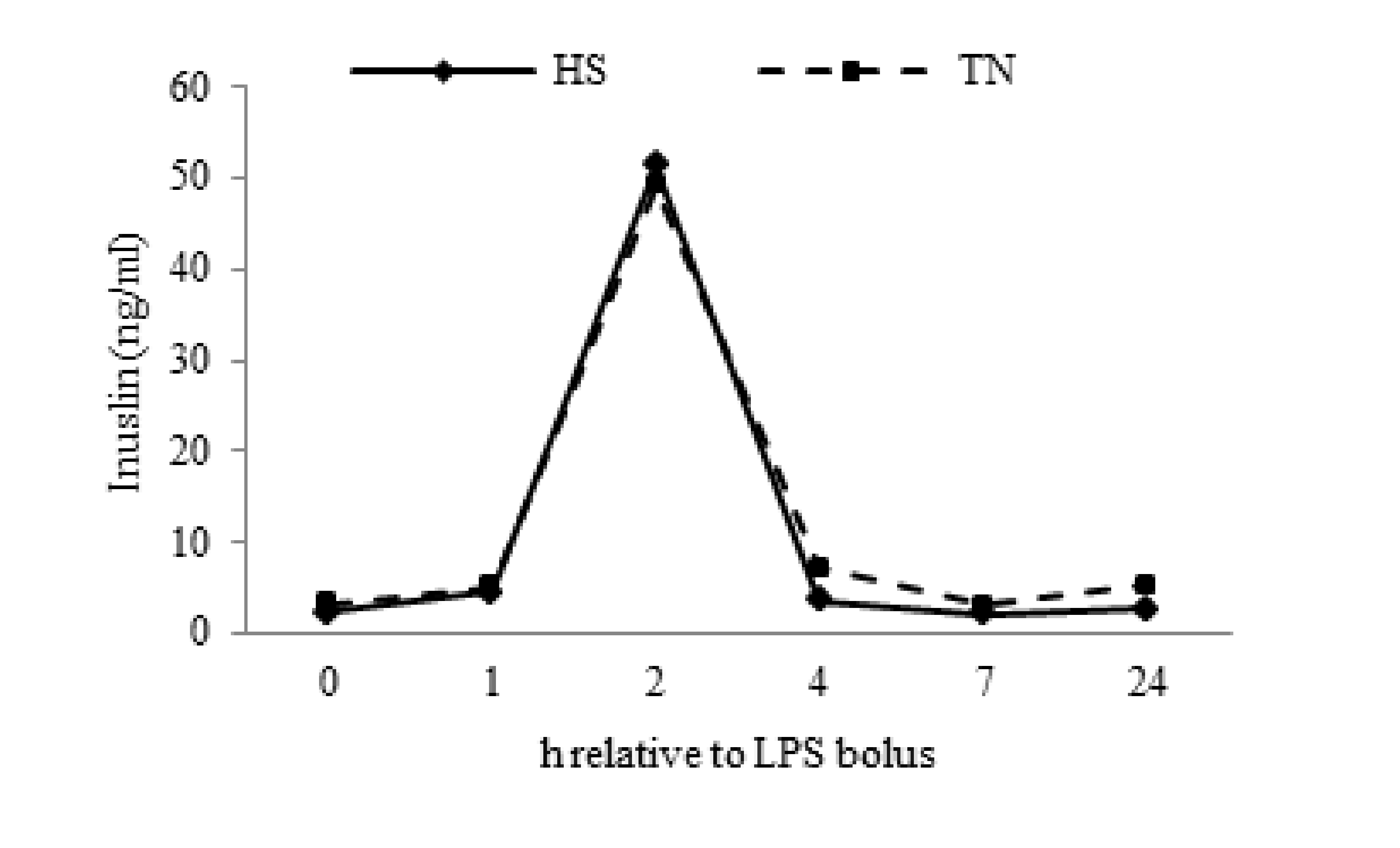
- What’s insulin’s role during immuneactivation and inflammation?

Mammary LPS Infusion Increased Circulating Insulin



Waldron et al., 2006

LPS Acutely Increases Insulin Secretion



Rhoads et al., 2009 ADSA Abstract

Professor Otto Warburg

THE METABOLISM OF TUMORS IN THE BODY.

By OTTO WARBURG, FRANZ WIND, and ERWIN NEGELEIN.

(From the Kaiser Wilhelm Institut für Biologie, Berlin-Dahlem, Germany.)

(Received for publication, April 29, 1926.)

Translation: “Metabolism of “Leukocytes

Stoffwechsel der weißen Blutzellen

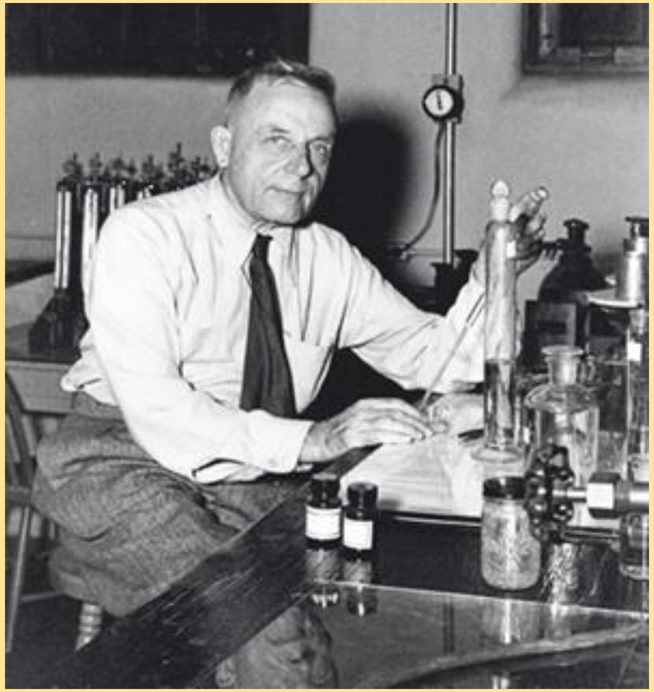
Von Otto Warburg, Karlfried Gawehn und August-Wilhelm Geissler

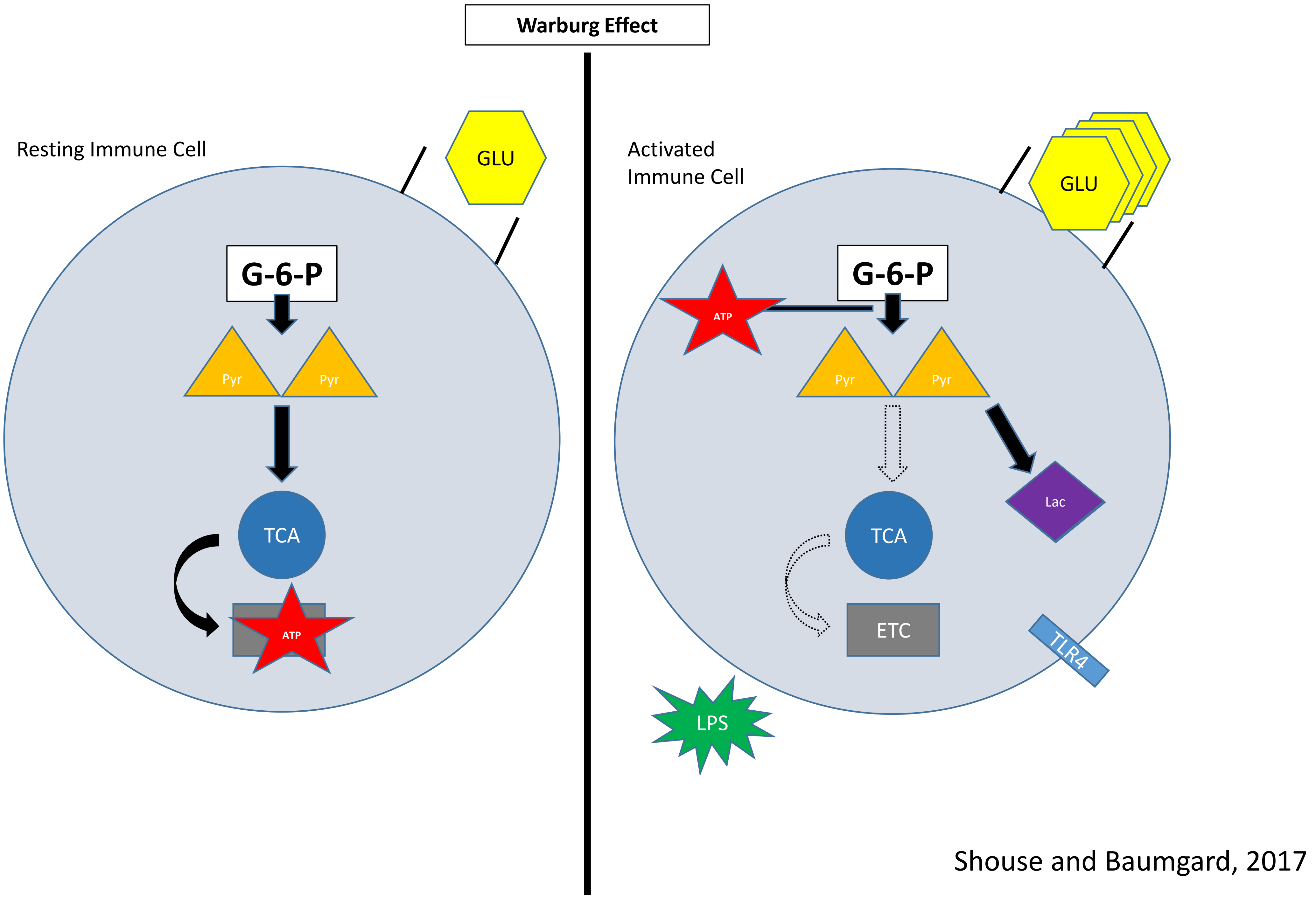
Aus dem Max-Planck-Institut für Zellphysiologie, Berlin-Dahlem

(Z. Naturforschg. **13 b**, 515—516 [1958]; eingegangen am 21. Juni 1958)

Der „Krebsstoffwechsel“ der normalen weißen Blutzellen, der vielfach, in der letzten Zeit z. B. von W. Remmele und F. Seelich [1], gefunden wurde, ist ein Artefakt infolge mechanischer und chemischer Schädigungen.

- First recognized the unique metabolism of cancer cells (1927)
  - Large glucose consumers
  - Switch from oxidative phosphorylation → aerobic glycolysis
  - 1931 Noble Prize
- Also observed activated lymphocytes become highly glycolytic (1958)
  - Leukocytes are insulin sensitive
- Mentored Hans Krebs
- Drinking buddy with Albert Einstein




Warburg Effect
Resting Immune Cell
GLU
G-6-P
Pyr
Pyr
TCA
ATP
Activated
Immune Cell
GLU
G-6-P
ATP
Pyr
Pyr
Lac
TCA
ETC
TLR4
LPS
Shouse and Baumgard, 2017

How much glucose is the entire body using??

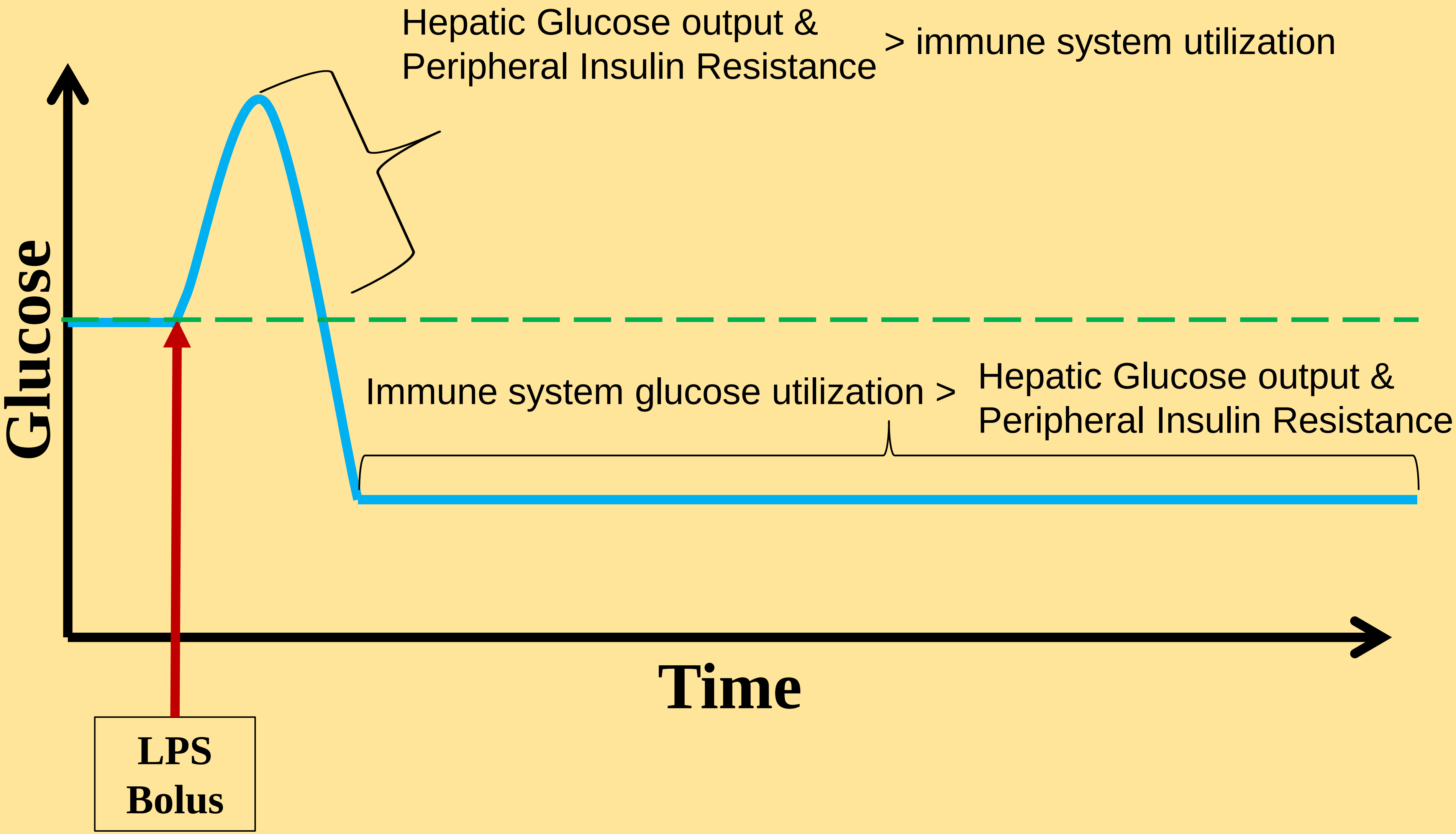
80 years later and we still not know how much glucose the immune system needs *in vivo*?

Prerequisite for developing mitigation strategies

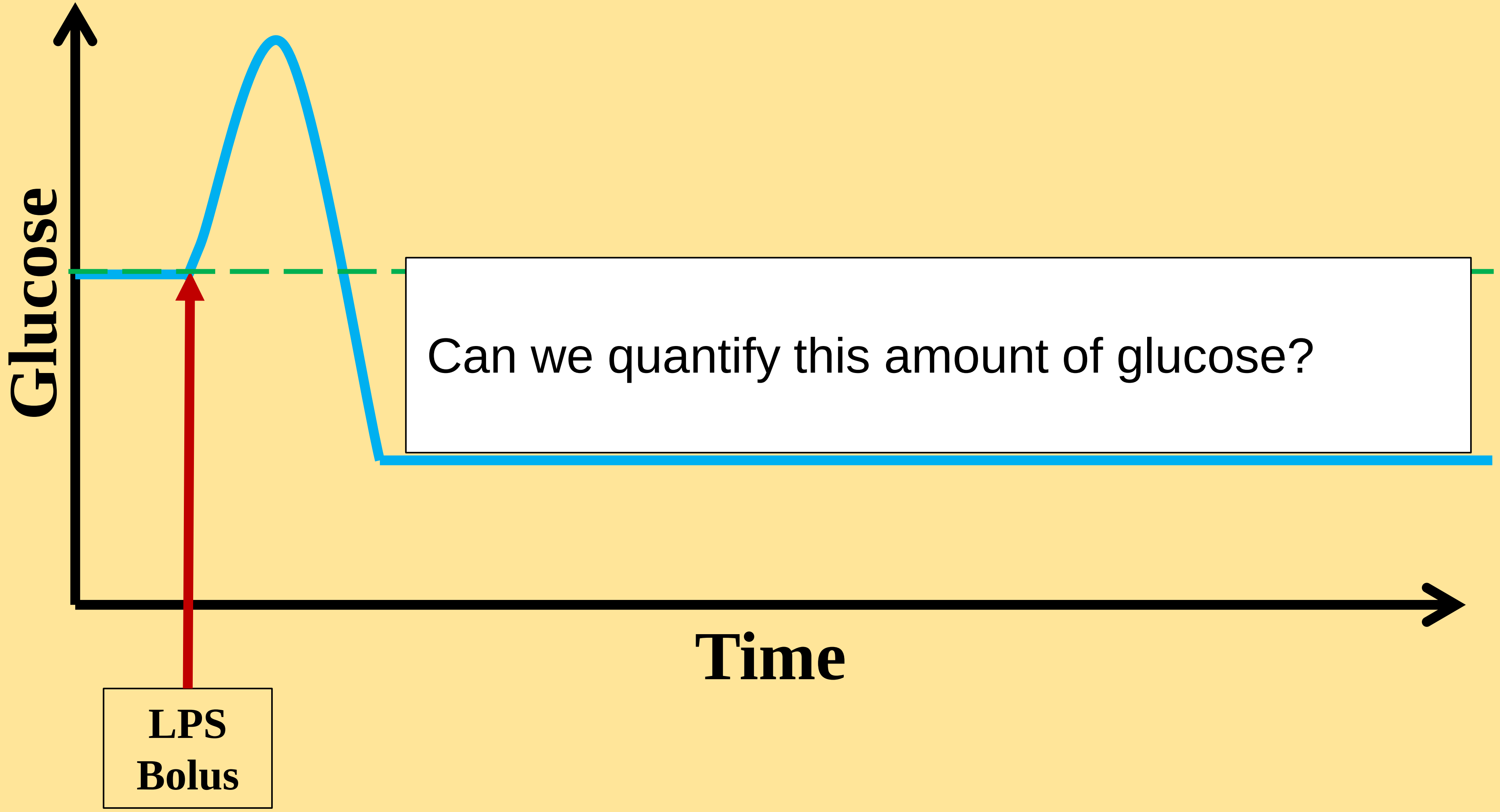
What's the Problem?:

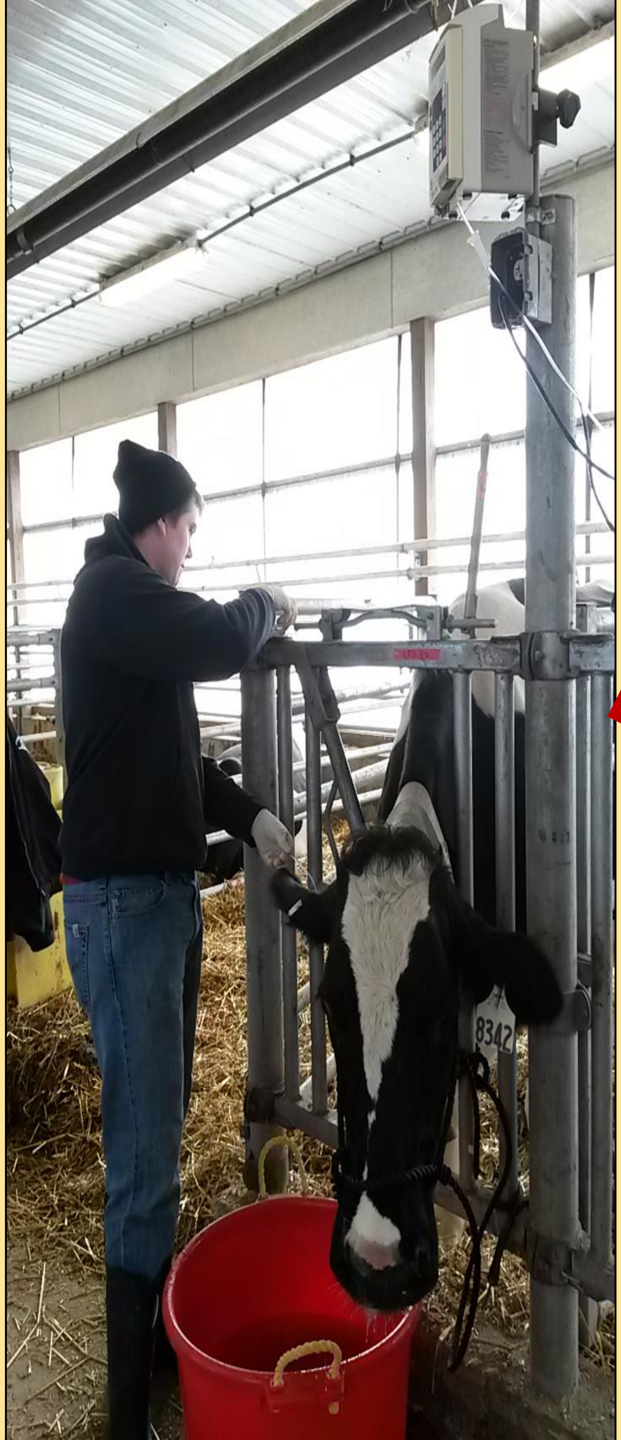
- Dynamic and ubiquitous distribution of the immune system throughout tissues
  - Allows for quasi tissue/organ quantification but….
  - Complicates whole-body quantification

LPS Challenge & Blood Glucose



LPS Challenge & Blood Glucose

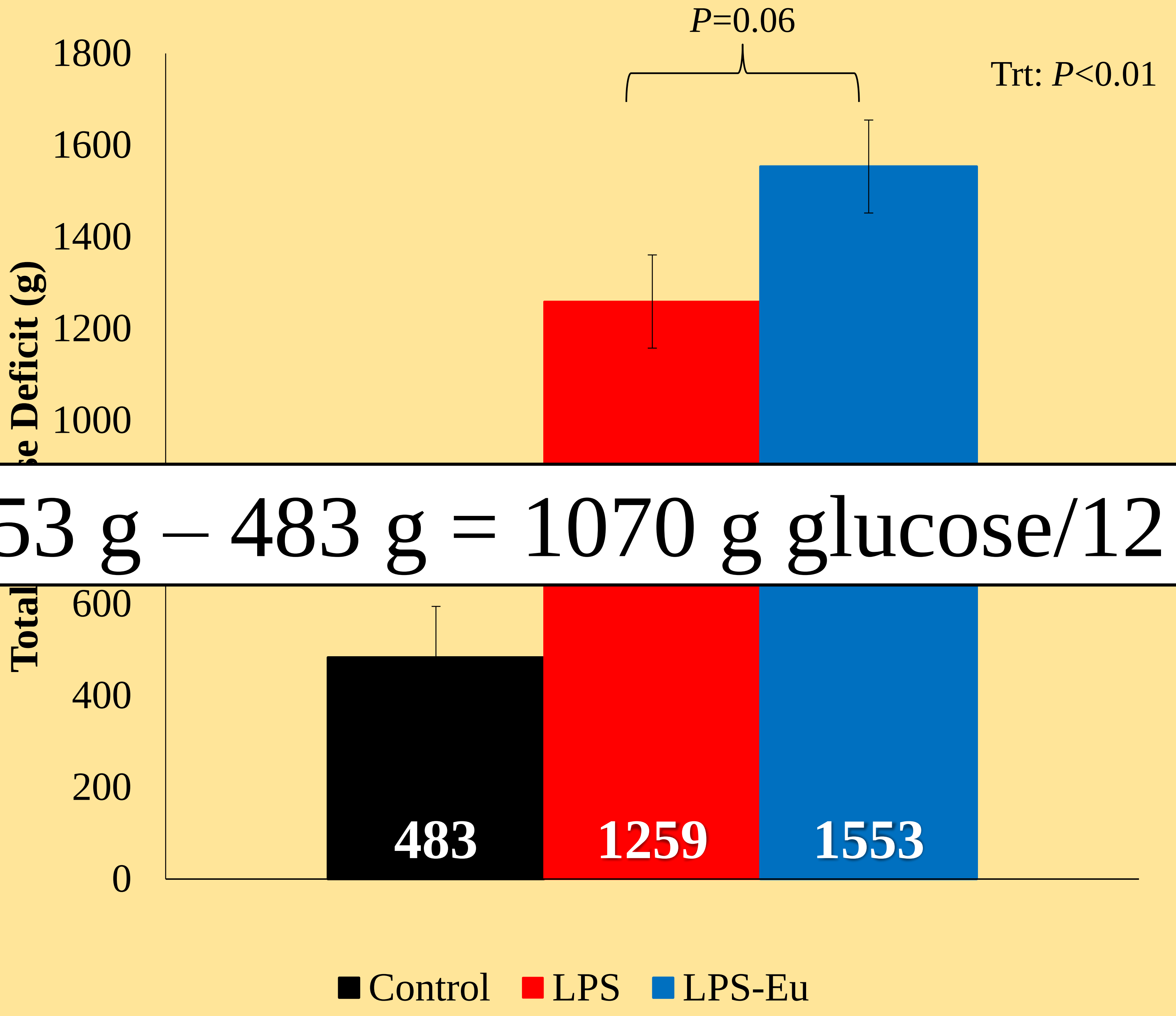




Cow # 8341 Target [Glu] Range: **61-67**

Min	Blood Sample (✓)	[Glucose] (mg/dL)	Glucose ROI (mL/hr)	Tr (F)
60 (1 hr)	✓	96	0	101.3
70		84	0	
80		79	0	
90	✓	91	0	100.8
100		98	0	
110		116	0	
120 (2 hr)	✓	115	0	101.2
130		102	0	
140		87	0	
150	✓	68	0	100.9
160		49	50	
170		54	50	
180 (3 hr)	CBC iStat Urine ✓✓✓	55	75	100.7
190		56	75	

Kvidera et al., 2015



1553 g – 483 g = 1070 g glucose/12 h

Kvidera et al., 2015

8.4 Mcal of energy!

Study Limitations

- Glucose uptake by other tissues
  - ↓ insulin sensitivity in adipose
    - (Song et al., 2006, Shi et al., 2006, Poggi et al., 2007)

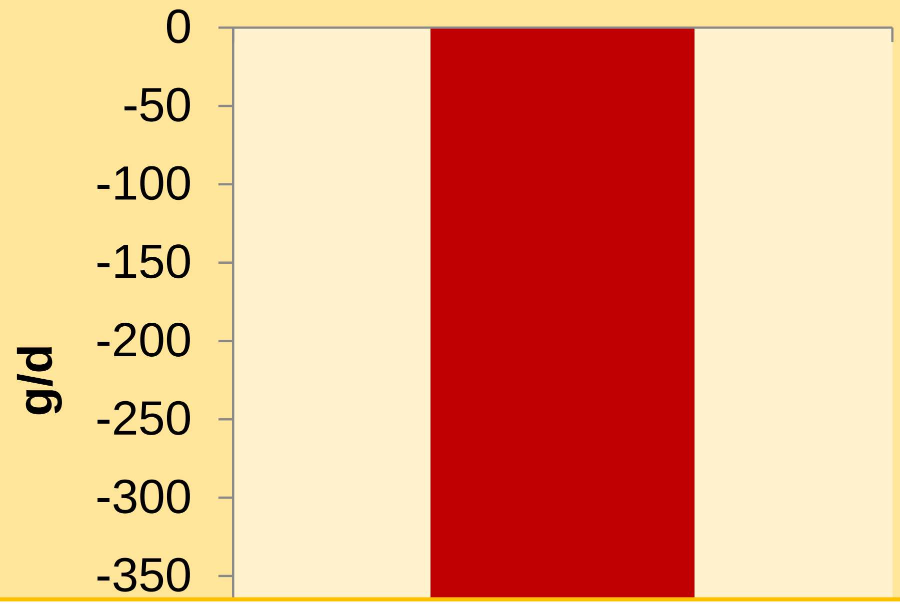
Conclusion: 1 kg/12 h is potentially underestimated!

- Glucose output by liver
  - Increased
    - (Lang et al., 1993, McGuinness et al., 1993, Ling et al., 1994)

Conserved Response

Species:	Immune glucose utilization
Steers:	1.0 g/kg $BW^{0.75}$/h (Kvidera et al., 2016)
Pigs:	1.1 g/kg $BW^{0.75}$/h (Kvidera et al., 2015)
Cows:	0.7 g/kg $BW^{0.75}$/h (Kvidera et al., 2017)
Cows:	1.0 g/kg $BW^{0.75}$/h (Horst et al., 2018)

Remember: We couldn't account for almost 1 pound of glucose during heat stress



Heat Stress Cows Secrete
~400 g less lactose/day than Pair-Fed Thermal Neutral Controls

Is the liver producing ~ 400 g less glucose/day??
or is extra-mammary tissues utilizing ~400 g more/day?

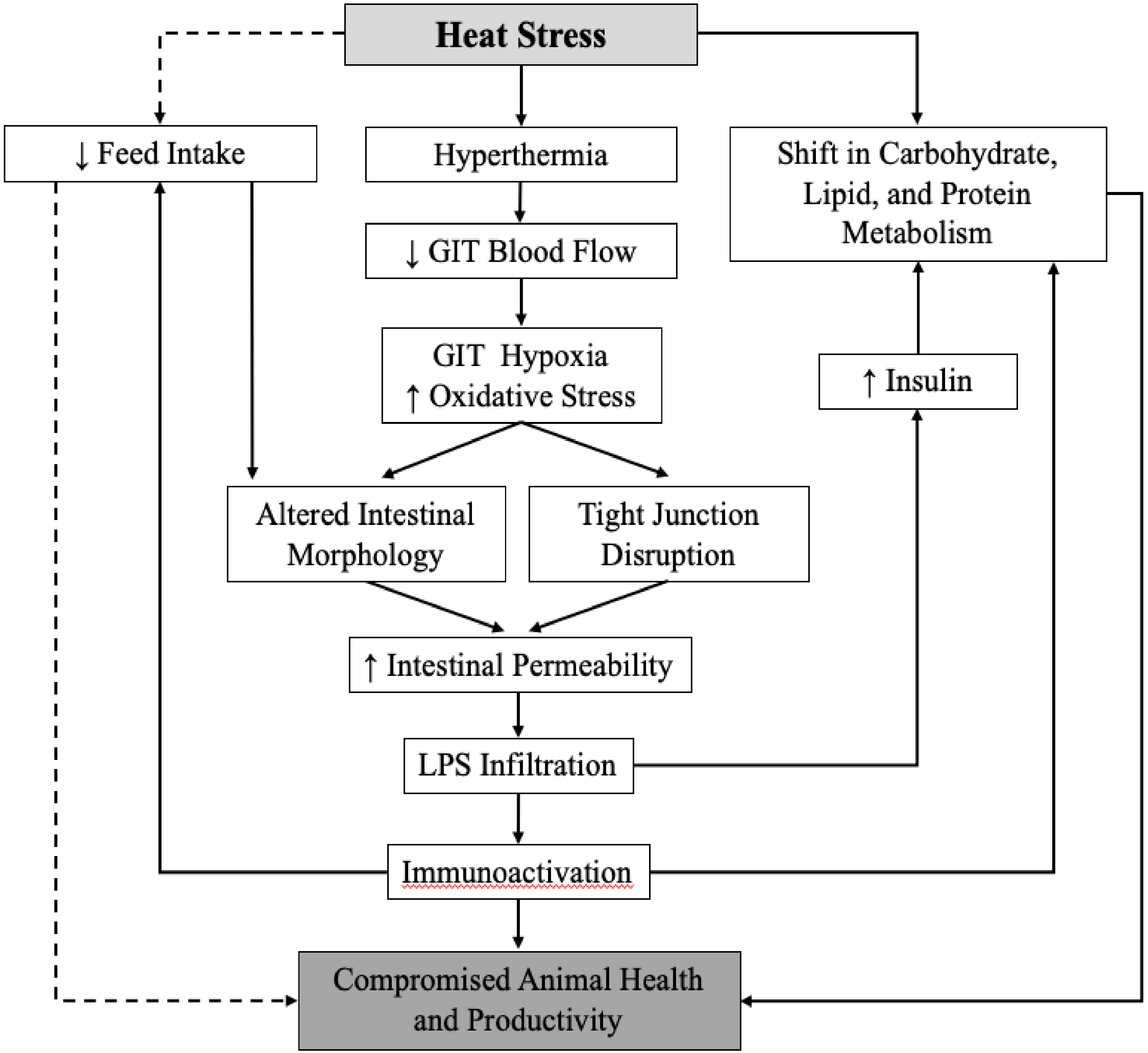
Rhoads et al., 2009
Wheelock et al., 2010

Practical Implications: Growth

- Immune System Glucose: ~1000 g/d
  - 1000 g of CHO x 4.1 kcal/g = 4,100 kcal
- Protein synthesis: 10 kcal/g (Patience, 2012)
- 4,100 kcal ÷ 10 kcal/g = 410 g of protein
- 410 g PTN ÷ ~30% dm = ~1,366 g of lean tissue

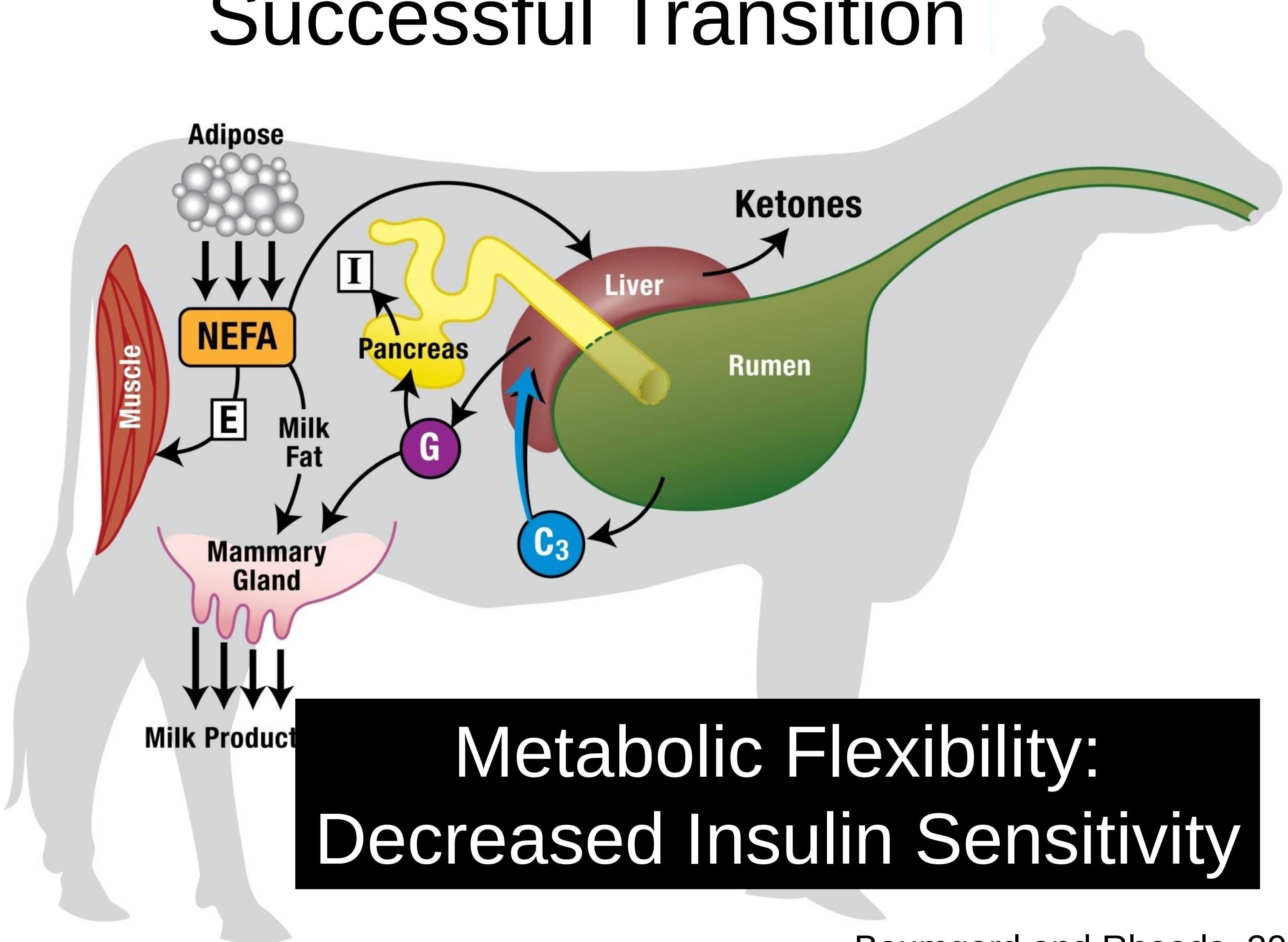
Metabolic Adaptations to Leaky Gut

Summary



Heat Stress
↓ Feed Intake
Hyperthermia
Shift in Carbohydrate, Lipid, and Protein Metabolism
↓ GIT Blood Flow
GIT Hypoxia
↑ Oxidative Stress
↑ Insulin
Altered Intestinal Morphology
Tight Junction Disruption
↑ Intestinal Permeability
LPS Infiltration
Immunoactivation
Compromised Animal Health and Productivity

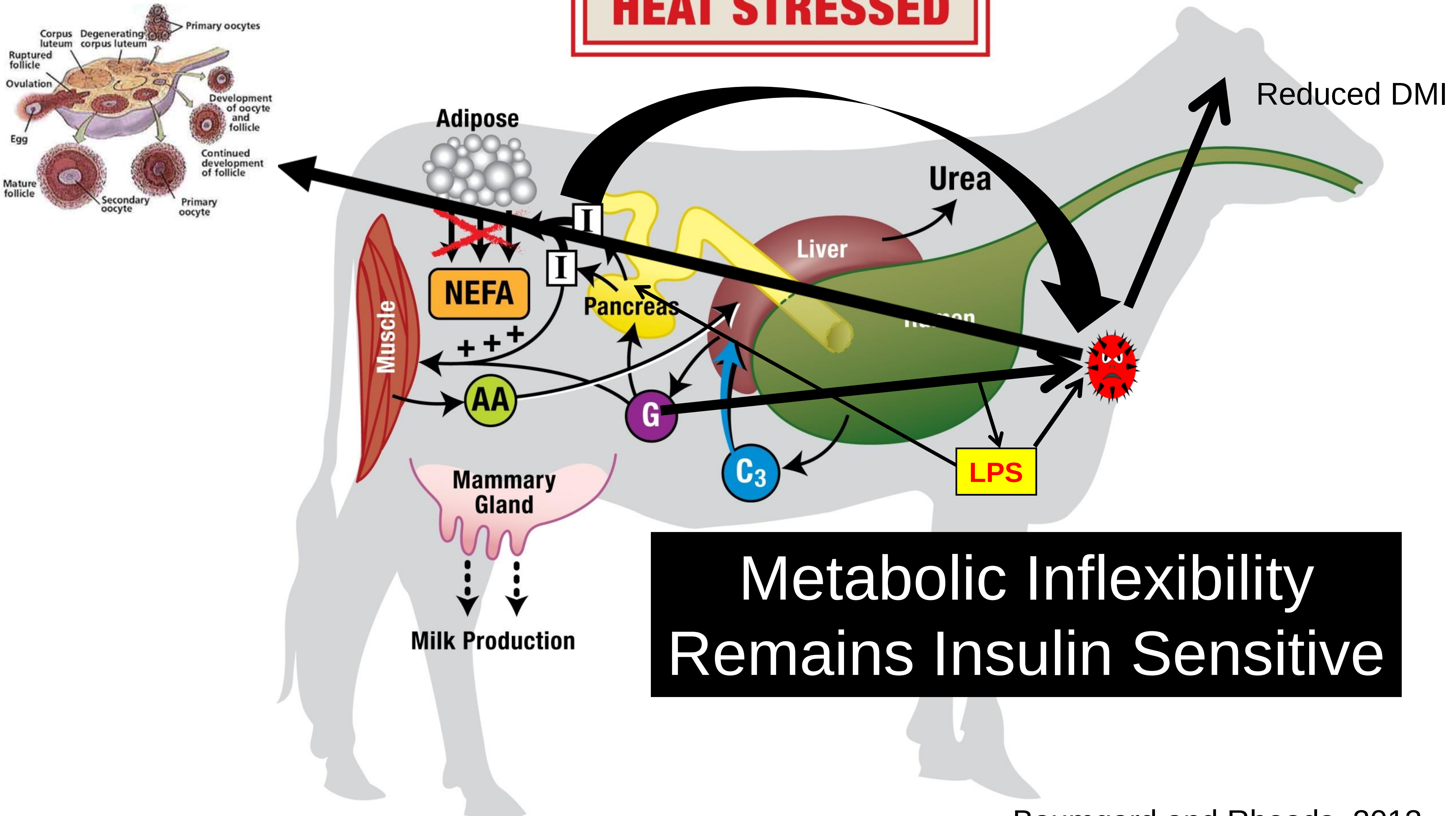
Successful Transition



Metabolic Flexibility:
Decreased Insulin Sensitivity

Baumgard and Rhoads, 2013

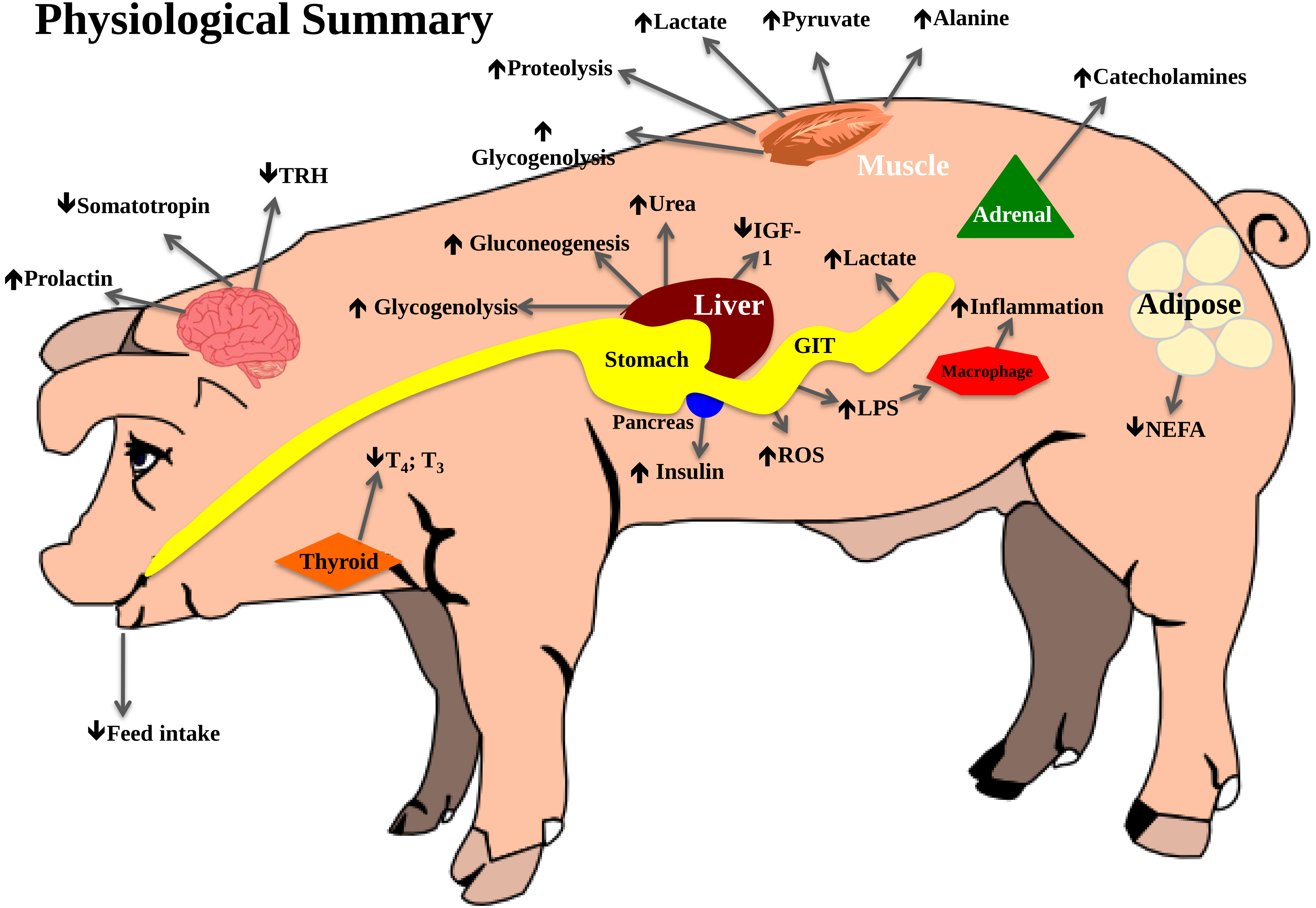
HEAT STRESSED



Metabolic Inflexibility
Remains Insulin Sensitive

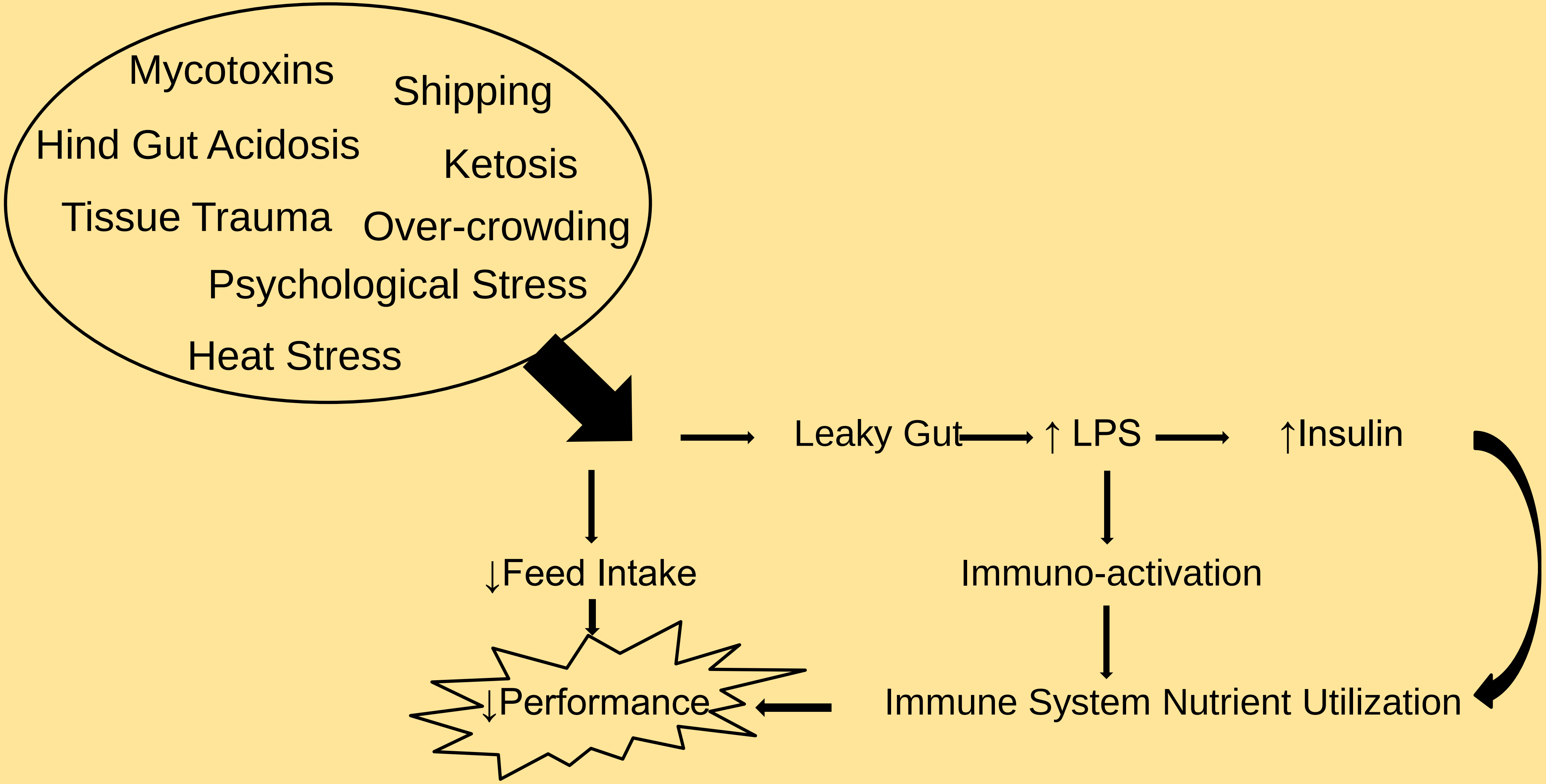
Baumgard and Rhoads, 2013

Heat Stress Metabolic and Physiological Summary



Baumgard et al., 2014

Stress Umbrella



Conclusions

- Reduced feed intake only explains 50%
- The GIT is the epicenter of the heat stress response
- Heat stressed induced intestinal hyperpermeability causes an immune response
- The immune system has a higher priority than making of milk, muscle, fetus etc.
- The activated immune system uses an enormous amount of glucose
- Products aimed at ameliorating leaky gut have the biggest opportunity to prevent seasonal losses

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    - # 2005-35203-16041
    - # 2008-35206-18817
    - # 2010-65206-20644
    - # 2011-67003-30007
    - # 2014-67015-21627
    - # 2015-10843
    - # 2017- 05931
    - # 2017-10843
- Alltech
- Zinpro Inc.
- FormAFeed
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- Novus


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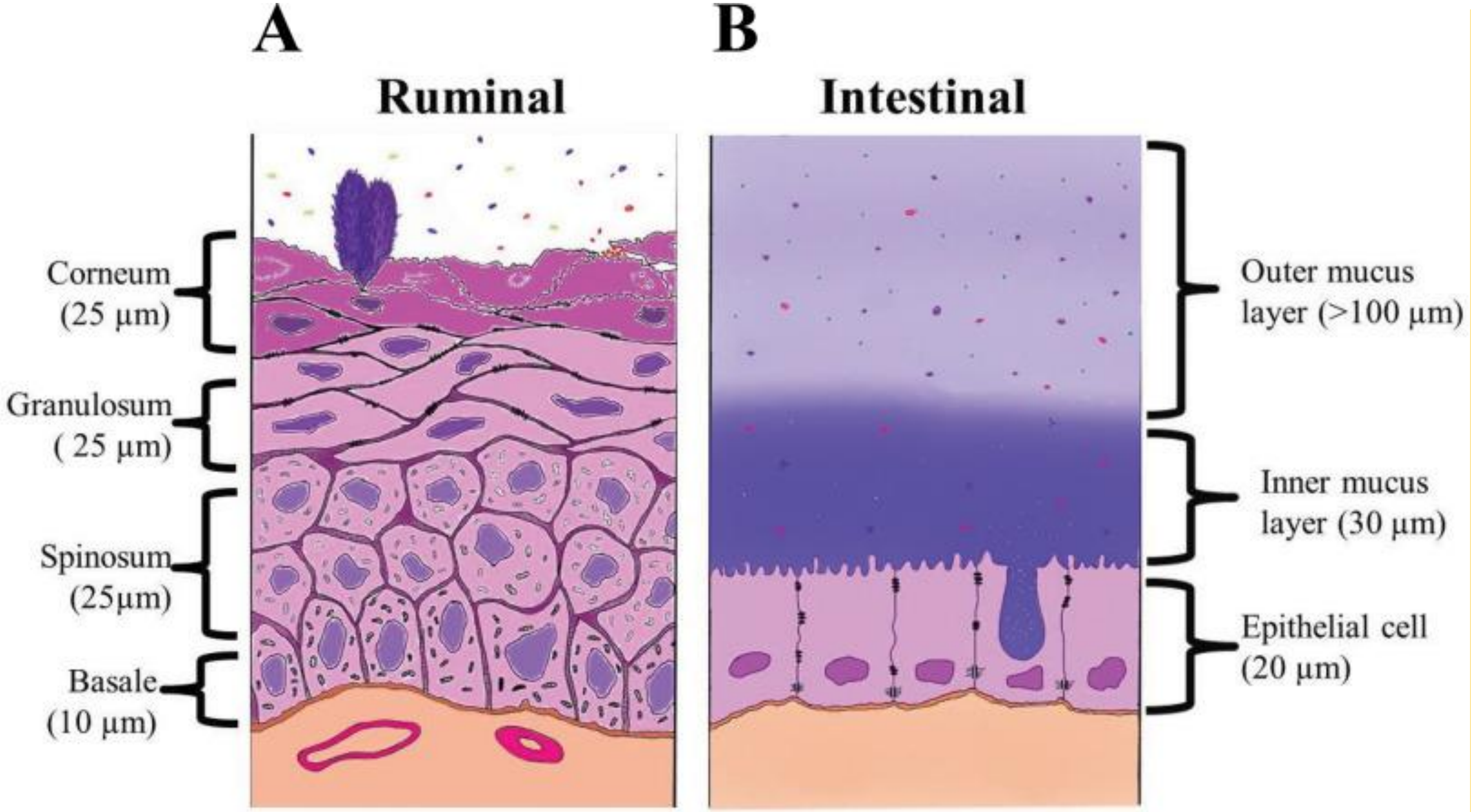
Gastrointestinal Epithelial: aka Gut Barrier

- Reticulo-rumen and omasum
  - Stratified squamous epithelium
    - 4 distinct strata
    - Multiple layers (maybe > 10 layers thick)
      - 85 um separating “outside” from self
    - No mucus
- Rest of GIT
  - Columnar epithelium
    - Single layer epithelium
      - 20 um separating “outside” from self
    - Mucus lined



Steele et al., 2016 JDS