Insulin Resistance: Friend or Foe?

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Metabolic Regulation of Body Fat Mobilization

- Regulation is very complex
- There are many hormones involved
- One of the most important hormones is insulin

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Metabolic Roles of Insulin

- Facilitates glucose entry into cells
- Inhibits hepatic gluconeogenesis
- Inhibits hepatic glycogenolysis
- Enhances adipose fatty acid synthesis
- Enhances adipose triglyceride synthesis
- Enhances adipose uptake of TG
- Inhibits adipose lipolysis

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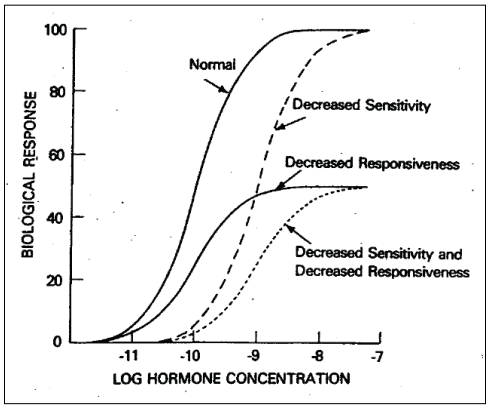
Insulin resistance (IR)



(Kahn, 1978)

Decreased Sensitivity

- Maximal response is unchanged
- Greater concentration of insulin is needed to elicit a normal response

Decreased Responsiveness

- Reduced maximal response

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Insulin Resistance (IR)

Definition:

"Normal concentrations of insulin produce a less than normal biologic response."

(Kahn, 1978)

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IR in Transition Cows

- IR is observed in mammals during late gestation and early lactation: Why?
  - IR in muscle decreases glucose uptake
  - IR in adipose decreases glucose uptake, decreases lipogenesis, and ***increases lipolysis***
  - Result is greater availability of glucose and fatty acids to the fetus and mammary gland which are insulin independent tissues (metabolism not controlled by insulin)

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IR: Important Concepts

- It is not all on or all off
- Cows "purposely" undergo insulin resistance to support gestation and lactation
- An example of homeorhesis: the orchestrated or coordinated control in metabolism of body tissues to support a physiological state
- It is a normal biological process for mammals

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Extreme Examples: Grizzly Bears

- Lactation and parturition during hibernation
  - Cubs nurse while sow is hibernating
  - Grow from <1 lb at birth to 10-20 lb at end of hibernation
  - During hibernation, the sow does not eat
    - Mobilizes tissue to support both herself and milk for her cubs
    - Awakens:

"Hungry as a bear"

Slide Courtesy of Rich Erdman

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Extreme Examples: Hooded Fur Seal

- Lactation period of less than 4 days
  - Cow does not eat
  - Pups gain 7 kg BW/d, most of which is blubber (fat) deposition
  - Direct transfer of maternal (blubber) to milk (61% Fat) to pup (blubber)


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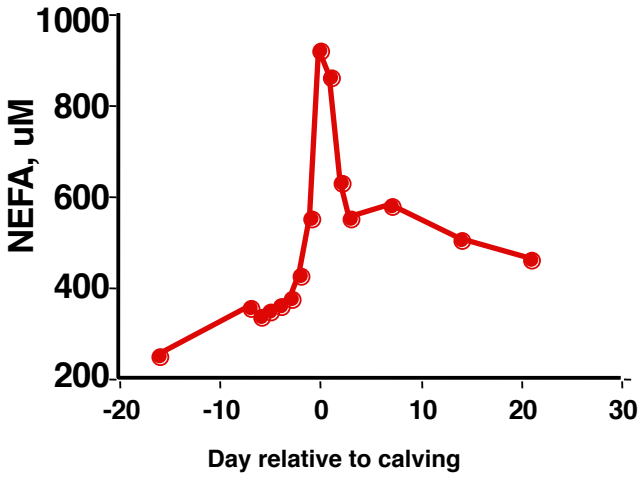
Transition Cow Plasma NEFA



Grummer, 1993

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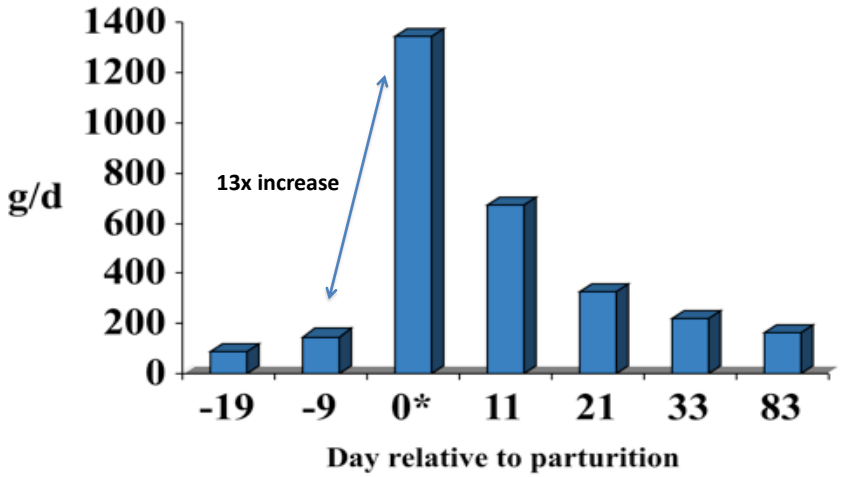
NEFA uptake by liver during the transition period. (Reynolds et al., 2003)



*Estimate

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IR: A Friend or Foe??

- Can cows become ***too*** insulin resistant?
  - Too much fatty acid mobilization? Conversely:
  - Too much glucose and fatty acid available to the mammary gland to support lactation?
- Are overfed dry cows "diabetic" and do they exhibit increased insulin resistance?

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Does too much IR = too much NEFA =

?????????

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Top 10 Reasons to Hate Elevated Blood NEFA

1. Increases liver fat (Bobe et al., 2004)
2. Increases hepatic ketone production (Cadorniga et a., 1997)
3. Increased risk of DA (Ospina et al., 2010)
4. Decreases hepatic gluconeogenesis (Li et al., 2011)
5. Decreases risk of pregnancy (Ospina et al., 2010)
6. Increases oxidative stress (Bradford, 2011)
7. Decreases immune function (Scalia, 2006)
8. Causes chronic inflammation (Sordillo, 2013)
9. Exacerbates insulin resistance (Pires et al, 2007)
10. Depresses DMI (Allen, 2009)

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Two Reasons to Love Elevated Blood NEFA

- Provide energy for tissues including the mammary gland
- Provide precursors for milk fat synthesis

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Is Reducing Insulin Resistance (Decreasing NEFA) Always Better??

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Controlled Energy "Goldilocks" Diet

- High in low quality forage, typically straw
- When consumed ad libitum, energy requirements are met but not exceeded
- Cows are less insulin resistant
  - Lower rates of lipolysis
  - Less fatty liver
  - Lower BHBA

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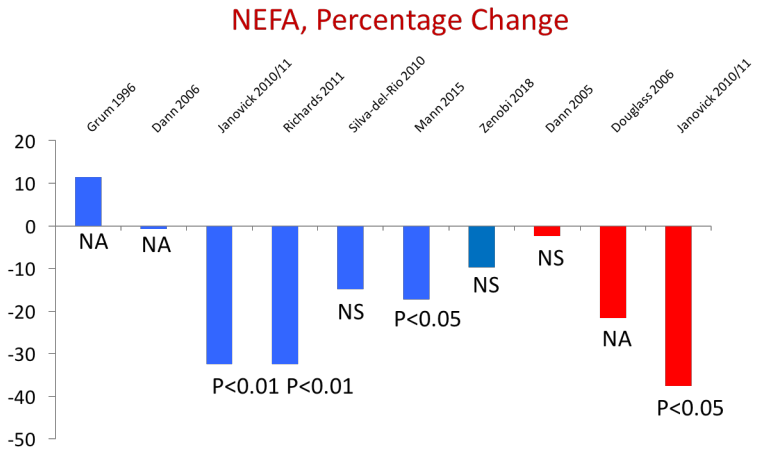
Response to Feeding Controlled Energy Diets



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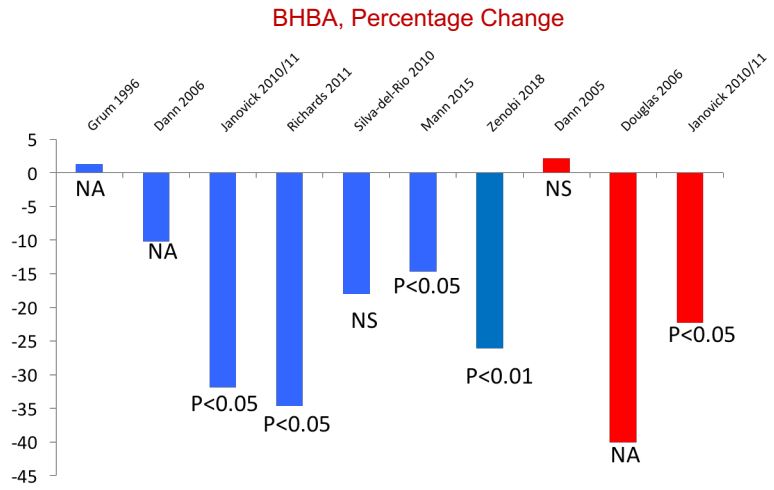

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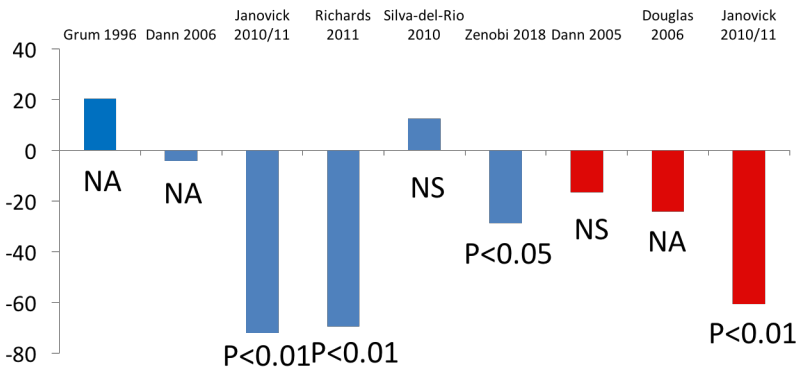

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What is rarely talked about……..

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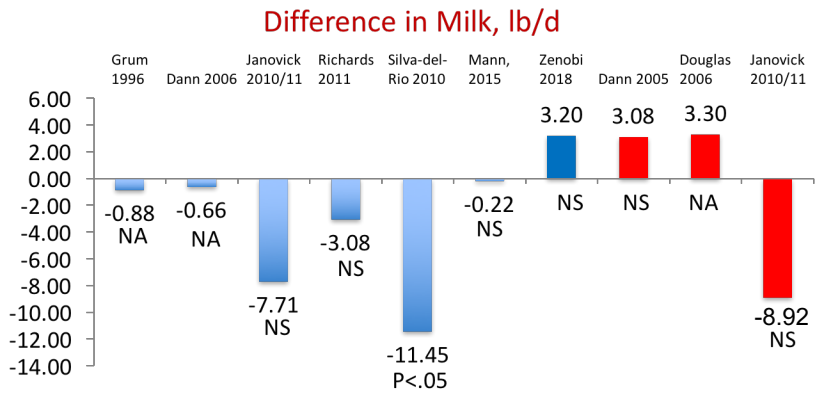
Response to Feeding Controlled Energy Diets



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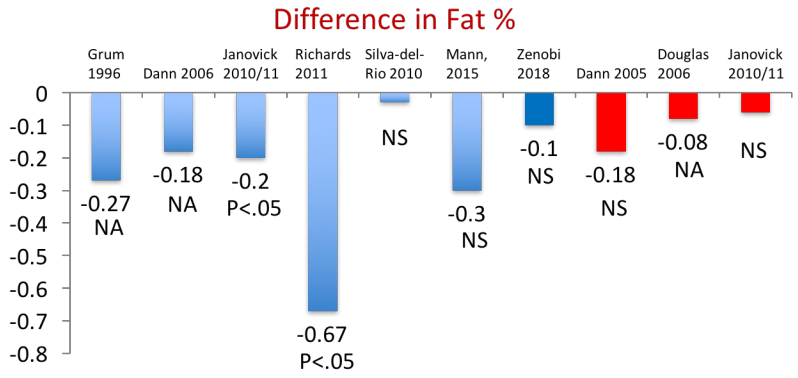

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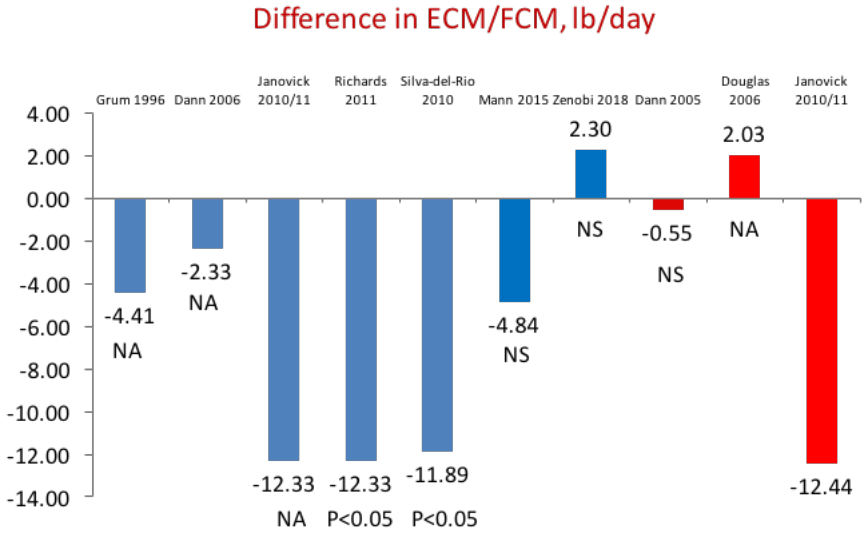

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This Data Makes Total Sense!!!!

- Cows fed controlled energy diets mobilize less fat (NEFA)
- NEFA are used by the mammary gland
  - Energy source
  - Precursor for milk fat synthesis
- If you reduce NEFA availability to the mammary gland, it should not be surprising that there *may be* downstream effects on lactation performance
- The goal is to have a balancing act: provide sufficient NEFA to the mammary gland to support lactation without the cow experiencing negative effects that may result if NEFA mobilization is excessive.

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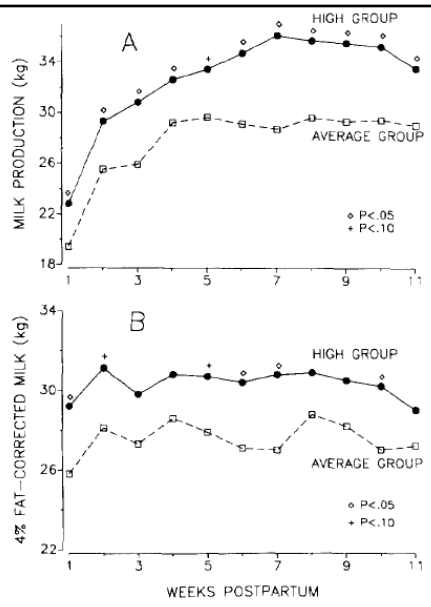
High vs. Average Genetic Cows

(Harrison et al., 1990)



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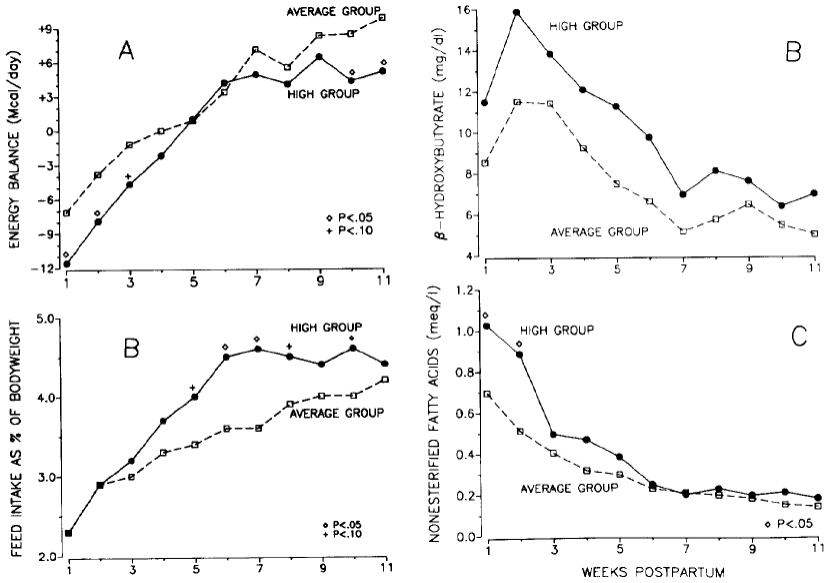

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IR and Genetic Potential: Glucose Challenge

	New Zealand HF	North American HF	P value
Milk yield, lb/d	67.8	74.7	<0.05
Fractional Turnover rate, %/min	2.0	1.8	<0.05
Glucose ½ life, min	35.0	39.5	0.08

↑ Greater IR

Chagas et al., 2009

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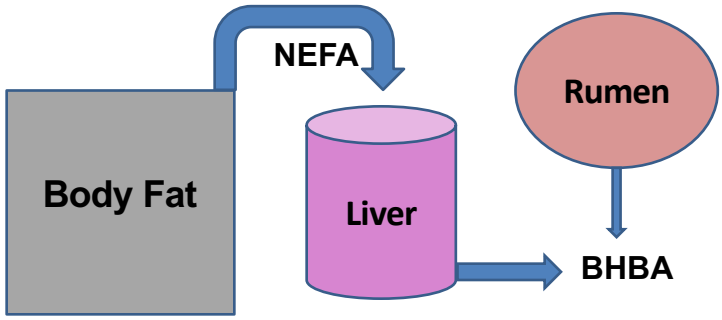
What Does this Mean in the Context of NEFA and BHBA Testing?



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Blood NEFA and BHBA

- These are used as indicators of negative energy balance
- Numerous studies suggest if levels get too high, milk yield is reduced and health and reproduction suffer
  - Postpartum NEFA > 700 uM
  - Postpartum BHBA > 1.2 mmol/L
- Many studies are excellent and are based on large animal numbers sampled across many farms
- Routine on-farm testing of BHBA has risen dramatically with the proliferation of quantitative hand-held meters

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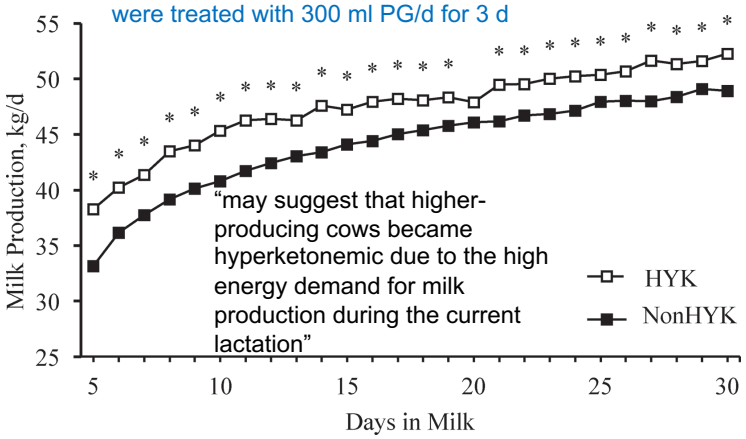
UW- Madison study: 570 Total cows
19.7% were hyperketonemic (BHBA > 1.2 mmol/L)

Note: Cow sampled twice weekly between d5 and 18 PP. HYK cows were treated with 300 ml PG/d for 3 d



"may suggest that higher-producing cows became hyperketonemic due to the high energy demand for milk production during the current lactation"

Rathbun, 2017

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Dutch Study- 23 herds

Van Holder et al., 2015

	< 1.2 mmol/L	1.2-2.9 mmol/L	≥3.0 mmol
	41.2%	47.2 %	11.6%
Colostrum, L (n=1,572)	4.7	5.6	7.2
Milk, lb/d (1st test day) (n=1,149)	76.2	83.5	81.1
Protein, % (n=1,149)	3.4	3.3	3.2
Fat, % (n=1,149)	4.2	4.3	4.6

Cows sampled between d7 and d14 postpartum

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"Too many of my cows are testing high for BHBA! But my cows are milking like crazy!"

Hmmmmmm?????????

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Bottom Line:

I am NOT against BHBA testing!

Caution: Like most blood tests, interpretation of results can be complicated.

One size fits all cutoffs for NEFA and BHBA may be deceptive!?

If NEFA and/or BHBA are high and cows are milking like crazy with no other issues…..well….. 😊

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Hmmmmmmmm……

"Nutritional restriction to adipose tissue mobilisation might be necessary, but there is a philosophical problem. We have selected cows that have increased reliance on mobilised body reserves as a source of nutrients for milk production. The farmer has paid the geneticist for this- are we now going to ask him to pay the nutritionist to work in the opposite direction? We have our priorities wrong. We should explore what can be done to help the liver deal with mobilised fatty acids before considering whether we need to try to reduce the amount of fatty acid supplied to the liver."

J. R. Newbold. 2005. Liver Function in Dairy Cows. Recent Advances in Animal Nutrition

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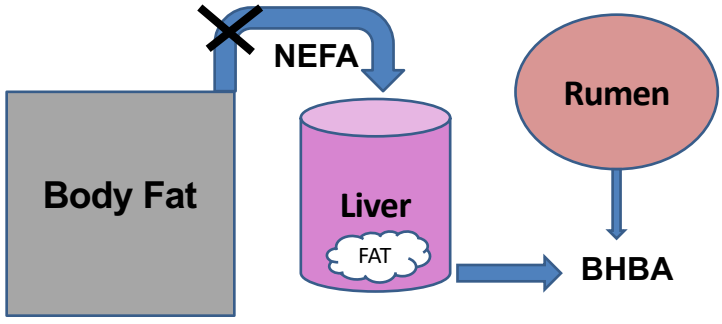
Historically



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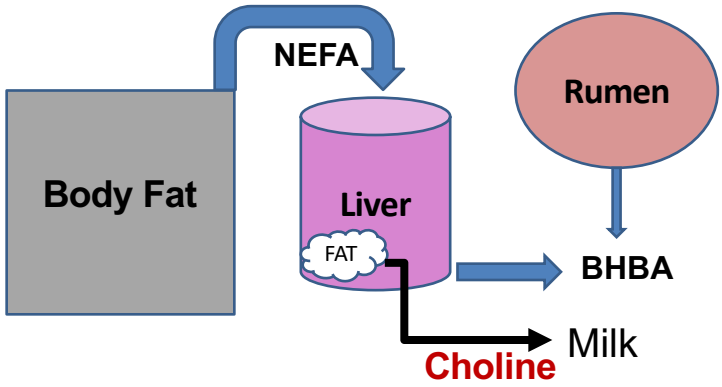
Newbold's Vision



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Questions For You to Think About

- Are elevated [NEFA] or [BHBA] always bad???
- Do one size fit all "cut-offs" for [NEFA] or [BHBA] alarms always serve us well? Low vs high genetic potential cows?
- What do you tell a dairy producer if "too many" cows are testing high for [NEFA] or [BHBA] but his cows are milking like crazy? And seem healthy?
- How will you manage fat mobilization?
- Does ideal body condition score vary according to how you manage fat mobilization?

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