RON'S IMPACT ON THE WORLD DAIRY INDUSTRY

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Professor Ron Butler is a renowned animal scientist! His scholarly publications reflect research conducted with 12 different species. His graduate and post-graduate training was completed in three top laboratories in the USA, and his early research on disconnection of the pituitary from the hypothalamus in rhesus monkeys plowed new ground in neuroendocrinology.

OUR CONNECTIONS

Ron and I traveled parallel paths. We graduated with B.S. degrees from different universities in 1966 and pursued graduate training in reproductive physiology and endocrinology. I first became acquainted with Ron when I visited Purdue University in 1969 to learn how to assay progesterone in blood from dairy cows. I was taught to do assays by Allen Garverick, who was a PhD student in the laboratory of Professor Ralph Erb. Nearby was the laboratory of Professor Paul Malven, where Ron was pursuing a PhD degree.

In 1993, Ron and I had a once-in-a-lifetime happenstance. We were invited to participate in a national symposium on nutrition and reproduction in Zeist, The Netherlands. My Delta Airlines Boeing 747 flight from Atlanta to Amsterdam was delayed 4 hr, because a catering truck backed into our plane just before we pushed back from the gate. We had to disembark and get another plane. When I arrived in Amsterdam, conference hosts asked if I would speak ahead of Ron, because his flight had been delayed. When Ron arrived, we learned that his TWA Boeing 747 flight from JFK to Amsterdam was taxiing to the runway when an unmanned catering truck rolled down the ramp into his plane. When we calculated the probability of this happening to both of us, the zeros after the decimal ran for several pages.

Ron's family and mine connected more closely in the early 1990's when my daughter Stephanie and Ron's daughter Stacy became classmates at Cornell's Hotel School. In visits to Ithaca, I saw Ron regularly.

Beyond these connections, Ron and I both pursued studies related to dairy cattle fertility and impact of nutrition and energy balance on reproduction in livestock. Our projects turned out to be complementary and we often cited each other's work. His work on energy balance and protein nutrition in high-producing dairy cows set the stage for many others to pursue studies and develop methods and technologies to deal with these two important issues.

IMPACT ON THE DAIRY INDUSTRY

Measuring impact is not simple, but I doubt there is a dairy farmer or dairy nutritionist or dairy cattle veterinarian in the developed world that does not deal with negative energy balance or excess blood or milk urea nitrogen on a regular basis. This is where the practical application of research findings from Ron's team has made its global mark.

Important research findings move quickly from the laboratory to adoption within an industry. Publication of research findings in credible journals and presentation of these findings at national or international meetings accelerates adoption of better husbandry practices. To assess Ron's impact from a scholarly standpoint, it is informative to look at how often his publications have been cited. According to Google Scholar, his top 10 papers had been cited 6,348 times as of 29 August 2018 (Appendix Table 1). Notice that these papers deal primarily with two topics: energy balance in the periparturient cow and impact of protein nutrition on fertility.

ENERGY BALANCE

Butler and Smith. The most cited paper with W R Butler as an author was published in 1999 in the Journal of Dairy Science by Ron Butler and David Smith. It was from an American Dairy Science Association symposium on *Interactions of Nutrition and Reproduction*. This paper provides an excellent summary of relationships between energy balance and reproduction in the dairy cow.

Nevertheless, my perception is that Ron's earliest and most significant contribution in this area was from his 1983 paper with Bob Everett and Carl Coppock.

Butler, Everett and Coppock. In this paper, Ron, Bob and Carl utilized data from a previous study that focused on utilization of urea in diets of 13 Holstein cows in early lactation. The original study was published by Kwan et al. (1977). Cows in this study produced an average of 7,334 kg (16,135 lbs.) in 305-day lactations.

The Butler team measured hormones in blood from these cows to estimate interval to first ovulation and used feed intakes and milk production to estimate energy balance. Then they looked at relationships among energy balance and several reproductive traits. Their most significant finding was that cows ovulated and started estrous cycles while they were still in daily negative energy balance.

There are several important lessons from this paper:

- Milk yield is related inversely to energy balance – cows that produce more milk generally have a more negative energy balance (Figure 1).
- Days to first ovulation is related inversely to energy balance – cows with more negative energy balances take longer to ovulate after parturition (Figure 2)
- Energy balance reached its nadir (most negative point) near the time of peak milk yield

- First ovulation occurred just after the energy balance nadir, before cows reached positive energy balance.
- Finally, there is valuable information in existing data sets that may not have been included in the original published paper.

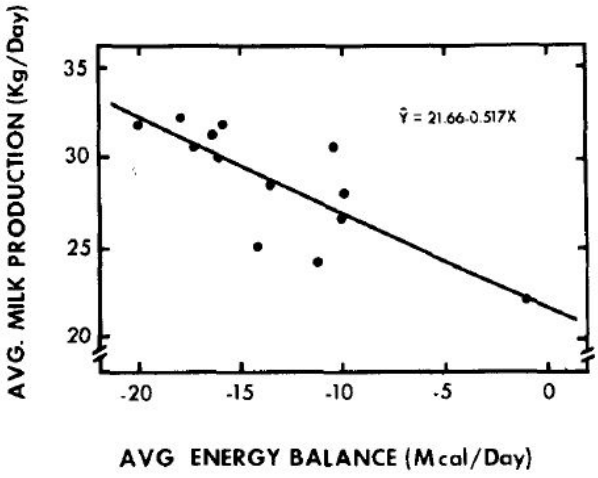

Figure 1. Relationship between milk yield daily energy balance.

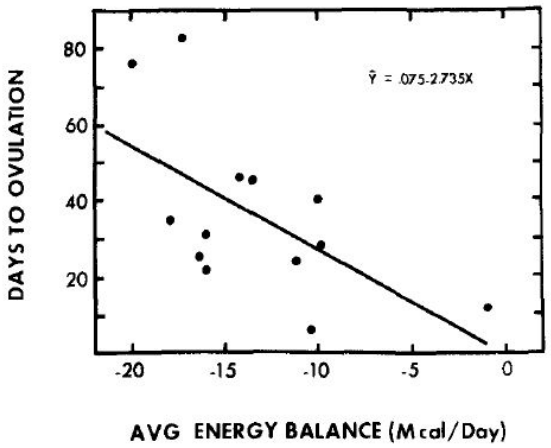

Figure 2. Relationship between days to first ovulation and daily energy balance.

Ron's team was among the first to demonstrate a positive effect of feeding supplemental fat on development of ovulatory follicles about 2 wk postpartum in high-producing Holstein cows (Beam and Butler,1997). They fed three levels of tallow (3.3, 5.2 and 7.1% of ration DM) and noted that cows fed the two higher levels had more ovulatory follicles at 2 wk postpartum. This focus on dietary fat and postpartum follicle development laid groundwork for development of fat-based dietary supplements that are used broadly in the dairy industry.

Ron's work caused many reproductive biologists and nutritionists to become more aware of antagonistic relationships between milk yield and energy balance, between negative energy balance and postpartum anestrus and between negative energy balance and fertility after AI. This led to numerous studies focused on feeding during the dry period and transition period to reduce amount of weight loss, and it refocused attention on how body condition at calving can impact subsequent weight loss. It also led to increased attention on what happens physiologically with rapid weight loss, particularly mobilization of fatty acids and changes in blood glucose, insulin, IGF and somatotropin. There was also interest in whether negative energy balance exerted longer term effects on germ cells and uterine function.

Britt (1992) proposed that developing follicles and oocytes could be affected adversely if their prolonged development occurred during a period of severe negative energy balance (Britt Hypothesis; Figure 3). Substantial data support this hypothesis and that the adverse effects may be mediated through epigenetic mechanisms. For example, Carvalho et al. (2014) reported that conception rate at timed AI at 80 $\pm$ 3 days postpartum was 25%, 38% and 84% for Holstein cows that lost, maintained or gained body condition score during 3 wk postpartum. Additionally, they showed that oocytes from cows that lost most body condition were fertilized, but then died at a high rate during the first 7 d of development, a classical epigenetic-type effect.

In the future as we mine dairy data from the "cloud" we will be looking for temporal relationships between environmental factors like energy balance and subsequent responses, some of which may occur months or years later. For example, we know that feeding calves to gain more in their first 2 months of life is reflected in their yield in first lactation. What is the long-term impact of severe negative energy balance in a cow's life? Ron would encourage us to ask that type of question.

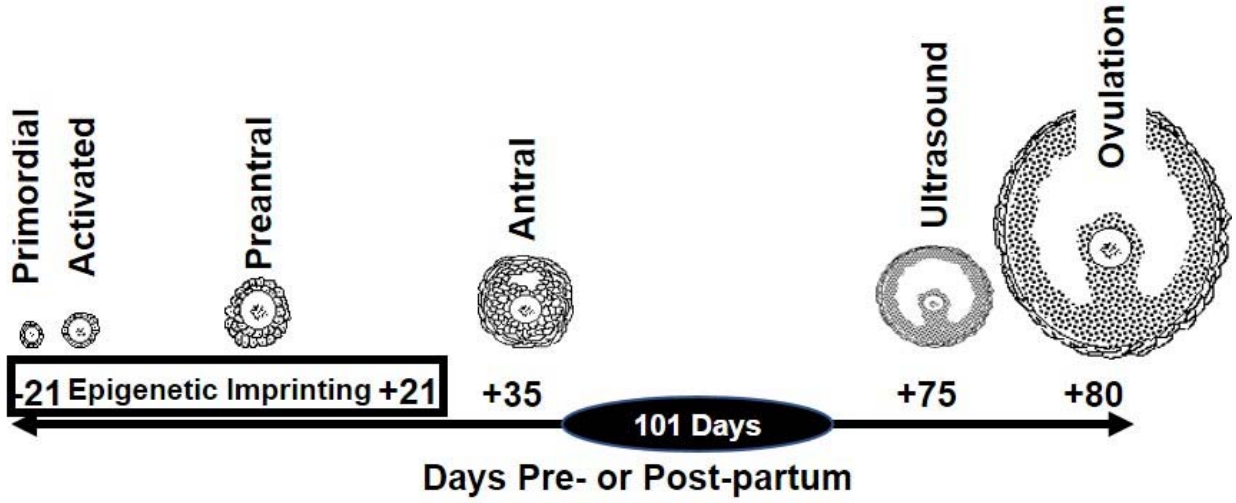

Figure 3. Illustration of a potential mechanism whereby negative energy balance during the transition period can affect the developing oocyte and result in failure of conception 11 to 12 weeks postpartum. Adopted from Britt et al. (2018).

Ron's work has had lasting impacts. Over the last 3 decades, dairy scientists, nutritionists, veterinarians and farmers responded in many ways to address adverse impacts of negative energy balance in the postpartum cow. For example:

- Body condition scoring became a routine practice
- Body condition scores at calving were nudged downward
- Rations were reformulated to improve digestibility and intake for fresh cows
- Transition management focused on 3 weeks before to 3 weeks after calving
- Dietary lipids were altered to address fat's potential impact on intake
- Dietary fatty acids were developed to that have beneficial effects on fertility
- Micronutrients, yeasts and other ingredients were boosted in fresh cow TMRs

There is a move to determine whether we can develop dairy cows that do not experience severe negative energy balance and yet still produce equivalent amounts of milk in a complete lactation (Zachut and Moallem, 2017). Analyses of data from 92 cows selected randomly from an Israeli research herd (Volcani Center; Rishon LeZion, Israel) demonstrated that cows differ consistently in postpartum weight loss over 4 consecutive lactations (Figure 4).

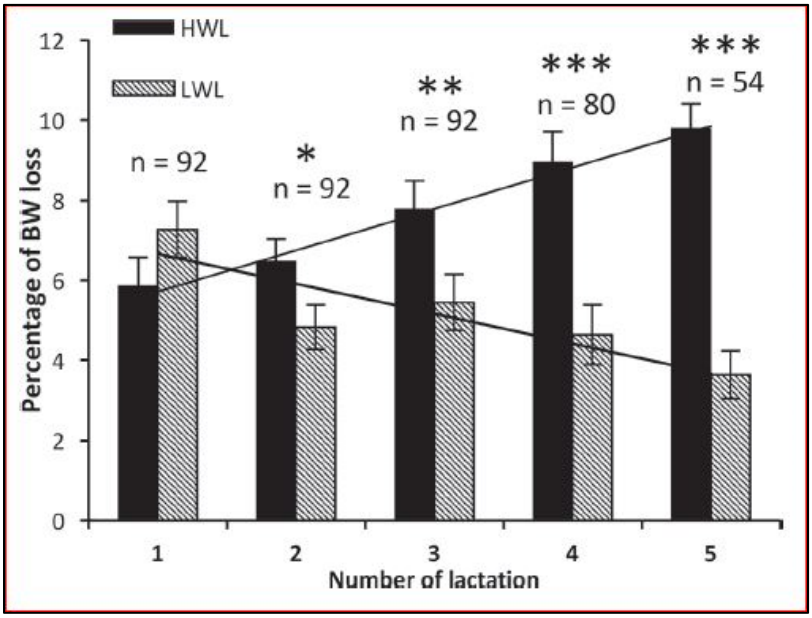

Figure 4. Differences in weight loss during early lactation among two groups of Holstein cows identified to have different patterns in weight loss. Adapted from Zachut and Moallem, 2017.

Application of genomic selection is likely to accelerate progress in identifying bulls that sire cows which produce the same amount of milk, are healthier and do not experience swings in energy balance that we see in today's modern dairy cow. Recent studies of daughters of Brown Swiss bulls revealed that some bulls sire daughters that

are clearly more robust and healthier and produce similar amounts of milk and components to daughters of bulls that do not transmit this robustness (Ha et al., 2017)

Our efforts to understand impacts of negative energy balance on many traits in dairy cattle trace their roots back to Ron's work in the postpartum cow. But he also led us to look at another nutritional-based issue – what are the impacts on fertility of over-feeding protein.

EXCESS SOLUBLE PROTEIN AND FERTILITY

If a little is good, let's add some more. That may have been our attitude for a long period about how much protein and what form of protein to include in rations of dairy cows. We knew we had to feed the organisms in the rumen, and we could do that easily with products like urea. Gradually crude protein levels in rations crept upward, reaching more than 20% in many cases.

On the other hand, fertility was declining, and inquisitive folks started looking at what was happening. Ron's work with energy balance and his nature to let graduate students seek a relevant problem to pursue led to a series of papers that illustrated how too much soluble protein could lead to lower fertility in dairy cows.

His research team showed that too much soluble protein could change the pH of the uterine lumen at a critical time and this led to substantial reductions in fertility. To avoid complications with energy and protein, they did their insightful work with Holstein heifers that were not in negative energy balance and not producing milk.

This was challenging work. How does one measure pH in the lumen of the uterus repeatedly over several days? How does one maintain as much similarity among rations for experimental groups and still vary the amount of crude protein significantly? Through ingenuity, they conducted experiments that provided a lot of insight. They kept rations similar by simply adding a bit more urea to one and tweaking a few ingredients in the other. It worked!

Higher soluble protein levels led to significantly lower conception rates in fertile heifers! This was associated with a drop in pH in the uterine lumen at a critical time of early embryonic development. They measured milk or blood urea nitrogen to estimate the excess amount of protein. Subsequent work demonstrated that the change in uterine pH in response to excess protein was due to changes in the transport of ions across the endometrium. It is now accepted wisdom among dairy nutritionists and veterinarians that excessive dietary soluble protein is not only expensive, but also impairs fertility through these alterations in the uterine environment.

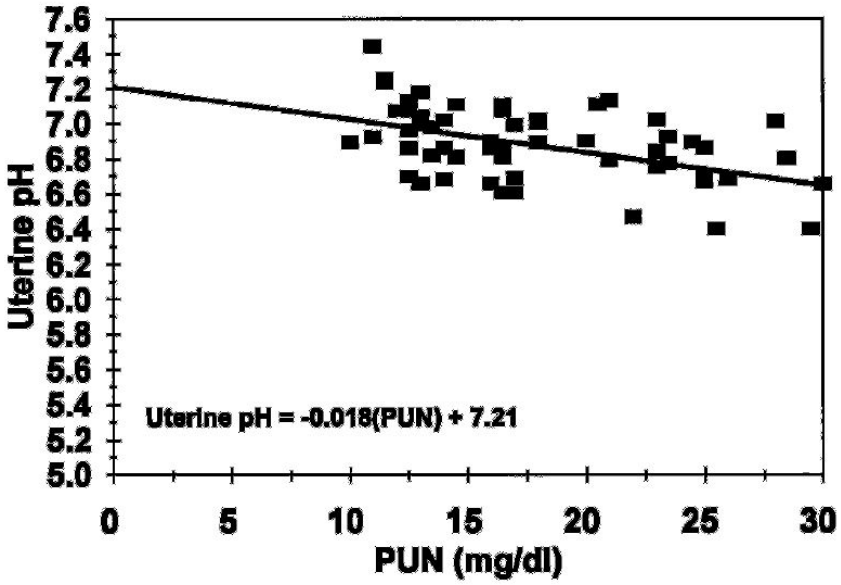

Figure 5. Uterine pH in heifers with various concentrations of plasma urea nitrogen (PUN) in blood on day 7 after estrus. Adapted from Elrod and Butler (1993).

The response to these dietary protein studies was quick. Every milk analyses laboratory added MUN to their stable of assays. Nutritionists and veterinarians started monitoring MUN, BUN and PUN and asking whether it was getting into the critical range. At the same time, our nutritional knowledge and models became more sophisticated in matching available carbohydrate and protein sources to achieve more efficient fermentation in the rumen and less wastage of nutrients.

All of this made our industry much more efficient in using protein in our rations. Protein percentages started creeping down and we were putting less nitrogen into soils and waterways. It is having a long-term benefit on our ecosystems.

Few scientists have had multiple long-term impacts on practices that have benefited the dairy industry worldwide. Ron's research on mechanisms through which nutrition affect postpartum reproduction and fertility led to improvements in feeding and management that are now hallmarks of best management practices. Well done Ron!

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Appendix Table 1. Top 10 cited scientific papers authored by W. R. Butler*

Title and Authors	Citations
Interrelationships between **energy balance** and postpartum reproductive function in dairy cattle; 1999; WR Butler, RD Smith; Journal of Dairy Science 72 (3), 767-783.	1,402
Nutritional interactions with reproductive performance in dairy cattle; 2000; WR Butler; Animal Reproduction Science 60, 449-457.	833
Effects of **energy balance** on follicular development and first ovulation in postpartum dairy cows; SW Beam, 1999; WR Butler; Journal of Reproduction and Fertility Supplement-, 411-424.	629
Effect of **protein nutrition** on ovarian and uterine physiology in dairy cattle; 1998; WR Butler; Journal of Dairy Science 81 (9), 2533-2539.	623
Plasma and **milk urea nitrogen** in relation to pregnancy rate in lactating dairy cattle; 1996; WR Butler, JJ Calaman, SW Beam; Journal of Animal Science 74 (4), 858-865.	558
Energy balance relationships with follicular development, ovulation and fertility in postpartum dairy cows; 2003; WR Butler; Livestock Production Science 83 (2-3), 211-218.	548
Energy balance and ovarian follicle development prior to the first ovulation postpartum in dairy cows receiving three levels of dietary fat; 1997; SW Beam, WR Butler; Biology of Reproduction 56 (1), 133-142.	528
Reduction of fertility and alteration of uterine pH in heifers fed excess ruminally **degradable protein**.; 1993; CC Elrod, WR Butler; Journal of Animal Science 71 (3), 694-701.	458
The relationships between **energy balance**, milk production and ovulation in postpartum Holstein cows; 1981; WR Butler, RW Everett, CE Coppock; Journal of Animal Science 53 (3), 742-748.	414
Decreased concentration of plasma leptin in periparturient dairy cows is caused by **negative energy balance**; 2001; SS Block, WR Butler, RA Ehrhardt, AW Bell, ME Van Amburgh, YS Boisclair. Journal of Endocrinology 171 (2), 339-348.	355

*(Google Scholar, https://scholar.google.com/citations?user=__d-NQoAAAAJ&hl=en&oi=sra Accessed 29 August 2018)