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Managing complexity: Dealing with systemic crosstalk in bovine physiology

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ABSTRACT

Dairy producers rely heavily on advisors with deep expertise in nutrition, reproduction, and health. However, a shift is occurring, driven both by farm size and by advances in biology. Larger dairy businesses can investigate management options with a degree of precision never before possible; simultaneously, the lines between the metabolic, immune, and reproductive systems are becoming blurred. For example, new research has revealed a surprising role for immune cells in regulating metabolism and documented the nutrient requirements of the immune system. The gut epithelium has garnered new attention as a tissue that actively manages the commensal microbiome, entrains the responses of the neonatal immune system, and provides a barrier limiting movement of molecules from the gut lumen. New hormone discoveries have added adipose tissue, bone, and muscle to the list of endocrine organs. Finally, nutrients are now seen not only as substrates and cofactors, but also as signals that can alter cellular function. What does all of this mean for the dairy industry? Consultants are increasingly reaching across disciplinary boundaries to best support the physiology of the cow. However, research is needed to translate proof-of-principle findings into applications in cattle. Key unanswered questions include the degree to which roles of the hindgut in monogastrics translate to ruminants, and whether some host–microbe crosstalk also occurs in the rumen; whether hormone release by storage organs during a catabolic state affects reproductive function; and the degree to which immunostimulation by dietary signals enhances or disrupts health and productivity. It is critical to address these questions with multiple approaches. Mechanistic studies provide a nuanced understanding of signal interactions, but large-scale commercial studies are needed to evaluate effects on multiple production outcomes in the environment of interest, and meta-analyses best integrate findings into a cohesive understanding of responses to diet. Incorporating all aspects of animal health and productivity in management decisions will remain an art for the foreseeable future, but this should not dissuade the industry from pursuing a more holistic approach to management of the cow.

Key words: dairy cow, nutrition, nutrigenomics, nutraceutical, gastrointestinal microbiology

INTRODUCTION

The dairy industry has made impressive advances over the past century in productivity and resource efficiency. These improvements can be attributed to an increased understanding of the biology of the dairy cow, and the application of this knowledge to develop new technologies and improve management practices. Our understanding of nutrition has likewise developed, to the extent that the bulk of the opportunity for further advancement may now lie in exploring the crosstalk that exists between different tissue systems, their combined effects on nutrient metabolism, and how specific feed components affect tissue function.

Improvements in nutrition have allowed cows to express their increasingly high genetic potential for milk production, which has improved the efficiency of dairy production primarily by diluting maintenance costs (i.e., fewer cows and less feed needed to produce the same amount of milk). However, as demonstrated by VandeHaar et al. (2016), the steady increase in efficiency that we have witnessed through this mechanism in the past 70 yr will not continue forever. Sooner or later, the dairy cow will approach her biological limit for capturing ingested energy as productive energy, largely due to trade-offs between level of DMI and residence time in the gastrointestinal tract. Therefore, to continue to improve resource efficiency in the dairy industry, we need to expand our focus to include other inefficiencies in the system.

The lost resources caused by morbidity, mortality, and infertility must contribute substantially to the suboptimal efficiency of the dairy industry, although a

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comprehensive analysis is lacking. To derive a minimal estimate of resource losses due to stressors, we considered losses from just heat stress (St-Pierre et al., 2003), mastitis (Bar et al., 2008), and hyperketonemia (McArt et al., 2015); we used financial losses as a proxy for wasted resources, but excluded veterinary costs. Based on the cited analyses, these 3 problems drain almost $2.2 billion annually from the US dairy industry in the form of lost milk (direct and indirect effects) and death loss, representing over 5% of the ~$40 billion in dairy farm cash receipts for milk sold in the United States annually. If nutrition can be used to combat these problems, it is clear that there are major economic and resource efficiency benefits to be gained. Therefore, it is worthwhile to consider effects of nutrition on efficiency metrics beyond milk and DMI.

Our primary goal in this review is to highlight important scientific advances that might influence dairy nutrition, and to suggest ways that researchers and nutrition consultants can progress with these new insights in mind.

THE CHANGING LANDSCAPE OF NUTRITION SCIENCE

An Evolving Field

Perhaps the earliest American effort to comprehensively address the nutritional needs of cattle appeared in a book by Armsby (1880). At that time, substantial progress had already been made in understanding the digestion and assimilation of fat, carbohydrate, protein, and minerals. In the early 1900s, however, studies of single-grain diets for cattle and purified diets in monogastrics made it clear that these nutrients alone were insufficient to maintain optimal health and growth. This led to a period of rapid advances in understanding micronutrient requirements, particularly the identification of vitamins (Carpenter, 2003). By the end of this period, nearly all nutrients could be evaluated in terms of contributions to energetic needs, anabolic substrate requirements, or as cofactors in essential metabolic pathways. This relatively straightforward view of nutrition was dominant through most of the 20th century. In dairy nutrition, these concepts were generally applied to assess whether different diets would support a higher level of milk production, with incremental increases in productivity viewed as evidence that a nutrient was at least marginally inadequate in the control diet.

In many ways, this classical approach to nutrition ("Nutrition 1.0") might be considered overly simplistic today. We next highlight 5 key areas of nutrition science that have gradually supplanted this traditional view of nutrition with "Nutrition 2.0" (Figure 1).

The Guts of the Matter

Ruminant nutritionists, because they focus on foregut-fermenting animals with an obvious reliance on commensal microbes, have long recognized the need to "feed the rumen bugs" and maintain gastrointestinal health of cattle. Indeed, early publications studying the human gut microbiome leaned heavily on decades of previous work by rumen microbiologists (Bäckhed et al., 2005). Still, few would have predicted the vast impact of commensal microbes that has been revealed in the past 2 decades.

Given that cows depend heavily on the microbes inhabiting the rumen to convert indigestible plant mass to digestible compounds and essential nutrients, it is not difficult to imagine that the large, complex ruminal microbial population has enormous nutritional, physiological, and pathological interactions with the cow. More than 200 yr ago, the transfer of rumen contents was already being used as a therapeutic tool; the nutrients and microorganisms transferred into the rumen of a sick animal stimulate ruminal fermentation and motility, and there are likely undiscovered effects as well (DePeters and George, 2014). Some evidence suggests that individual animals can, by unknown mechanisms, cultivate a relatively consistent individualized microbiome, even in the face of a complete exchange of ruminal contents (Weimer et al., 2010). Another study (Jami and Mizrahi, 2012) examined rumen microbiota across individual animals and found that although the bacterial taxa may vary considerably between cows, they appear to be phylogenetically related, suggesting that ecological niches in the rumen select taxa that share similar genetic features. This individuality does not imply that diet changes cannot alter the rumen microbiome; many such examples have been reported (Firkins and Yu, 2015). Rather, these findings suggest that animal–diet interactions drive the ecology of the rumen.

The more surprising findings have come from rodents, whose size and lack of dependence on fermentation allows investigators to more easily utilize gnotobiotic (germ-free) models and to establish near monocultures in the gut. Studies have now suggested that the composition of the intestinal microbiota directly or indirectly affects body composition, allergic inflammation, bone metabolism, cancer risk, atherosclerosis, and even brain function (Dorrestein et al., 2014; Sharon et al., 2014). Gut microbes can therefore play a huge role in mediating the effects of dietary nutrients on host physiology. For example, one high-profile publication showed that intestinal microbial metabolism of L-carnitine to trimethylamine-*N*-oxide accelerates atherosclerosis in mice (Koeth et al., 2013). This response was eliminated