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Grand Challenges to Livestock Physiology and Management

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Globally, animal-source foods are an important element of many diets and are of increasing importance in providing essential nutrients particularly for at-risk populations. This includes pregnant and lactating women, children <2 years of age, and the elderly, where animal-based nutrients including high-quality digestible protein, essential fatty acids, and key vitamins like vitamin B12, and minerals such as iron, zinc, and calcium, are critical to prevent physical and cognitive stunting (Alonso et al., 2019; Hackney et al., 2019; Adesogan et al., 2020). Rising incomes also increase demand for livestock products and estimates of future consumption patterns indicate that low- and middle-income countries will drive increases in consumption of meat, milk, and eggs (Mottet et al., 2018). As demand for foods derived from livestock—however defined—continues to grow, pressure to increase the output and improve efficiency of production will also rise. Furthermore, consumer preferences regarding production practices will likely favor less intensive methods than those used previously. While genetic assessment and improved breeding have allowed for and will continue to promote improved phenotypes from a productivity perspective, genetic progress relies upon appropriate nutrition and management for maximal phenotypic expression of genetic potential to be realized. Therefore, new information on the physiological impacts of management interventions and selective breeding are essential to improve productivity in a sustainable manner.

One opportunity to optimize phenotype may focus on new precision technologies enabling individual animal monitoring and management. Advances in imaging, automation, sensors, electronic data exchange through "the cloud," and data analytics offer extensive opportunities for specific interventions best aligned with physiological state and external inputs, even for animals housed under comingled conditions. Robotic milking and in-line milk composition analysis, for example, offer repeated opportunities to assess the cow's productive state and health (Diaz-Olivares et al., 2020; Michie et al., 2020). Could these data also be harnessed to indicate the affective state of the cow? Certainly, sensor technologies are more readily available for use in production animals to continuously monitor factors like body temperature, locomotion, heart rate, breath composition (CH_4, H_2, CO_2, and O_2), and feeding behavior. Application of these types of information to assess an animal's perceptions of its environment and improve animal welfare has already been proposed (Ede et al., 2019). However, how these measures can best be applied to reflect a particular affective state or its direction (positive or negative) remain elusive. For instance, animal arousal can readily be detected using heart rate variability or plasma cortisol, but other indicators to differentiate the type of arousal rarely correspond exclusively with painful vs. pleasurable events (Ede et al., 2019).

Quantifying the relationships between management interventions and productivity outcomes alongside animal welfare indicators to create "indices of performance" beyond simpler efficiency measures would be a path to document the process in real time, increase consumer confidence,

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and aid in product marketing. At present, the greatest obstacle lies not in the acquisition and storage of data (inputs) to create such an index, but in determining the appropriate indicators and understanding their inter-relationships for implementation to achieve the desired outcomes. Likewise, housing applications that are best suited to optimize health, productivity, and welfare of the animal while minimizing negative environmental outcomes could be assessed and targeted to maximize systems-level outputs beyond individual indicators of performance. Thus, developing the appropriate schema to use from the deluge of behavioral and physiological data available on individual animals within large production settings is one of the greatest challenges we face in animal physiology and management. One possible approach will be to harness data streams to serve multiple endpoints in the food system. For example, mid-infrared (MIR) technology is used at the cow level to determine levels of components including fat and protein, which are of interest when assessing the value of milk to specific manufacturing applications (Soyeurt et al., 2010). Somatic cell count (SCC) of milk is a primary quality metric for cheese and other dairy products, and SCC can also be evaluated at the cow or tanker level on the farm using MIR (Franzoi et al., 2020). These data could be of interest to processors to adjust for effects of seasonal and management factors on milk quality, provide incentive payments to improve quality, or even route milk for specific manufacturing endpoints directly from the farm. The resulting benefits accrue at the farm through improved health management, but also at the processor and consumer levels in the way of product quality and processing efficiency.

A second challenge to the animal physiology and management community is the effective use of new molecular technologies in livestock production and understanding the implications of their use. Historically, application of transgenic technologies to animals was too inefficient or costly for general use in food animal production. However, recent breakthroughs in molecular biology have made use of these technologies feasible on a broader, perhaps even industry wide scale. For example, the more classical approach of somatic cell nuclear transfer was used to effectively create pigs with digestive enzymes derived from microbes that enabled the pigs to efficiently digest forms of phosphorous and nitrogen that otherwise would be unavailable and lost to the environment in their manure (Wang et al., 2020). However, newer gene editing approaches, such as CRISPR, can now be used to modify expression of specific pathways in an effort to improve animal performance and health. Indeed, manipulation of disease resistance is on the horizon with CRISPR (Van Eenennaam, 2019). Using more conventional methods, "slick" cattle having shorter and less dense hair coats are already being produced as a means to improve thermotolerance, and the slick phenotype is a likely target for CRISPR as well (Hansen, 2020). Despite the knowledge that many of these edits to the genetic code are fundamentally the same as those existing in production animals through natural mating, some edits will involve introduction of novel genetic elements. In both cases, management of their physiologic phenotype may require determining the subtle or less subtle shifts in nutrient supply, housing, or reproductive interventions required to fully realize the benefits of the targeted gene editing. Thus, setting aside issues around consumer acceptance, a crucial gap remains in our knowledge of the physiological implications of some of these models, and more importantly, how they will be managed for optimal productivity.

Beyond intentional genetic manipulations, recent evidence suggests that epigenetic programming, especially *in utero* or early after birth, can dramatically impact the ultimate performance of animals and be transgenerational in effect (Laporta et al., 2020). A number of models of *in utero* programming are now available to consider impacts of physiological and management interventions on subsequent performance of the offspring. For example, in cattle, insults resulting from nutrient deficiencies (Caton et al., 2020), disease challenge (Burdick Sanchez et al., 2017; Carroll et al., 2017), and environmental factors (Ouellet et al., 2020) can all impact the calf *in utero*. These events alter the trajectory of development and, ultimately, life-long animal performance. Similar examples are found in pigs and other livestock species, including poultry *in ovo* (Ferket, 2021), suggesting that *in utero/in ovo* and early life events may limit productive outcomes and even be passed on to offspring, further depressing efficiency (Reynolds et al., 2019). Careful assessment of the epigenetic outcomes of environmental and nutritional insults may yield new approaches to optimize output with targeted manipulation of early life events, but also lead to greater understanding of physiological control systems of animal productivity and health.

Greenhouse gas (GHG) emissions are another major challenge to animal production going forward, and mitigation of GHG output is the focus of significant research effort especially in ruminants. Some methods, such as short-term ionophore feeding or dietary lipids, alter the rumen microbial profile and its fermentation, producing favorable production outcomes with regard to health and feed efficiency (Llonch et al., 2017). But less is known regarding the physiological effects of newer technologies that alter GHG production and how those may impact animal performance and welfare. Can microbiome manipulation be another avenue to yield GHG reductions while maintaining productivity? Will the aforementioned CRISPR approach be used to modify specific gene expression of our livestock or their gastrointestinal microbes to favor lower GHG output? Not outside the realm of possibility, application of CRISPR technology has, in fact, been proposed to manipulate the human microbiome to improve the health of people (Ramachandran and Bikard, 2019). How best to apply these advances in food-animal management will likely hold the attention of physiologists and animal scientists for decades to come.

Likewise, multiple areas have yet to be explored sufficiently in livestock physiology that have proven useful in humans and other model species, which may now be gaining some research attention. A few of these include investigations of the microbiota-gut-brain axis and impacts on physiology including growth performance (Ming et al., 2021) and welfare (O'Callaghan et al., 2016; Kraimi et al., 2019); effective exploitation of organoids in basic research (Beaumont et al., 2021; Kar et al., 2021); and use of nano-technology for delivery of therapeutic compounds (Hill and Li, 2017; Shokraneh et al., 2020). Comprehensive bioinformatic analysis and interpretation of transcriptomic and metabolomic data collected from livestock tissues during normal development or critical disease states are also needed. Advancements in these areas will lead to important discoveries and novel interventions to enhance all areas of livestock production. Unfortunately, the persistent lack of reagents and assays specifically designed for use in livestock species (e.g., antibodies to key proteins) also remains a barrier to physiological investigations which warrants future investment.

Finally, whereas certain management practices such as grazing or free range may be preferred by consumers over confined feeding particularly from an animal welfare lens, some aspects of feeding and management are of interest due to their impacts on product quality. For instance, compounds that affect flavor of meat and eggs, including fatty acids, some nutraceutical compounds, and other feed additives (e.g., Guo et al., 2019; Mwangi et al., 2019; Costa et al., 2020; Feng et al., 2020; Yu et al., 2020) are of considerable interest when responses can be confirmed in a production setting. However, the mechanisms of action of these compounds need to be well-described and verified. Furthermore, local and regional preferences with regard to product attributes—from flavor intensity to preservation—can all be affected by the underlying production system and may be lost with the introduction of exotic breeds or shifts in production practices. For example, the transition of pastoral systems to place-based (ranch) systems will likely alter inputs and, therefore, product characteristics. Thus, the ability to maintain the desirable attributes of animal products as management practices evolve will require an understanding of the physiology underlying the effects of the practices and their complex interactions with one another and in different genetic backgrounds.

CONCLUSIONS

The foregoing examples are not intended to be exhaustive, but rather are intended to stimulate thought on management and other factors that may be used to optimize productivity and consumer acceptability while minimizing the negative aspects of animal-source food production. In many cases, these approaches will need to be adapted to local or regional genetic backgrounds to ensure consistency of animal and product responses. Education of producers and consumers in regard to advantages and potential disadvantages will be required to sustain adoption of technologies to meet the growing demand for animal products over the next 50 years.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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