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German, J Bruce

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The future of yogurt: scientific and regulatory needs[1–4]

J Bruce German

ABSTRACT

Lactation biology, microbial selection, and human diversity are central themes that could guide investment in scientific research, industrial innovation, and regulatory policy oversight to propel yogurt into the central role for health-promoting food products. The ability of yogurt to provide the nourishing properties of milk together with the live microorganisms from fermentation provides a unique combination of food assets. Academic research must now define the various targets on which these biological assets act to improve health and develop the metrics that can quantitatively document their benefits. The food industry must reconcile that yogurt and its microorganisms cannot be expected to provide measurable benefits for all consumers, at all doses, and at all times. A supportive regulatory oversight must demand safety and yet encourage innovations that support a value proposition for yogurt in health. Health valuation in the marketplace will be driven by parallel innovations, including accurate assessment technologies, validated microbial ingredients, and health-aware consumers. *Am J Clin Nutr* 2014;99(suppl):1271S–8S.

INTRODUCTION

Yogurt is perhaps the most complex and biologically active of all foods in the marketplace. Its assets, costs, and values are all linked to its biological nature. The science to understand its potential benefits and the regulatory policies to ensure its safety must recognize the complex biology underlying what is, on first glance, simple yogurt. Yogurt is the combination of 3 factors: milk, the product of hundreds of millions of years of lactation evolution; industrial bacteria, the result of centuries of human selection of microbial cultures; and finally, consumers, including the reality of human variation and the need to address the breadth of our diversity. Understanding all 3 is necessary to fully appreciating the potential value of yogurt in the future.

MILK AND LACTATION

Lactation is at the core of mammalian success. The emergence of Mammalia ~200 million y ago brought a remarkable aspect of reproductive strategy of mothers: to feed infants with the secretions of an epithelial gland tissue network (1). Through the ensuing millennia, selective pressure drew remarkable constituents into this increasingly complex nourishment system. Milk is ostensibly encoded by the lactation genetic elements (2). This subset of the mammalian genome has been under selective pressure by maternal and infant survival and their long-term reproductive success. Therefore, selective pressure through mammalian evolution was relentless on the balance of the beneficial attributes of milk and their cost (3, 4). Everything in milk costs the mother, putting her survival at a selective disadvantage. Hence, if a constituent in milk does not result in value for the infant, it is at strong negative pressure because of its cost to the mother. However, if any element of milk provides a nutritional, protective, or developmental advantage to the infant, it is difficult to imagine a more positive selective pressure on a genetic trait. At its core, yogurt is a milk-delivery system for noninfants.

MICROBIAL CULTURE

Microorganisms are an integral part of our food supply, both directly and indirectly. Although much academic research, industrial technologies, and regulatory surveillance have been designed to eliminate microorganisms from food, this view is now changing. Microorganisms are increasingly viewed as valuable assets in the bioprocessing of commodities, with their own contributions of metabolites, structures, and bioactive components (5). Yogurt is a model of such assets. The future of food processing will include more "biological" innovations as microorganisms become controllable. In truth, microorganisms have participated throughout history as important modifiers of the safety, nutritional value, and flavor of a select group of high-value foods. Microorganisms provide hydrolytic enzymes to degrade plant components (phytate). Microorganisms release metabolites (ethanol and lactic acid). Finally, microorganisms release biopolymers that act on other organisms as signals. These biopolymers range from endotoxins that act on the host to quorum-sensing factors that act on the microorganisms in the lumen. In traditional yogurt, the mixed-culture system of *Lactobacillus* and *Streptococcus* (6) delivers a remarkable combination of enzymes and metabolites that enhance

[1] From the Foods for Health Institute, University of California, Davis, Davis, CA.

[2] Presented at the satellite symposium "First Global Summit on the Health Effects of Yogurt," held in Boston, MA, at ASN's Scientific Sessions at Experimental Biology 2013, 24 April 2013. The conference was organized by the ASN, the Nutrition Society, Danone Institute International, and the Dairy Research Institute. The supplement scientific guest editors were Sharon M Donovan, University of Illinois, Urbana, IL, and Raanan Shamir, Schneider Children's Medical Center and Tel Aviv University, Israel.

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[4] Address correspondence and reprint requests to JB German, University of California, Davis, CA 95616. E-mail: jbgerman@ucdavis.edu.

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safety, nourishment, taste, and flavor. The future of food fermentation in its broadest biotechnology perspectives can learn valuable lessons from this traditional artisan system.

The most innovative and scientifically challenging new dimension of nutrition and diet research is the intimate relation between humans and microorganisms. All sciences related to food are similarly realizing the importance of microorganisms as constituents in and on our foods, as biotechnology partners in and on our processing technologies, and as ecological partners in and on—us. New tools and models are revealing an astonishing importance to the diversity of microbes inhabiting specific ecological sites throughout humans (7–11). This research also shows just how much we "pay attention" to them. The microbiota, the diverse populations of microorganisms in and on humans, affects the following:

- the development of the response and regulation of immunity from barrier composition to integrity and acquired immunity from protection to allergy;
- metabolic regulation, from fuel scavenging to whole-body tissue prioritization;
- physiologic processes such as acute blood flow regulation; and
- neurologic processes from infant development to adult regulation.

The disciplines of nutrition and food science are wrestling with the following questions: what components of the bacteria are we sensing to influence our health and how are foods influencing the "health" of the microbial ecosystems within us? Yogurt is the food that today most relates to that relation.

HUMAN DIVERSITY

Food and nutrition are still struggling with a fundamental truth: humans are not the same. Although sex, age, and lifestyle differences have always been recognized as demanding dietary diversity, more subtle differences are now emerging for which solutions must be found. These differences include essential nutrients, but they do not stop there. Lactation and milk provide innovative solutions to mammalian diversity. The first nutritional priority of milk is the provision of all essential nutrients at the minimum level for infant growth and development. Because these same nutrients are as essential to the mother as to the infant, providing essential nutrients in milk comes at a potentially devastating cost to the mother. Hence, milk delivers essential nutrients in bioavailable forms (12, 13). The value of yogurt differs between adults. For example, the elderly are at risk of nutrient deficiencies resulting from low caloric intakes and poor nutrient absorption. Certain genetic polymorphisms are associated with poor uptake of nutrients, including folate (*MTHFR*; 14). Food components can slow nutrient absorption (eg, iron; 15–17). Digestion differs between humans, notably the digestion of lactose. The vast majority of the human population is lactose intolerant after infancy. Genetic polymorphisms in the lactase gene regulatory regions emerged with dairying as an agricultural practice (18). The presence of this endogenous genetic lactose "tolerance" in adults presumably provided selective advantages to those who had this attribute (19). Yogurt provides this enzymatic activity with external microorganisms.

YOGURT: PAST, PRESENT, AND FUTURE

Past success

In its history, yogurt has been a unique product combining valuable elements of lactation, microbial culture, and human diversity. Yogurt delivered the nutritional elements of milk, essential nutrients in highly absorbable forms, bioactive proteins, and lipids. The safety and stability of yogurt as a dairy product were enhanced by the culture by lactic acid bacteria, lowering the pH and producing significant quantities of lactic acid. Finally, because yogurt reduces the lactose amount and provides active bacteria with the lactase enzyme, this rendered it a dairy product for humans who were lactose intolerant.

Present reality

The current role of yogurt in the diet is one of the more successful and yet contentious issues in the entire food marketplace. Yogurt enjoys considerable market share in the overall diet of many parts of the world and yet consumers have little understanding of its value to their health. Even the core assets of yogurt are not universally accepted in the regulatory arena or understood by consumers. The value propositions of yogurt have been altered significantly in the context of the regulatory judgments of recent actions of the European Food Safety Authority and the US Food and Drug Administration. These 2 agencies have been working to establish consensus language to guide scientific research to substantiate health claims for foods (20, 21). The path is complex, and yet certain themes are instructive. Most examples of successful development of scientific evidence that has reached regulatory approval have relied on simple nutrient status (calcium and bone) or have use well-established biomarkers of accepted metabolic relations to long-term disease (cholesterol and heart disease). Yogurt, with its role of delivering live bacteria, does not fall within either of these simple categories. It is therefore not surprising that there is not yet any scientific consensus on the benefits of yogurt and the presence/abundance of live bacteria beyond its traditional role of providing essential nutrients in a dairy product to those with lactose intolerance (22). Thus, despite considerable evidence that yogurt as a food product is beneficial to health, its scientific evidence portfolio, regulatory position, and consumer perception remain underappreciated. This current situation does, however, provide the opportunity for a bright future, if investments are applied.

Future promise of yogurt

Yogurt has the potential to be the vital player in the spectrum of food products that provide a wide range of health benefits to individuals through specific influence on their intestinal microbiota. To reach this potential, however, important strides in both scientific understanding and regulatory oversight must be made. The scientific understanding of the intestinal microbiota is still being assembled. For yogurt, how much of the intestinal microbiota and its influence on whole-body health are alterable by diet. For regulatory oversight, the scientific, industrial, and regulatory communities must agree on quantifiable measures of those microbiota-dependent health properties. Within such a context, companies can then show with these metrics that these

health properties have been significantly improved by their dietary interventions.

Industry must invest in the development of yogurt's potential. Industrial processes and products will need to become more transparent and their expectations for claimable health benefits more clearly defined. Industry will also need to participate in the development, validation, and implementation of technologies that accurately measure yogurt products and their quality, safety, and efficacy. It would be most efficient if the science and its regulatory applications were pursued in parallel.

THE INTESTINE AND ITS COMPLEX MICROBIOTA

The mucosal surfaces of humans are teeming with microorganisms. The intestinal mucosa and the intestinal contents of each human host a large reservoir of microorganisms that are now described as relatively constant as an ecosystem despite the continuous passage of diverse bacteria from the diet (8). Whereas "resilience" of the ecosystem is a relative term, the numbers (~100 trillion) and the complexity of each individual's microbiota are dauntingly complex. Variation among humans exists in every aspect measured: age, geography, etc (23). Despite the complexity and diversity, the gut microbiota population and the human host are apparently working in a mutualistic way to maintain the microbiota as a coherent system (24), if not numerically, at least functionally (25). These efforts at maintaining functions, presumably the result of billions of years of mutualistic coevolution, underlie and at least instruct a broad range of human immunologic (26), metabolic (27), physiologic (25), even neurologic processes (28). When these systems falter, both acute and chronic disease results. The science of how to and why guide our microbiota will drive a next generation of foods.

RESEARCH TARGETS AND KNOWLEDGE MANAGEMENT NEEDED FOR YOGURT

The basic information needed from scientific research and its translation from agriculture to yogurt to personal health is shown in **Figure 1**. The scientific tools to build the data are largely in place. It is now possible to direct these tools to yogurt. The translation of the knowledge will require new ingredients, products, and processes, and technologies to measure and document them. Research scientists, regulatory agencies, and industrial partners will need to work together to ensure that their respective goals and methods are aligned. Such coordination will be facilitated by developing bioinformatics tools to merge the disparate data sets—for example, of microbial genomes, milk components, and human microbiota functions—into a more comprehensive and annotated knowledge of the relations between the input variables of yogurt (bacteria and milk) and their consequences in different humans.

The success of this research and development agenda will depend on close collaboration and appropriate commitment in

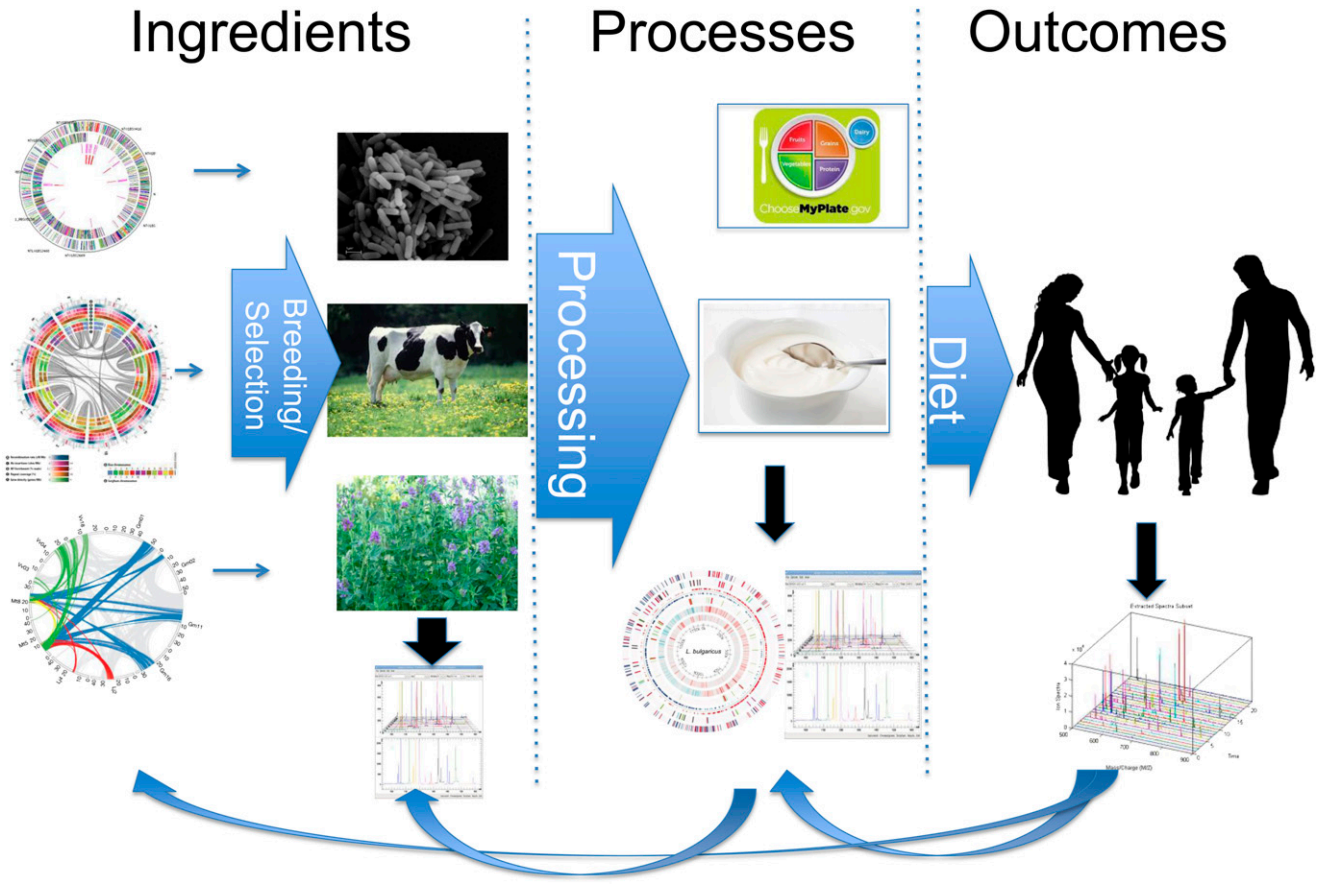

FIGURE 1. The knowledge flows needed to understand the benefits of yogurt and to deliver them to appropriate consumers.

TABLE 1
Summary of research and translation targets for yogurt

	Academic	Industrial	Regulatory
Ingredients			
Milk	Analytic method development Compositional analysis and annotation	Method deployment Compositional analysis of ingredients	Method validation and international standardization of methodologies for composition and quality
Bacteria	Genomic sequencing and annotation Microbial ecology Strain annotation	Strain-specific documentation	Establish standard nomenclatures for quantity, bioviability, and strain specificity of bacteria
Processes			
Unit operations and fermentation	Quantitative understanding of effects of temperature, pressure, homogenization, and shear on milk and bacteria	Support for and partnering with academic institutions for pilot scale production	Validation of new technologies for quality and safety Coherent, transparent regulations for standard of identity and labeling
Health outcomes	Discovery of targets of health as function and performance	Diversify products for different consumers and diverse endpoints. Construct publicly accessible databases of product compositions	Visible criteria for regulatory approval Validation of intermediate endpoints of health Support for standards of health measures Regulatory policy oversight for health assessment

time and resources by all 3 vested sectors: academic research, regulatory agencies, and industrial partners. The challenge is that these 3 sectors have very different goals for research (**Table 1**). Academic scholars need projects that provide long-term competitive funding. For industry, the key is to identify investable values emerging from research. For regulatory policy, transparency in protecting public safety is the priority. Academic research will generate peer-reviewed publications, yet the knowledge must also lead to products, markers, and devices. Regulatory bodies need to participate actively in building consensus, standardization, and validation of quality and safety metrics and diagnostic markers of efficacy. Industry has the opportunity to move beyond simple food product development and participate in the commercialization of technologies to document health efficacy. The interactions and knowledge flows between partners are shown in **Figure 2**. Importantly, both research and practice are working on similar overall goals; they are not necessarily using identical materials and tools and thus they need to communicate, translate from one domain to another, and ensure that outcomes are measurable.

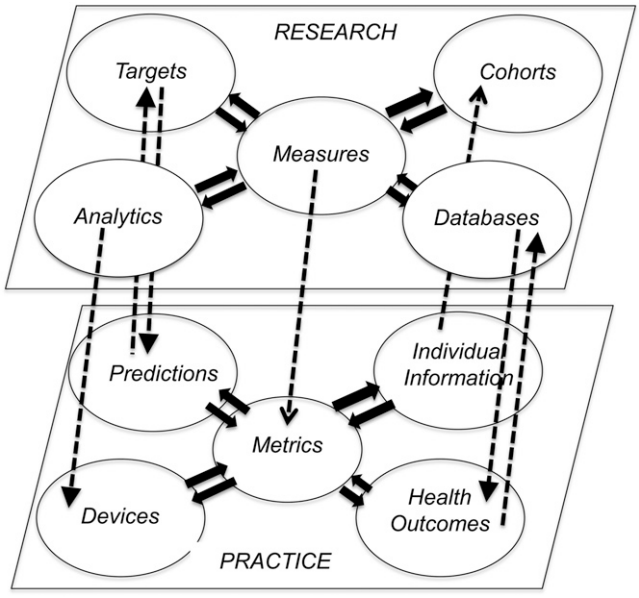

FIGURE 2. The distinct databases of research and practice for health improvements by yogurt as a food product.

INGREDIENTS

The core ingredients of yogurt sound deceptively simple: milk and bacteria. The diversity of both is a challenge and an opportunity.

Milk

Milk is not necessarily a uniform commodity ingredient for yogurt. The basic composition of milk differs according to multiple variables, including the animal's breed (29, 30) and diet (31), milking style (32), and the animal's rumen (33). Although processing has emphasized uniformity, milk research now has the tools available to build a more detailed understanding of the components of milk and to alter their concentrations. For example, milk proteins are not only sources of amino acids for nutrition. Research shows the sequence and structural complexity of milk proteins (34). Milk proteins are, in part, strings of encrypted peptides, the activity of which is released on selective proteolytic digestion. The first generation of research suggests that these peptides have unique biological activities, many of which could be released before yogurt consumption (35). Similar complex structures and functions are being

recognized for the lipids, oligosaccharides, and various small molecules in milk (36).

The future of yogurt will depend not only on building a more detailed knowledge of milk's structures and functions but also on understanding the diverse structures that can be released during production. Such a future will be accelerated by an accessible, annotated database of milk components. Regulatory scrutiny of the marketplace will also require that industries deploy the analytic toolsets capable of documenting the presence of bioactive components in the raw material ingredients and final products.

Bacteria

Bacteria used to produce traditional yogurt are increasingly well described, their growth properties defined, and entire genomes sequenced (6, 37). Annotating the yogurt bacterial genomes for flavor, structure, and stability traits is an important goal for yogurt product quality. With the growing recognition that yogurt provides a viable delivery system for probiotics, a broader range of the *Lactobacillus* bacteria are being explored for their ability to enhance the health properties and value of yogurt (38). The first comprehensive genome-sequencing project for the lactobacilli established a strategy for the entire field (39). Since this visionary start, research has been competitive and comprehensive approaches have not emerged to build a unified and consensus knowledge set of the yogurt bacteria. Nonetheless, scientific progress has been impressive, with increasingly detailed genomic knowledge of the diversity of microorganisms available to milk and cultured dairy products and of their functional differences (40). New technologies such as pangenomic sequencing and detailing gene by gene, functional trait by functional trait, and metabolite by metabolite differences in strain functionalities represent a model for building the future knowledge base of yogurt.

The informatics tools for managing comprehensive sets of bacteria in mixed cultures, their interactions with milk as a matrix, the components produced from milk and microbial metabolites in the ingredient streams for yogurt, and the precise health metrics after their consumption are not yet in place and will need to be developed. On the positive side, this means that experimental designs and methods, marker validation, and informatics tools can be placed simultaneously into a coherent systems approach for yogurt innovations and validations (41).

PROCESSES

Yogurt processing is integral to the final product quality, safety, and health efficacy. Recent successes in expanding the diversity of yogurt processing and composition, notably "Greek style" yogurt, have shown that there is considerable flexibility to innovate within the category. These same successes, however, highlight the lack of industry standards for product labeling, lack of policy consensus of yogurt standards of identity, and lack of scientific support for the purported benefits. For example, so-called Greek-style yogurt swept into the 2010 yogurt marketplace with a simple proposition of being higher in solids and protein. Although this modification in composition is traditionally accomplished by a filtration step during the final stages of processing, many products labeled "Greek style" achieve a higher solids and protein composition by explicitly adding milk protein ingredients at the beginning or end of the process. Producers, regulators, and consumers are now debating: are these methods the same?

As yogurt diversifies, regulatory policy will be faced with important decisions as to what constitutes "yogurt," how far the compositions can diverge before products can no longer be considered within the category, and how to label these various alternatives. Industries are faced with the conflicting pressures of formulating and positioning products within the rapidly changing, competitive marketplace and maintaining labeling standards and consumer transparency.

Food processing is about to be transformed by genomics sequencing tools. Genomics sequencing–based microbial detection systems are now available for relatively routine surveillance of entire processing facilities. Techniques can map entire microbial communities from cows and plants to entire crops and food-processing and health facilities (42–45). Detailed knowledge of the microbial communities, including bacteria, yeast, molds, and even bacteriophages, within entire yogurt-processing environments, will enhance safety, quality, and going forward, the health propositions possible.

HEALTH OUTCOMES AND YOGURT

Yogurt is already perceived by consumers as having health benefits. Going forward, yogurt is a food category poised to translate scientific research. In many respects, yogurt is ideally situated to lead science and technology into a future of greater health through diet. The question is, can research be mobilized to realize this future?

Progress in discovering the relations between yogurt and health would be significantly enhanced with 3 simple changes in strategy:

1) Focus on prevention and protection rather than therapeutic cure.

2) Unify lactation research across all mammals, including human and bovine.

3) Develop markers based on mechanisms of action to translate science into regulatory dossiers of efficacy and demonstrated proof of benefits.

Prevention

Health is approached largely from a disease-centric perspective. Diseases are defined by specific functional departures from "normal" health. The goal of curative health science is to understand the mechanisms underlying those diseases and to discover interventions—chemical, biological, or procedural—to reverse them. Preventing diseases before they occur is not necessarily the same. Prevention implies that interventions (again, chemical, biological, or procedural) act preemptively on healthy individuals to lower the risk of disease (ie, to improve health). Prevention in practice would strengthen processes that block agents that cause diseases, to rebalance endogenous processes that are chronically dysregulated sufficiently to lead to disease and to enhance the activity or sensitivity of surveillance processes that detect damaged molecules, cells, or tissues that would become diseased. The

challenge for science is to bring these broad principles into mechanistically defined and demonstrable action. Scientists are using very imaginative approaches to identity the targets of disease diagnostics and therapeutics; those same toolsets can now be applied to discover the targets, metrics, and products of prevention.

Lactation

Lactation has been driven by relentless Darwinian selective pressure for protection and prevention. Yogurt would profit by bringing a scientifically detailed, molecular understanding of how milk from all mammals, especially humans, achieves its benefits. Once established, those mechanisms can be translated into innovative yogurt products and benefits. The following 4 broad categories of benefits to infants would be of immediate value across the age spectrum, if science could unravel the mechanisms by which milk achieves these effects: immunity, metabolism, physiology, and microbiota.

Immunity is a massively complex system consisting of multiple innate structures and functions together with an even greater diversity of acquired processes. Appropriate functioning of immunity is necessary to the protection of life and the prevention of disease. Yet, imbalances in immunity can cause disease. Failure to regulate immunity appropriately thus contributes both to increased risk of infectious disease when immune responses are insufficient and yet contributes to increased risk of diseases of inflammation and autoimmunity when immunity is inappropriate and excessive. Diets that prevent disease must therefore improve both aspects of immunity. The failure of the immune system to respond sufficiently to pathogenic invasion is seen in young infants, as a result of delayed development, and in the elderly who are at risk of immune senescence and suppression (46). Human milk has been documented to enhance the development of acquired immunity in infants and these same mechanisms could translate to adults, if they were understood (47).

Scientific consensus has not yet developed a full nomenclature to describe inflammation. Nonetheless, however it is defined, inflammation is associated with, if not considered central to, virtually all noncommunicative, degenerative diseases (heart disease, diabetes, cancer, arthritis, asthma, stroke, etc) (48). If inflammation could be reduced, the benefits to long-term health would be remarkable. However, there is a problem. Inflammation is also at key points essential to the successful immune response to pathogens. Therefore, interventions to reduce inflammation carry the risk of increased infectious disease. The balance of immunity is at the core of this diverse protection system, and at present no strategy has emerged that can maintain appropriate immune response and simultaneously prevent chronic inflammation. Yet, human milk is very well described as providing multiple, diverse mechanisms that are anti-inflammatory, while at the same time enhancing overall immune protection of the infant (49). The mysteries of inflammation—from the diverse mechanisms that cause it to the ingredients to manage it—are hidden within lactation biology.

Metabolism in higher organisms is in many ways as complex and pervasive as immunity. The appropriate distribution of fuels and substrates to support all of the disparate systemic processes is the function of metabolic regulation. The inappropriate distribution of fuel is now recognized to be driving obesity, cachexia, heart disease, diabetes, and many cancers (50). Once again, aggressive pharmacologic approaches to alter metabolic regulation are fraught with risk. Milk has not only been shown to be associated with appropriate metabolic regulation in infants, but dairy intake has also been associated with risk protection in adults (51). Thus, the mechanism by which milk supports metabolism is evidently translatable across all ages and mammalian species. The secrets to metabolic control are in lactation biology.

Physiologic processes, when unbalanced, are increasingly recognized as drivers of chronic disease. Simple blood flow is an example of the complexity of the problem. When physiologic processes are working appropriately, blood flow is acutely directed to tissues in demand, fueling performance and removing byproducts. When not working appropriately, impaired blood flow, measured as hypertension, is a major driver of cardiovascular disease (52). Milk clearly targets blood flow regulation. One of the classes of bioactive factors (antihypertensive peptides) and their targets of action (angiotensin-converting enzyme) have already been brought to practice as functional food ingredients (53). The path to understanding physiologic regulation is through lactation biology.

The microbiota of humans is a key contributor to the regulation of metabolic, physiologic, immunologic, and even neurologic processes. The most compelling evidence for the importance of the microbiota to human health and the ability to manipulate it through diet comes from milk. The mammary gland and lactation providing milk for infant nourishment have been central to mammalian evolutionary success (54). Milk nourishes the infant and yet costs the mother. One class of molecules has been particularly perplexing in this context. Glycans (complex sugar polymers and their conjugates) are indigestible by infants (55). Ongoing research has established that these components are selectively feeding not the infant but specific bacteria within the infant's intestine (56–58). The diverse saccharide structures and linkages in the glycans of milk are matched to stereospecific catalytic activities of a group of bacterial enzymes within the genomes of bacteria unique to infants (58–60). The microbiota of breastfed infants is remarkably distinct during the first year of life (61, 62). Milk itself is a source of living microorganisms, implicating milk as a delivery system for maternally derived bacteria destined for the infant (63, 64). Once again, the roadmap to colonizing and guiding a complex microbial ecosystem in the intestine of humans is contained within the lactation genome of mammals. Research just needs to "decode" it.

METRICS/DIAGNOSTICS OF YOGURT AND HEALTH

A key to improving health in the population and to capturing value in food products and services is to develop the technologies to accurately measure individual health. Success in diagnosing disease by identifying analytes in blood associated with particular diseases has driven the drug marketplace. Unfortunately, this basic strategy will need to be modified for measuring health and preventing disease, because there is no disease to diagnose. Health itself must be assessed. Assessing health means measuring the functioning of the various systems, structures, and processes that constitute the normal healthy state. In a food marketplace in which consumers are measured for personal health, the value of yogurt can be shown by its ability to enhance those functions.

Disease is typically detected by static measures: diagnostics. The processes of health are revealed by challenging those processes explicitly (65–67). The challenge approach to health assessment includes the measurement of the dynamic fluxes of metabolites through specific biochemical pathways in response to a defined nutritional input. A standard glucose challenge, for example, has been a hallmark of metabolic assessment for decades, and this principle has been shown to be expandable to multiple nutrients (65). This "challenge" principle shows aspects of metabolism that are unavailable in the fasted state. Analogous to running a race to assess the performance of athletes, analyzing the metabolic, immunologic, physiologic, and even neurologic responses to a standard stimulus can assess the quality of the performance of those systems.

Scientists can and should drive a new view of health, measurable by absolute, quantitative criteria. The metrics of what to measure, when, how accurately, and in response to what challenge are appropriate research goals for academic science. However, scientists developing health metrics must now go beyond simply chronicling disease processes. Finally, these scientific measures must move out of the laboratories and into common practice. This ultimate goal of building a health assessment marketplace will require devices that are sufficiently accurate to be of predictive value but sufficiently noninvasive, cost-effective, and convenient to be practical. Engineers will need to be at least as diligent and engaged in building the tools of health measurement as they are in the tools of automotive performance. Deploying personal health measures will build a more knowledgeable consumer population. A more knowledgeable consumer population will drive a more competitive and more valuable marketplace. To reach this more measured consumer population, regulators will need to guide, validate, and monitor the accuracy of health measurement as an industry. In a measured health marketplace, yogurt's value will rise.

Health assessment needs a policy advocate. There needs to be a regulatory body that champions the development of health assessment indicators out of academic research. Although disease diagnostics provide a framework, there are some important differences. The costs of approving disease diagnostics are high, for good reason. The consequences of an error, either type 1 (false positive) or type 2 (false negative), based on a diagnostic outcome decision for disease can be catastrophic. Hence, the time and effort needed to minimize error rates for disease diagnostics are justified. However, for measures of health, the situation is different. Health will be measured more routinely, and the decisions taken are less impactful. Hence, a distinct regulatory oversight system for the development, validation, and monitoring of the marketplace of health assessment should be more flexible and reactive.

CONCLUSIONS

The long history of the health values of yogurt are chronicled throughout this series of accompanying articles in the supplement issue. The future of yogurt is in the hands of scientists, technologists, and policy makers. There is a clear opportunity to build the knowledge, tools, and products needed to position a portfolio of new foods based on the concepts of traditional yogurt. Academic research, industrial partners, and policy regulators working together will achieve this future. Research will need to establish the mechanisms by which yogurt acts on specific aspects of health and the metrics to document them. Industries will accelerate progress by providing materials for development and clinical trials. Regulators will provide a more competitive commercial marketplace for health by supporting the development, validation, and deployment of technologies to measure human health and to show the value of health-supporting food products.

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REFERENCES

1. Lefèvre CM, Sharp JA, Nicholas KR. Evolution of lactation: ancient origin and extreme adaptations of the lactation system. Annu Rev Genomics Hum Genet 2010;11:219–38.
2. Lemay DG, Neville MC, Rudolph MC, Pollard KS, German JB. Gene regulatory networks in lactation: identification of global principles using bioinformatics. BMC Syst Biol 2007;1:1–24.
3. Hinde K, German JB. Food in an evolutionary context: insights from mother's milk. J Sci Food Agric 2012;92:2219–23.
4. Hinde K, Milligan LA. Primate milk: proximate mechanisms and ultimate perspectives. Evol Anthropol 2011;20:9–23.
5. Gobbetti M, Cagno RD, De Angelis M. Functional microorganisms for functional food quality. Crit Rev Food Sci Nutr 2010;50:716–27.
6. Sieuwerts S, Molenaar D, van Hijum SA, Beerthuyzen M, Stevens MJ, Janssen PW, Ingham CJ, de Bok FA, de Vos WM, van Hylckama Vlieg JE. Mixed-culture transcriptome analysis reveals the molecular basis of mixed-culture growth in Streptococcus thermophilus and Lactobacillus bulgaricus. Appl Environ Microbiol 2010;76:7775–84.
7. Ley RE, Lozupone CA, Hamady M, Knight R, Gordon JI. Worlds within worlds: evolution of the vertebrate gut microbiota. Nat Rev Microbiol 2008;6:776–88.
8. Lozupone CA, Stombaugh JI, Gordon JI, Jansson JK, Knight R. Diversity, stability and resilience of the human gut microbiota. Nature 2012;489: 220–30.
9. Nicholson JK, Holmes E, Kinross J, Burcelin R, Gibson G, Jia W, Pettersson S. Host-gut microbiota metabolic interactions. Science 2012;336:1262–7.
10. Palmer C, Bik EM, DiGiulio DB, Relman DA, Brown PO. Development of the human infant intestinal microbiota. PLoS Biol 2007; 5:e177.
11. Sommer F, Backhed F. The gut microbiota—masters of host development and physiology. Nat Rev Microbiol 2013;11:227–38.
12. Meisel H, FitzGerald RJ. Biofunctional peptides from milk proteins: mineral binding and cytomodulatory effects. Curr Pharm Des 2003;9: 1289–95.
13. German JB, Dillard CJ, Ward RE. Bioactive components in milk. Curr Opin Clin Nutr Metab Care 2002;5:653–8.
14. Yang QH, Botto LD, Gallagher M, Friedman JM, Sanders CL, Koontz D, Nikolova S, Erickson JD, Steinberg K. Prevalence and effects of gene-gene and gene-nutrient interactions on serum folate and serum total homocysteine concentrations in the United States: findings from the Third National Health and Nutrition Examination Survey DNA bank. Am J Clin Nutr 2008;88:232–46.
15. Singh M, Sanderson P, Hurrell RF, Fairweather-Tait SJ, Geissler C, Prentice A, Beard JL. Iron bioavailability: UK Food Standards Agency workshop report. Br J Nutr 2006;96:985–90.
16. Sanz-Penella JM, Laparra JM, Sanz Y, Haros M. Assessment of iron bioavailability in whole wheat bread by addition of phytase-producing bifidobacteria. J Agric Food Chem 2012;60:3190–5.
17. Mario Sanz-Penella J, Laparra JM, Sanz Y, Haros M. Bread supplemented with amaranth (Amaranthus cruentus): effect of phytates on in vitro iron absorption. Plant Foods Hum Nutr 2012;67:50–6.
18. Itan Y, Jones BL, Ingram CJ, Swallow DM, Thomas MG. A worldwide correlation of lactase persistence phenotype and genotypes. BMC Evol Biol 2010;10:1–11.
19. Ingram CJ, Mulcare CA, Itan Y, Thomas MG, Swallow DM. Lactose digestion and the evolutionary genetics of lactase persistence. Hum Genet 2009;124:579–91.
20. Ellwood KC, Trumbo PR, Kavanaugh CJ. How the US Food and Drug Administration evaluates the scientific evidence for health claims. Nutr Rev 2010;68:114–21.

21. Vero V, Gasbarrini A. The EFSA health claims 'learning experience'. Int J Food Sci Nutr 2012;63(suppl 1):14–6.
22. Katan MB. Why the European Food Safety Authority was right to reject health claims for probiotics. Benef Microbes 2012;3:85–9.
23. Yatsunenko T, Rey FE, Manary MJ, Trehan I, Dominguez-Bello MG, Contreras M, Magris M, Hidalgo G, Baldassano RN, Anokhin AP, et al. Human gut microbiome viewed across age and geography. Nature 2012;486:222–7.
24. Hooper LV, Macpherson AJ. Immune adaptations that maintain homeostasis with the intestinal microbiota. Nat Rev Immunol 2010;10: 159–69.
25. Lozupone C, Faust K, Raes J, Faith JJ, Frank DN, Zaneveld J, Gordon JI, Knight R. Identifying genomic and metabolic features that can underlie early successional and opportunistic lifestyles of human gut symbionts. Genome Res 2012;22:1974–84.
26. Smith PM, Howitt MR, Panikov N, Michaud M, Gallini CA, Bohlooly-Y M, Glickman JN, Garrett WS. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. Science 2013;341:569–73.
27. Raybould HE. Gut microbiota, epithelial function and derangements in obesity. J Physiol 2012;590:441–6.
28. Forsythe P, Kunze WA, Bienenstock J. On communication between gut microbes and the brain. Curr Opin Gastroenterol 2012;28:557–62.
29. Perna A, Intaglietta I, Simonetti A, Gambacorta E. Effect of genetic type and casein haplotype on antioxidant activity of yogurts during storage. J Dairy Sci 2013;96:3435–41.
30. Skibiel AL, Downing LM, Orr TJ, Hood WR. The evolution of the nutrient composition of mammalian milks. J Anim Ecol 2013;82(6):1254–64.
31. Romanzin A, Corazzin M, Piasentier E, Bovolenta S. Effect of rearing system (mountain pasture vs. indoor) of Simmental cows on milk composition and Montasio cheese characteristics. J Dairy Res 2013;80 (4):390–9.
32. Martin B, Pomiès D, Pradel P, Verdier-Metz I, Rémond B. Yield and sensory properties of cheese made with milk from Holstein or Montbeliarde cows milked twice or once daily. J Dairy Sci 2009;92:4730–7.
33. Kurokawa Y, Shibata H, Tateno S, Kanda S, Takaura K, Ishida S, Itabashi H. Rumen fermentation, milk production and conjugated linoleic acid in the milk of cows fed high fiber diets added with dried distillers grains with solubles. Anim Sci J 2013;84:106–12.
34. Dallas DC, Guerrero A, Khaldi N, Castillo PA, Martin WF, Smilowitz JT, Bevins CL, Barile D, German JB, Lebrilla CB. Extensive in vivo human milk peptidomics reveals specific proteolysis yielding protective antimicrobial peptides. J Proteome Res 2013;12:2295–304.
35. Madureira AR, Tavares T, Gomes AM, Pintado ME, Malcata FX. Invited review: physiological properties of bioactive peptides obtained from whey proteins. J Dairy Sci 2010;93:437–55.
36. Ward RE, German JB. Understanding milk's bioactive components: a goal for the genomics toolbox. J Nutr 2004;134:962S–7S.
37. Thevenard B, Rasoava N, Fourcassié P, Monnet V, Boyaval P, Rul F. Characterization of Streptococcus thermophilus two-component systems: in silico analysis, functional analysis and expression of response regulator genes in pure or mixed culture with its yogurt partner, Lactobacillus delbrueckii subsp. bulgaricus. Int J Food Microbiol 2011; 151:171–81.
38. Vázquez C, Botella-Carretero JI, García-Albiach R, Pozuelo MJ, Rodríguez-Baños M, Baquero F, Baltadjieva MA, del Campo R. Screening in a Lactobacillus Delbrueckii subsp. Bulgaricus collection to select a strain able to survive to the human intestinal tract. Nutr Hosp 2013;28:1227–35.
39. Makarova K, Slesarev A, Wolf Y, Sorokin A, Mirkin B, Koonin E, Pavlov A, Pavlova N, Karamychev V, Polouchine N, et al. Comparative genomics of the lactic acid bacteria. Proc Natl Acad Sci USA 2006; 103:15611–6.
40. Smokvina T, Wels M, Polka J, Chervaux C, Brisse S, Boekhorst J, van Hylckama Vlieg JE, Siezen RJ. Lactobacillus paracasei comparative genomics: towards species pan-genome definition and exploitation of diversity. PLoS ONE 2013;8:e68731.
41. Lemay DG, Zivkovic AM, German JB. Building the bridges to bioinformatics in nutrition research. Am J Clin Nutr 2007;86:1261–9.
42. Bokulich NA, Ohta M, Richardson PM, Mills DA. Monitoring seasonal changes in winery-resident microbiota. PLoS ONE 2013;8:e66437.
43. Bokulich NA, Mills DA. Facility-specific "house" microbiome drives microbial landscapes of artisan cheesemaking plants. Appl Environ Microbiol 2013;79:5214–23.
44. Bokulich NA, Mills DA, Underwood MA. Surface microbes in the neonatal intensive care unit: changes with routine cleaning and over time. J Clin Microbiol 2013;51:2617–24.
45. Setati ME, Jacobson D, Andong UC, Bauer F. The vineyard yeast microbiome, a mixed model microbial map. PLoS ONE 2012;7: e52609.
46. Goronzy JJ, Weyand CM. Understanding immunosenescence to improve responses to vaccines. Nat Immunol 2013;14:428–36.
47. Ballard O, Morrow AL. Human milk composition: nutrients and bioactive factors. Pediatr Clin North Am 2013;60:49–74.
48. Tabas I, Glass CK. Anti-inflammatory therapy in chronic disease: challenges and opportunities. Science 2013;339:166–72.
49. Goldman AS. Evolution of immune functions of the mammary gland and protection of the infant. Breastfeed Med 2012;7:132–42.
50. Grundy SM. Pre-diabetes, metabolic syndrome, and cardiovascular risk. J Am Coll Cardiol 2012;59:635–43.
51. Rice BH, Quann EE, Miller GD. Meeting and exceeding dairy recommendations: effects of dairy consumption on nutrient intakes and risk of chronic disease. Nutr Rev 2013;71:209–23.
52. Floras JS. Blood pressure variability: a novel and important risk factor. Can J Cardiol 2013;29:557–63.
53. Phelan M, Kerins D. The potential role of milk-derived peptides in cardiovascular disease. Food Funct 2011;2:153–67.
54. Lemay DG, Lynn DJ, Martin WF, Neville MC, Casey TM, Rincon G, Kriventseva EV, Barris WC, Hinrichs AS, Molenaar AJ. The bovine lactation genome: insights into the evolution of mammalian milk. Genome Biol 2009;10:1–18.
55. Zivkovic AM, German JB, Lebrilla CB, Mills DA. Human milk glycobiome and its impact on the infant gastrointestinal microbiota. Proc Natl Acad Sci USA 2011;108(suppl 1):4653–8.
56. Ward RE, Niñonuevo M, Mills DA, Lebrilla CB, German JB. In vitro fermentability of human milk oligosaccharides by several strains of bifidobacteria. Mol Nutr Food Res 2007;51:1398–405.
57. Sela DA, Garrido D, Lerno L, Wu S, Tan K, Eom HJ, Joachimiak A, Lebrilla CB, Mills DA. Bifidobacterium longum subsp. infantis ATCC 15697 alpha-fucosidases are active on fucosylated human milk oligosaccharides. Appl Environ Microbiol 2012;78:795–803.
58. Sela DA, Chapman J, Adeuya A, Kim JH, Chen F, Whitehead TR, Lapidus A, Rokhsar DS, Lebrilla CB, German JB, et al. The genome sequence of Bifidobacterium longum subsp. infantis reveals adaptations for milk utilization within the infant microbiome. Proc Natl Acad Sci USA 2008;105:18964–9.
59. Marcobal A, Barboza M, Sonnenburg ED, Pudlo N, Martens EC, Desai P, Lebrilla CB, Weimer BC, Mills DA, German JB, et al. Bacteroides in the infant gut consume milk oligosaccharides via mucus-utilization pathways. Cell Host Microbe 2011;10:507–14.
60. Garrido D, Nwosu C, Ruiz-Moyano S, Aldredge D, German JB, Lebrilla CB, Mills DA. Endo-β-N-acetylglucosaminidases from infant gut-associated bifidobacteria release complex N-glycans from human milk glycoproteins. Mol Cell Proteomics 2012;11:775–85.
61. Underwood MA. Human milk for the premature infant. Pediatr Clin North Am 2013;60:189–207.
62. Donovan SM, Wang M, Li M, Friedberg I, Schwartz SL, Chapkin RS. Host-microbe interactions in the neonatal intestine: role of human milk oligosaccharides. Adv Nutr 2012;3(suppl):450S–5S.
63. Ward TL, Hosid S, Ioshikhes I, Altosaar I. Human milk metagenome: a functional capacity analysis. BMC Microbiol 2013;13:1–12.
64. Quigley L, O'Sullivan O, Stanton C, Beresford TP, Ross RP, Fitzgerald GF, Cotter PD. The complex microbiota of raw milk. FEMS Microbiol Rev 2013;37:664–98.
65. Krug S, Kastenmüller G, Stückler F, Rist MJ, Skurk T, Sailer M, Raffler J, Römisch-Margl W, Adamski J, Prehn C, et al. The dynamic range of the human metabolome revealed by challenges. FASEB J 2012;26:2607–19.
66. Pellis L, van Erk MJ, van Ommen B, Bakker GC, Hendriks HF, Cnubben NH, Kleemann R, van Someren EP, Bobeldijk I, Rubingh CM, et al. Plasma metabolomics and proteomics profiling after a postprandial challenge reveal subtle diet effects on human metabolic status. Metabolomics 2012;8:347–59.
67. Zivkovic AM, Wiest MM, Nguyen U, Nording ML, Watkins SM, German JB. Assessing individual metabolic responsiveness to a lipid challenge using a targeted metabolomic approach. Metabolomics 2009; 5:209–18.