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A 100-Year Review: Metabolic modifiers in dairy cattle nutrition[1]

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ABSTRACT

The first issue of the *Journal of Dairy Science* in 1917 opened with the text of the speech by Raymond A. Pearson, president of the Iowa State College of Agriculture, at the dedication of the new dairy building at the University of Nebraska (J. Dairy Sci. 1:4–18, 1917). Fittingly, this was the birth of a new research facility and more importantly, the beginning of a new journal devoted to the sciences of milk production and manufacture of products from milk. Metabolic modifiers of dairy cow metabolism enhance, change, or interfere with normal metabolic processes in the ruminant digestive tract or alter postabsorption partitioning of nutrients among body tissues. Papers on metabolic modifiers became more frequent in the journal around 1950. Dairy farming changed radically between 1955 and 1965. Changes in housing and feeding moved more cows outside, and cows and heifers in all stages of lactation, including the dry period, were fed as a single group. Rations became wetter with the shift to corn silage as the major forage in many rations. Liberal grain feeding met the requirements of high-producing cows and increased production per cow but introduced new challenges; for example, managing and feeding cows as a group. These changes led to the introduction of new strategies that identified and expanded the use of metabolic modifiers. Research was directed at characterizing the new problems for the dairy cow created by group feeding. Metabolic modifiers went beyond feeding the cow and included environmental and housing factors and additives to reduce the incidence and severity of many new conditions and pathologies. New collaborations began among dairy cattle specialties that broadened our understanding of the workings of the cow. The *Journal of Dairy Science* then and now plays an enormously important role in dissemination of the findings of dairy scientists worldwide that address existing and new technologies.

Key words: metabolic modifier, feed additive, ionophore, 100-year review

INTRODUCTION

The first article in the first issue of the *Journal of Dairy Science* in 1917 was the text of the speech by Raymond A. Pearson, president of the Iowa State College of Agriculture, at the dedication of the new dairy building at the University of Nebraska (Pearson, 1917). Fittingly, this was the birth of a new research facility and, more importantly, the beginning of a new journal devoted to the sciences of milk production and manufacture of products from milk. Approximately 15 papers related to metabolic modifiers were published in the *Journal of Dairy Science* from 1917 to 1940 (Appendix Table A1). Salt was the first metabolic modifier described (Joffe, 1918). Climate, season, and stage of lactation, along with feed-related compounds, were reported as factors affecting milk yield and composition. Sources of metabolic modifiers include microorganisms or their products (e.g., ionophores), feed additives, hormones, and nutrients in feed. Some require exhaustive studies to demonstrate safety and efficacy to the target animal and the environment by regulatory agencies. Animal drugs are regulated in the United States by The Center of Veterinary Medicine (**CVM**), a branch of the Food and Drug Administration (**FDA**). Many feed additives are classified as "generally regarded as safe" (GRAS) substances and have little or no regulatory oversight. Makers of these products often make claims not substantiated in peer-reviewed journals.

Chapter 9 of *Nutrient Requirements of Dairy Cattle* (7th rev. ed.; NRC, 2001) identified and described unique aspects of dairy cattle nutrition during the transition period that covered metabolic disorders, reproductive tract problems, and prevention measures to reduce incidence of these conditions. The final section of that publication, "Performance Modifiers," described feed additives, microbial products, and bovine somatotropin.

THE LACTATION CYCLE AND TRANSITION PERIOD

The day following the conclusion of lactation should be recognized as the first day of the next lactation cycle.

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The dry period is a time for preparing for the ensuing lactation. Fetal growth is greatest during the last 2 mo of pregnancy. At the end of lactation, milking ceases and cows are generally treated with long-acting antibiotics that kill most existing bacteria and protect the gland from infection. Cows are fed a high-NDF forage/low-concentrate diet that rebuilds rumen papillae and musculature. The population of rumen bacteria reverts to a high proportion of gram-positive species. Stoppage of milking puts in motion a series of actions that begin the ensuing lactation. Involution of the mammary gland invokes a series of events that replaces old secretory tissue with new alveolar tissue. Iron needed for bacterial growth is bound by lactoferrin. The teat end is sealed by a keratin plug that prevents entrance of bacteria into the gland.

The transition period lasts from 10 to 14 d before calving to 4 to 6 d after calving. As calving approaches, the proportion of concentrate in the ration is increased. The rumen population switches to a more gram-negative flora. Hormonal changes occur that begin the process of lactation. Colostrum is produced and fills the gland. The cow must supply energy, protein, vitamins, and minerals for colostrum production at a time when feed intake is decreasing. The transition of the cow to the lactating state has begun and, with it, the heightened potential of metabolic conditions and infections.

The transition period is an intersection of multiple digestive and metabolic systems with actions that must be operative at the time of calving. Failure of one or more of these systems leads to metabolic and infectious diseases that compromise the cow's well-being and may lead to culling or death. Loss of a cow represents a major loss of income for the producer.

Large shifts in metabolism occur during the transition period that place cows, especially those in later parities, at high risk for metabolic conditions related to energy, mineral, and vitamin deficits. Dry matter intake begins to decrease, especially in final 2 to 4 d before calving (Bertics et al., 1992), and intake may be 0 to 4 kg on the day of calving. Those cows with a major reduction in DMI are at high risk for an assortment of metabolic and bacterial diseases, notably parturient paresis, ketosis, mastitis, retained placenta, and metritis. Birth of the calf creates abdominal space that increases the odds for displaced abomasum. Inclusion of monensin in the feed or as a controlled release capsule administered precalving reduces clinical ketosis and displaced abomasum after calving (Duffield et al., 2002). Goff and Horst (1997) provide an excellent review on metabolic, mechanical, and infectious diseases in cows during the transition period. Without any metabolic or infectious disease, DMI increases 2 to 4 d after calving with high potential for success.

Parturient Paresis (Milk Fever)

Onset of lactation increases mineral demands, especially calcium for smooth muscle contraction. Hibbs (1950) provided a history of published observations of a disease that occurred around time of parturition that became known as milk fever. One reference to milk fever was described in writings by the German scientist Eberhardt in 1793. In the first half of the 19th century, therapies such as hot packs, blankets, and blood-letting were used. Hibbs (1950) described 30 causes of the disease and many remedies followed but all failed. One recommendation was that if a cow survived a second parturition with treatment for milk fever, "prepare the beast for the butcher."

In 1897, J. J. Schmidt examined colostrums with a microscope from affected cows with the disease and attributed milk fever to a viral infection. Treatment of the affected gland with 1% potassium iodide solution cleared the infection but not the condition. Mortality was reduced from greater than 60% to about 15%. In 1901, udder inflation successfully reduced mortality to 1% and became the treatment of choice. Mastitis increased, however, due to use of unsterilized equipment.

New theories were proposed as the cause of milk fever, including hypoglycemia, hyperglycemia, and parathyroid gland insufficiency—all without success. Scientists in the mid-1930s began to shift the research focus to calcium and phosphorus. Fish (1929) reported that the Ca:P ratio in blood from normal cows was 2.3:1, whereas in cows with milk fever, it was 1:9.

Hibbs et al. (1946) suggested that vitamin D was involved in milk fever because the incidence was higher in winter months when cows were maintained indoors and less exposed to solar radiation than in summer, when cows had access to pasture.

Normal blood calcium is 9 to 10 mg/100 mL (Nelson et al., 2016). As blood calcium declines, cows become subclinical (reduced serum calcium but no outward signs); partial or full paralysis with recumbency occurs at a calcium level of $\leq$5 to 6 mg/100 mL. Various ration strategies for feeding close-up dry cows have been developed that reduce the incidence and severity of parturient paresis. These include the amount and ratio of Ca and P, administration of vitamin D per os or by injection, and manipulating alkalinity in diets. The primary goal of these strategies is to maintain or increase blood calcium.

Cows with parturient paresis may also experience reduced milk production, mastitis, retained placenta, and ketosis, and they are at greater risk for culling than herdmates. Multiparous cows, especially those with a long dry period, are at high risk for parturient paresis. Smooth muscle in intestinal and uterine tissues is incapable of strong muscular contractions. Risk of milk fever is low in heifers. Breed is a significant risk factor for milk fever in the order: Jersey > Guernsey > Brown Swiss > Holsteins.

Curtis et al. (1984, 1985) used path analysis and logistic regression as a statistical tool to describe periparturient disorders as multifaceted, in that the occurrence of one disorder contributed to others. They collected 1,979 lactation records from 31 farms enrolled in the New York DHIA. Information on 1,374 cows included age, parity (≥2), calving date, previous lactation 30-d mature-equivalent yield, days dry, and estimated nutrient intakes for calcium, phosphorus, protein, and energy during the final 3 wk of the dry period. Conditions evaluated included mastitis, dystocia, parturient paresis, ketosis, left displaced abomasum (**LDA**), metritis, and mastitis.

Age (lactation number) followed by estimated transmitting ability of cows were the most important risk factors contributing to the occurrence of parturient paresis, mastitis, and retained placenta. Parturient paresis was the most significant disease in terms of developing additional conditions and infections. A long dry period increased risk for retained placenta. Cows that developed retained placenta were at increased risk for dystocia, mastitis, and retained placenta. Dystocia, retained placenta, and LDA, in turn, contributed to a high risk for metritis.

The immune system is the primary defense system in the body. Support for immunity should be considered a productive function rather than a maintenance function. The 2 branches of the immune system are the acquired and innate systems. Like the armed forces of a government, the immune system lies in wait for the battle and requires energy and nutrients for its preparedness. The acquired component includes antibodies produced by vaccination or previous exposure to pathogens. Lymphocytes from the innate branch are the "special forces" cells. These cells—the macrophages neutrophils, and basophils—respond to an immediate invasion by a foreign body with release of chemical and biological agents to remove the threat of disease.

The immune system is highly involved in the events of parturition. Birthing begins as the immune system recognizes the placenta as a foreign tissue. Placental attachments are disconnected and release of oxytocin begins muscle contractions to expel the fetus and associated membranes and fluids. Glucose requirements by the dairy cow are increased by an activated immune system (Kvidera et al., 2017). A compromised immune system results in reduced neutrophil function (Kimura et al., 2002) and loss of smooth muscle control. The reduced functions are major factors leading to dystocia, retained placenta, metritis, and mastitis. A subsequent paper by Kimura et al. (2006) demonstrated that intracellular calcium was reduced in peripheral blood mononuclear cells, decreasing to a nadir on the day of calving. Bradford et al. (2015) provide an in-depth review of the role on the immune system during the transition period for initiation of calving, expelling placental tissues, and protecting against infection.

Several feeding strategies to reduce milk fever have proven effective in reducing its severity and incidence. In one study, a low calcium diet (8 g/454 g) prevented milk fever (Goings et al., 1974). Although the approach was successful, implementation was difficult because of the availability of suitable feeds to achieve such low dietary calcium. Functions of vitamin D are hormonal in nature, affecting release of parathyroid hormone and stimulating synthesis and release of 1,25-dihydroxycholecalciferol, mobilization of bone calcium, and enhancement of renal resorption of calcium (Nelson et al., 2016).

Mineral acids were used in Scandinavia in the mid-1900s to preserve high-moisture grass silages and tubers such as sugar beets and potatoes. These diets also reduced parturient paresis in transition cows (Ender and Dishington, 1970). The combination of acids, primarily sulfuric and hydrochloric, produced a negative dietary cation-anion difference (DCAD) diet that maintained blood Ca concentrations during the calving period. Block (1984) fed cationic and anionic DCAD diets to 20 cows (12 Holstein and 8 Ayrshire) in a 2-year switchback design. Ten cows received an anionic diet and 10 cows were fed a cationic diet in year 1. In year 2, cows were switched to the other diet. Diets were fed beginning at 45 d prepartum and continued through calving. Cows fed the anionic diet had no milk fever, whereas 47.4% of cows fed the cationic diet had milk fever. Dry matter intake (as % of BW) averaged 1.85 and 1.81 for cationic and anionic diets, and milk yield was 496 kg greater for cows fed anionic diets per lactation during the 2-year study.

Ketosis

Clinical ketosis is a metabolic disorder of dairy cattle characterized by increased concentrations in blood of acetoacetate (**AcAc**) and β-hydroxybutyrate (BHB). Woody Hayes, former head coach of football at The Ohio State University, shunned the forward pass because 4 things that can happen with a forward pass that are analogous to the transition period: (1) the pass is completed (as is the successful transition to lactation); (2) the pass is incomplete (cows experience subclinical ketosis); (3) the pass is intercepted (clinical ketosis requires immediate attention); and (4) the game is lost after the a last-ditch effort to score fails (the cow dies).

Ketosis occurs soon after calving when feed intake is low and the sudden increase in energy demand for milk production causes rapid mobilization of long-chain fatty acids from adipose tissue. The fatty acid release overwhelms the liver's capacity for complete oxidation, resulting in the production of AcAc and BHB. The disease is called pregnancy toxemia in sheep and it occurs in ewes carrying twins or triplets (Schultz, 1968).

Prevalence of ketosis was 25% in fresh cows in 5 countries in Europe. Deceased risk was observed in larger herds and in those feeding TMR (Berge and Vertenten, 2014). Cows with moderate (3.25–3.75) or excessive (>3.75) BCS were more likely to have subclinical or clinical ketosis. A BCS of 3.5 or higher increased the risk of ketosis. Cows that developed ketosis were less likely to conceive at first service and had a longer interval between calving and conception (Gillund et al., 2001).

Elevated thyroxine and growth hormone (**GH**) concentrations in blood were identified in cows as causes of ketosis (Emery and Williams, 1964; Emery et al., 1964). Incidence in November and December was 19% and severity was increased by triiodothyronine implants (Emery and Williams, 1964). Kronfeld (1965) injected GH into cows ($n = 2$), reported increased blood AcAc and BHB, and suggested GH as a causative factor in clinical ketosis.

Corrective measures for ketosis are aimed at mechanisms that increase glucose production through gluconeogenesis or therapies such as propylene glycol (Emery et al., 1964; Christensen et al., 1997; McArt et al., 2011; Piantoni and Allen 2015), salts of propionic acid, and monensin (Sauer et al., 1989). Topdressing nicotinic acid (niacin) for 7 d increased milk production and blood glucose and reduced BHB (Fronk and Schultz 1979). Similar results were reported by Dufva et al. (1983) when cows were fed 6 g of niacin/d prepartum and 12 g/d postpartum. Waterman et al. (1972) gave four 40-g doses of nicotinic acid at 2-h intervals. Appetite returned to normal within 18 h but a relapse occurred 30 h later. However, blood metabolites and intake returned to normal shortly thereafter. Monensin reduced extent and severity of ketosis (Sauer et al., 1989).

Subclinical ketosis (**SCK**) is most likely to occur during the first 2 wk postpartum and is associated with reduced blood glucose and elevated blood BHB concentration. Recovery is associated with normal blood glucose and triglycerides and reduced ketones and nonesterified fatty acids (**NEFA**; Schwalm et al. 1972). Cows with elevated serum BHB prepartum experience reduced DMI and fewer visits to the feed bunk. Time spent in decrements of 10 min and decrease of 1 kg of feed increased risk of SCK(Goldhawk et al., 2009).

Cows with SCK had significantly higher odds for displaced abomasum and metritis, lower odds of conceiving at first service, and lower milk production in the first 30 d in milk (Walsh et al., 2007; McArt et al., 2012; Raboisson et al., 2014). Body condition score, calf sex (male), time after calving (3–16 d in milk) and, parity × herd were risk factors for increased risk of culling by 60 d in milk (Roberts et al., 2012; McArt et al., 2013). Cows with reduced serum calcium and elevated serum BHB and NEFA concentrations, immediately after parturition had an increased risk of culling in early lactation (Chapinal et al., 2012; Roberts et al., 2012).

Transition cows with subclinical ketosis spent less time ruminating than normal cows (Kaufman et al. 2016). Tatone et al. (2017) reported a prevalence of ketosis in Ontario of 21%, which was lowest from July to November, and was 1.46 times higher in Jersey compared with Holsteins. Interestingly, cows milked by automatic milking systems were at increased odds for ketosis, which is likely caused by feeding management. McArt and Oetzel (2015) evaluated the effect of oral calcium supplements provided postpartum on economic loss. The greatest loss ($8,313 per 1,000 calvings) was for cows with high 305-d mature-equivalent milk yield and that were lame.

Fatty Liver

Fatty liver is a metabolic condition occurring in the peripartum period. Fat is mobilized from adipose tissue and fatty acids are released into the blood as a source of energy in response to reduced DMI in the transition period. Mobilization of body fat increases the risk of fatty liver in dairy cows when fatty acid uptake by the liver exceeds its oxidation and release. Liver function is reduced by the condition of fatty liver. The "fat cow syndrome" was described by Morrow (1976) as a condition caused by feeding a high-energy ration to cows in all stages of lactation grouped together. Excess energy intake by late-lactation cows led to fattening and gross infiltration of fat into the liver and other extrahepatic tissues.

Supplee et al. (1945) suggested that choline (**Chol**) was important in the diet for prevention of storage of fat in the liver. Choline is involved in fatty acid transport but is rapidly degraded in the rumen (Sharma and Erdman 1988). A deficiency around parturition contributes to fatty liver. Accumulation of fat in the liver increases 4 to 5 times in the 2 wk before calving (Grummer, 1993). Choline and methionine (Met) are key nutrients for maintaining normal concentration of fat in the liver. Betaine (trimethylglycine) is a natural product found in sugar beets that also reduces fat accumulation in the liver.

Systems involved in processing and export of fatty acids from the liver are enhanced by rumen-protected (**rp**)Chol during the transition period (Zom et al., 2011; Goselink et al., 2013). Numerous studies have shown that feeding rpChol reduces fat accumulation in the liver in the periparturient period. Moreover, rpChol increased glycogen and tended to reduce storage of fatty acids as triglycerides in the liver (Piepenbrink and Overton, 2003). Feed reduction for 10 d was used as an experimental model to induce fatty liver in dry cows approximately 6 wk before calving. Plasma BHB and triacylglycerol were less in cows fed rpChol. Dry cows with feed-induced fatty liver had lower liver triglycerides when fed rpChol (Cooke et al., 2007). Cows fed rpChol had lower concentrations of NEFA around parturition (Monteiro et al., 2014).

Rumen-protected choline increased milk by 2.0 to 2.5 kg/d with a small decrease in milk fat percent (Sharma and Erdman, 1988). Milk and milk fat yields were greater in cows fed rpChol than in cows fed control and rumen-protected Met (rpMet). Cows fed rpChol had lower concentration of NEFA around parturition (Monteiro et al., 2017).

Repeatability of milk, fat, and protein yields has not been consistent with rpMet and rpChol singly or in combination. Fat-corrected milk was increased in cows when 3 to 4 g of Chol/kg was fed (Erdman et al., 1984) but was ineffective at similar feeding rate in another study that included first-lactation cows (Atkins et al., 1988). Feeding rpChol to dairy cows beginning at 5 wk postpartum increased milk by 1 to 2.2 kg/d. Late-lactation cows showed no benefits of added Chol (Sharma and Erdman, 1988). Cows with high BCS ($\geq$ 4.0) benefit more from rpChol than cows with BCS of 3.0 to 3.3 (Guretzky et al., 2006; Zahra et al., 2006; Zhou et al., 2016b). Feeding rpMet and rpLys increased milk protein, total nitrogen, and casein nitrogen but not milk yield in early lactation Jersey and Holstein cows (Bertrand et al., 1998). Giallongo et al. (2016) fed a diet adequate in metabolizable protein and compared it with diets with rumen-protected Met, Lys, and His singly or in combination. Dry matter intake increased with rpHis and the combination of all 3 increased milk and milk component yields. Liver function, inflammation status, and neutrophil function were enhanced by rpChol and rpMet during the periparturient period (Osorio et al., 2013; Zhou et al., 2016a). Dry matter intake, milk, ECM, and milk fat yield and percent were increased by both (Osorio et al., 2013). Rumen-protected Met but not rpChol enhanced production (Zhou et al., 2016b). Immune status during the periparturient period was improved in cows supplemented with rpMet but not by rpChol (Osorio et al., 2013; Zhou et al., 2016a).

Feeding rumen-protected betaine had no beneficial effect on production measures in Met-limited diets (Davidson et al., 2008). Monteiro et al. (2017) reported increased milk yield and fat percent and elevated NEFA in cows when betaine was fed at the start of the dry period but not when feeding began 24 d before expected calving. Feeding betaine increased milk production during thermoneutral conditions [temperature-humidity index (**THI**) of 56.6] but decreased it compared with controls during heat stress (THI = 71.5). Water consumption increased more during heat stress for controls than for betaine-fed cattle (Hall et al., 2016).

Methionine hydroxy analog increased milk fat in the first 3 mo of lactation without affecting DMI and milk production (Holter et al., 1972). Subsequent studies have reported no effect on milk production (Pullen et al., 1989; Bertics and Grummer, 1999), less loss of body protein (Phillips et al., 2003), and increased milk production in low-protein diets (Piepenbrink et al., 2004). An isopropyl ester of Met hydroxy analog increased milk (2.7 kg/d), protein, and lactose yields (St-Pierre and Sylvester, 2005).

CONTROL OF RUMEN-RELATED DIGESTIVE DISORDERS

Displaced Abomasum

Displacement of the abomasum (**DA**) occurs in periparturient cattle due to reduced gut fill, atony of abomasal musculature, and gas production. At calving, the gravid uterus expands anterior and ventral, raising the rumen from the abdominal floor. After calving, the rumen descends and traps the abomasum to the left or right of normal position. Risk factors include high genetic merit, negative energy balance, high BCS, high-energy rations prepartum, and season. Left displacement is more common than right displacement, and most DA occur within 2 wk pre- or postpartum. Periods of reduced intake during the transition period and feeding high-energy diets (>1.65 Mcal/kg) prepartum increase risk of DA. Incidence is greater during extremes (hot or cold) in environmental temperatures (Coppock, 1974; Cameron et al., 1998).

Four complete feeds were fed to cows (n = 40) beginning 4 wk before expected calving date. Forage to concentrate ratios were 75:25, 60:40, 45:55, and 30:70 on DM basis. The forage was a 50:50 mixture of corn silage and alfalfa-bromegrass silage. Incidence of displacement was 0, 2, 4, and 4 cows for highest to lowest forage content of complete feeds. During the 4 wk before calving, cows with and without displacement after calving consumed DM at 1.28 and 1.55% of BW (Coppock et al., 1972).

Few cases of DA recover without aid; surgery involves suturing the abomasum back into place. Recumbent cows may be rolled to get the abomasum back into place but recurrence is more likely (Coppock, 1974). Survival to 1 yr following surgery to correct LDA was increased in those cows having higher serum concentrations of BHB and magnesium (Reynen et al., 2015).

LeBlanc et al. (2005) evaluated metabolic predictors of LDA in 20 herds in Ontario, Canada. Risk for displacement was 5.1% and median time for occurrence was 11 d. Cows with elevated NEFA ($\geq$0.5 mEq/mL) in serum were 3.6 times more likely to have LDA after calving. Retained placenta, metritis, and elevated serum NEFA and BHB were associated with increased risk of LDA.

Bloat

Two types of bloat occur—one in confined feeding and the other during grazing of legume pasture. In each, a stable foam is produced, increasing the viscosity of rumen fluid. Gas becomes trapped in the rumen and causes distention of the abomasum, leading to death within hours, likely due to suffocation. Bloat was prevented entirely in cattle grazing alfalfa when fed poloxalene (Bartley, 1965). Feeding monensin or lasalocid decreases incidence of bloat by (1) decreasing viscosity of rumen fluid; (2) changing the microbial ecology of the rumen; and (3) increasing the number of meals in a day while decreasing the size of each meal--- (McGuffey et al., 2001).

Cattle tend to consume feed to rumen fill, lie down, chew, and ruminate—a process that is repeated multiple times daily. Occasionally, fattened beef steers close to finish weight will lie down and die suddenly because of apparent bloat that stops respiration. Feedlot cattle fed monensin eat smaller and more frequent meals within a day such that fill and bloating are not as great a threat. Day-to-day variance in feed intake of beef steers on high concentrate (>85%) was reduced when monensin was included in the ration (Stock et al., 1995). The intake pattern of the dairy cow is similar to that in beef cattle when the proportion of concentrate in the diet is increased. Dairy cows fed monensin spent less time eating both pre- (126 vs. 143 min) and postpartum (81.4 vs. 88.8 min) and had less variation in rumen pH on the first day of changing to a lactation diet. (Mullins et al., 2012).

NUTRIENTS AS METABOLIC MODIFIERS

Water

Water is the nutrient with the largest daily requirement, and it constitutes 56 to 81% of BW. Milk is 85 to 88% water. Water for milk production was estimated to be 4:1 (water:milk) by McCandless and Gaessler (1919), and the water requirement for milk production is 2.0 to 2.7 kg/kg of milk (NRC, 2001). Water intake and water of metabolism are sources for the body, and loss occurs through urine, feces, expiration, and sweating. Water quality is described by its organoleptic qualities, physiochemical properties, presence of toxic chemicals, mineral content, and presence of bacteria (NRC, 2001).

Water intake increases as environmental temperature increases (Khelil-Arfa et al., 2014). Water aids in maintaining body temperature through evaporation. Cooling systems in dairies located in hot, arid areas take advantage of evaporative cooling to aid cows in maintaining core body temperature. Organisms die faster from water deprivation than from starvation.

Rumen water kinetics was incorporated into modeling of rumen VFA kinetics (Argyle and Baldwin 1988). Osmolality of rumen fluid increases immediately after feeding and expands liquid volume (4.7 L/kg of DMI) and VFA pool size. Water intake and movement of water from the body pool into the rumen is increased to reduce rumen osmotic pressure. Passage rate of water and small feed particles increases with increasing ruminal osmolarity. Much of the buffering effect of sodium bicarbonate and other bicarbonate salts is likely due to less time spent in the rumen by rapidly fermentable sources of starch.

Protein and Amino Acids

Protein supplements are the most expensive ingredient in dairy rations. Efficient use of protein supplements must consider bacterial utilization first to maximize economy. Nutritionists formulate protein in rations to meet requirements for the rumen bacteria and the dairy animal. Virtanen (1945) was awarded the Nobel Prize for his research and inventions in agricultural and nutrition chemistry, especially for his fodder preservation method. Virtanen later demonstrated that dairy cows could produce over 4,200 kg of milk in a single lactation on a protein-free ration (Virtanen, 1966).

Proteins are composed of 20 amino acids for maintenance and production functions. Ten AA are considered nonessential (NEAA) because body tissues can synthesize sufficient quantities to meet requirements. Ten are essential (EAA) because they must be supplied in the diet to meet requirements. Protein and AA supplied by the ration of high-producing dairy cows may not meet EAA requirements. The cow's requirements for absorbable EAA may be limited by ration composition due to the poor quality of feed proteins (e.g., zein) and insufficient fermentable energy to drive rumen microbial synthesis.

The protein types in meals from whole oilseeds are soluble in the rumen, degraded to ammonia by rumen bacteria, and incorporated into microbial protein. Although microbial protein is highly digestible, a net loss of nitrogen occurs. Heat and chemical methods decrease rumen degradation and increase rumen bypass of oilseed meals and whole oilseeds (Schingoethe et al., 1988; Scott et al., 1991; Grummer et al., 1994). The temperature and time to which supplements are exposed determine the extent of rumen bypass and total-tract digestibility. Overheating of meals and seeds produces Maillard products, a reaction between reducing sugars and AA that reduces protein degradation in the rumen and digestibility in the small intestine. In addition, oil in whole seeds may become rancid and unpalatable and can require special packaging to prevent leakage of oil during storage.

The dairy cow is supplied protein from rumen bacteria and rumen bypass protein. Meeting protein requirements for high production requires maximizing rumen bacterial production and rumen bypass of intact protein, and supplying rumen bypass AA or analogs. Milk yield was increased in cows receiving recombinant bST and fed high-rumen-bypass rations (McGuffey et al., 1990). Rumen bacteria, especially cellulolytics, require ammonia from degradable intake protein sources (e.g., urea, ammonia, and biuret) for growth. Rate of growth is dependent upon fermentable energy. Satter and Slyter (1974) observed that ammonia overflow in effluent from continuous cultures occurred when ammonia concentration exceeded 5 mg/100 mL. Satter and Roffler conducted a series of laboratory and feeding studies with cows in the mid-1970s (Roffler and Satter, 1975a,b; Satter and Roffler, 1975). They suggested that milk production would not increase when nonprotein nitrogen sources were added to rations beyond 12 to 13% CP. These publications immediately fostered debate among nutritionists skeptical of the idea. It did, however, result in new ideas on how to create rumen bypass protein supplements (Roffler and Satter, 1975a,b).

Chalupa (1975) suggested that more intact protein must avoid rumen degradation and reach the small intestines from protein supplements for increased milk production. Application of heat to protein meals or whole seeds increases rumen-undegradable protein (Mabjeesh et al., 1996).

Whole soybeans contain a trypsin inhibitor and other compounds that are destroyed by rumen bacteria but they must be processed to destroy these compounds when included in young calves. Reddy et al. (1993) fed calves, from birth to 8 or 10 wk of age, starters containing whole soybeans roasted at temperatures ranging from 99 to 163°C. The greatest gain occurred in calves when soybeans were roasted at 143 to 146°C for 30 min.

Treating protein meals with formaldehyde increased rumen bypass protein in steers (Spears et al., 1985) but a milk production response has been notably lacking in most studies. The FDA ruled that formaldehyde was not safe because of its carcinogenic nature and disallowed feeding of formaldehyde-treated feeds to livestock.

Lysine and methionine are generally regarded as the most limiting EAA in lactating dairy cows. Two criteria must be optimized: grams of absorbable AA per 100 g and the Lys:Met ratio. Lysine and Met (% of total EAA) comprise 16.3 and 5.1 of lean tissue and 16.0 and 5.5 of milk proteins (NRC, 2001). For optimum use by body tissues, the Lys requirement is 7.2 g/100 g of absorbed AA and the Met requirement is 3.2 g/100 g of absorbed AA (NRC, 2001).

Unprotected Met has a half-life in the rumen of approximately 2.4 h (Emery, 1971). Milk protein content was increased by supplemental Met and the weight of milk protein secreted was 4 g per 1-g increase in Met intake (Armentano et al., 1997). Vyas and Erdman (2009) concluded from a meta-analysis that marginal efficiency of use Lys and Met decreased as the dietary supply of both approached requirements.

Lipids

Lipids are involved in cellular membrane integrity and, as triglycerides, represent an energy-dense (9 kcal/g) storage form in the body. Fatty acids are absorbed in the small intestines and enter the lymphatic system where they are transported to the liver. Fatty acids in blood may be used by tissues as an energy source during periods of negative energy balance. Enzymatic hydrolysis by lipoprotein lipase releases glycerol and fatty acids into the blood and used as an energy source by tissues, including the brain, in severe negative energy balance. Fatty acids are hydrolyzed to 2- and 4-carbon entities in tissues and enter the Krebs cycle for production of ATP. Excessive oxidation leads to production of ketone bodies, which may lead to ketosis. Incomplete utilization of fatty acids leads to fatty liver. During positive energy balance, acetate and butyrate are absorbed by adipose tissues and converted into triglycerides for storage.

Fatty acids are saturated ($C_nH_{2n}O_2$) from C_6 to C_{16}. Palmitic acid (C_{16}) may contain one double bond. The 18-carbon fatty acids are stearic, oleic, linoleic, and linolenic acids and they contain 0, 1, 2, or 3 double bonds in the *cis* position at carbons 15, 12, and 9, respectively. Linoleic ($C_{18:2}$), linolenic ($C_{18:3}$), and arachidonic ($C_{20:4}$) acids are essential fatty acids. Arachidonic acid is elongated to produce docosahexaenoic acid ($C_{22:6}$), another essential fatty acid. Essential fatty acids are important constituents of cellular membranes.

Long-chain fatty acids are a source of energy for the cow. These may be supplied to the cow as oilseeds, animal-vegetable blends, or ruminal inert fat. Unsaturated fatty acids are rapidly converted to $C_{18:0}$ and $C_{18:1}$ in the rumen. Dietary UFA reduce the rate and extent of rumen fermentation. Reduced DMI, milk fat percent, milk protein percent, and fiber digestion are indications of reduced rumen fermentation. The milk response to added fat is curvilinear with about 16% of ME from fat, equating to 600 to 700 g or 3% added fat. Fat contained in forages and grains typically average 3 to 4%. Total fat in the diet should not exceed 7% of the total DM (Palmquist and Jenkins, 1980).

Feeding unprocessed whole oilseeds can have significant effects on rumen fermentation. Long-chain UFA are toxic to rumen bacteria. Biohydrogenation utilizes metabolic hydrogen to detoxify UFA. Rumen protected fats such as calcium soaps or amides reduce fat solubility in the rumen, allowing bypass to the lower tract for hydrolysis to fatty acids and glycerol.

Sutton (1989) provided an interesting anecdote from C. H. Eckles at the University of Missouri, who wrote to E. B. Powell in 1927: "to my knowledge, this or any other experiment station in the country has not in recent years conducted experiments for the purpose of determining if feed would affect the composition of milk. It is looked on as a definitely unsettled question". Powell (1939) later provided evidence that physical characteristics of roughage, did in fact, affect rumen fermentation with a major effect on milk fat percent. That characteristic of forage was described as "physically effective fiber." This quality of forage affects chewing and saliva secretion and regulates rumen pH (Allen, 1997).

Van Soest (1963) provided a review of the effect of diet on intermediary metabolism and reduced fat content of milk. Three theories were discussed: (1) reduced acetate production in the rumen; (2) deficiency of BHB in the mammary gland; and (3) endocrine factors. Factors affecting milk fat composition include amount of forage, forage:concentrate ratio, carbohydrate fractions of the concentrate, lipids, and meal frequency Sutton (1989).

Beitz and Davis (1964) compared milk fat depressing diets to a control diet (diet 1) by feeding a high-grain ration (diet 2) and one containing cod liver oil (diet 3). Grain intake [11.6 (diet 1), 9.9 (diet 2) 15.5 (diet 3) kg/d] and milk (25.7–26.0 kg/d) were not different. Milk fat percent averaged 3.21, 2.16, and 1.77 for the 3 rations, respectively. Rumen propionate was increased in the high-grain diet but not in the cod liver oil diet. Milk fatty acids ($C18_n$, where $n = 0, 1, 2, 3$) were significantly lower for fish oil and high-grain diets and, notably, all double bonds reported were in the *cis* position. One wonders if these workers considered *trans* acids as a causative factor of milk fat depression. Beitz (D. Beitz, Iowa State University; personal communication, 2017) said, "we knew of the existence of *trans* fatty acids but our GLC was not able to fully separate between *cis* and *trans* isomers." Bauman et al. (2006) cited Davis and Brown (1970), who noted that an increase in *trans* 18:1 in milk fat was associated with reduced milk fat percent.

Oil from plant sources increases concentrations of $C_{18:1}$, $C_{18:2}$, and $C_{18:3}$ in milk. Unsaturated fatty acids of plant origin have double bonds in the *cis* position at every 3-carbon unit beginning at carbon-9 from the C terminus. Conjugated fatty acids are isomers of oleic acid ($C_{18:1}$) and have a double bond separated by a single bond (−C−C=C−C−C). Fish and plant oils cause major reductions in milk fat percentage and alter fatty acid composition of milk fat (Chilliard et al., 2009). Content of $C_{20:5n\text{-}3}$ and $C_{22:6n\text{-}3}$ is increased by fish oil (Kairenius et al., 2015; Shingfield et al., 2006).

Unsaturated fatty acids are toxic to rumen bacteria. Rumen bacteria use metabolic hydrogen as a sink that detoxifies UFA. These actions also increase milk fat (Kennelly et al., 1999).

Milk fat from cows fed a control diet, an animal-vegetable blend of fat, coconut oil, safflower oil, flaxseed and monensin contains increased *trans* $C_{18:1}$ (Bell et al., 2006; Reveneau et al., 2012a). Medium-chain fatty acids, $C_{6:0}$, $C_{8:0}$, and $C_{10:0}$, which give milk its unique flavor, were reduced in all diets compared with control (2.9% fat) (Reveneau et al., 2012b). In a companion paper, total protozoal numbers and ruminal digestion of NDF were reduced when coconut oil was fed (Reveneau et al., 2012a). Milk fatty acids less than C_{16} were decreased and proportion and yield of *trans* $C_{18:1}$ and yield of *trans*-10,*cis*-12 CLA in milk fat were increased when monensin was fed (He et al., 2012).

Milk fat percentage is reduced under rumen conditions that promote biohydrogenation. Milk fat percentage and yield were reduced 30 and 35%, respectively, by cows fed low fiber and unsaturated fat rations compared with saturated fat in high-forage rations (Griinari et al., 1998). Cows fed the low-fiber unsaturated fat ration increased *trans*-10 C_{18} UFA in milk and decreased milk and fat yields compared with those fed high-forage rations. Baumgard et al. (2000) identified the *trans*-10,*cis*-12 isomer produced in the rumen as a potent inhibitor of de novo milk fat synthesis by the mammary gland. Two CLA isomers, *cis*-10,*trans*-12 and *trans*-9,*cis*-11 also inhibit milk fat synthesis.

Milk from pasture-fed cows had twice the concentration of CLA as cows fed a TMR (Kelly et al., 1998).

Corn silage-based but not alfalfa-based diets increased rumen concentration of *trans*-10,*cis*-$C_{18:2}$ in milk (Oelker et al., 2009).

Propyl-propane thiosulfate (PTSO), an organosulfate from garlic oil, increased total VFA and propionate at 2 h after feeding. Total VFA and saturated fat decreased and unsaturated fat increased in 24-h effluent collection in a dual-flow continuous culture system. Concentration of *trans*-10,*cis*-12 CLA was decreased 78% by the highest dose of PTSO (Foskolos et al., 2015).

Feeding CLA beginning 2 wk before calving through 21 d of lactation caused reduced milk fat percent and increased milk yield such that there was no difference in 3.5% FCM or energy balance, suggesting that CLA cows partitioned energy to adipose tissue. A mixture of 4 CLA isomers fed at 187 g/d decreased milk fat content by 49% in early postpartum cows (Moore et al., 2004). Calcium salts of CLA are effective in delivering CLA to the small intestines (Castañeda-Gutiérrez et al., 2005).

Minerals

Approximately 98% of total body calcium is found in bone, with the other 2% present in extracellular fluid (NRC, 2001). Blood contains 9 to 10 mg/100 mL and is regulated by parathyroid hormone (PTH). When blood calcium is low, release of PTH increases mobilization of calcium from bone to restore calcium concentration to normal. Calcium absorption is regulated by 1,25 dihydroxycholecalciferol derived from vitamin D. Aging causes bones to become less responsive to calcium release. Risk of parturient paresis increases with the number of calvings, as discussed previously.

Phosphorus is likely the most over-fed mineral (i.e., above requirement). Overfeeding has caused significant contamination of waterways due to surface run-off.

Magnesium ions are absorbed by rumen epithelium. Magnesium oxide is the most commonly used source of magnesium, and the particle size of MgO affects rate of solubility in the rumen (Jesse et al., 1981). Solubility in rumen fluid ranges from 25 to 75% in a pH range of 5.5 to 6.5 (Schonewille et al., 2008). Its solubility in rumen fluid declines rapidly as pH increases beyond 6.5. Absorption (% of intake) averages about 26% but ranges from 9.9 to 73.9%. Potassium reduces absorption of Mg such that in forages containing high K, Mg concentration in the diet must be increased. Grass tetany occurs in the spring in cattle grazing rapidly growing grass pastures especially high in potassium. Low-soluble forms of MgO likely exacerbate parturient paresis (Schonewille, 2013).

Dry matter intake and milk fat increase in a curvilinear response in lactating cows fed rations having a positive DCAD (Iwaniuk and Erdman, 2015). The response was 0.43 kg of DMI increase per 100-mEq increment up to 300 mEq and 0.19 and 0.13 kg of DMI at 400 and 500 mEq. A positive milk response reflects the increased DMI.

Selenium is deficient in soils in much of the area surrounding the Great Lakes in the United States and in Oregon and Washington State. Consequently, many feedstuffs are low or deficient in selenium. White muscle disease in sheep is a consequence of selenium deficiency. Selenium is a co-factor of the enzyme glutathione peroxidase. Diets may be supplemented with selenium up to 0.3 mg/kg per FDA regulations (NRC, 2001). Much of the research with selenium (often coupled with vitamin E) began in the mid-1970s.

Vitamins

Water-Soluble Vitamins. This section on vitamins was taken from a history written by Hibbs (1950). Vitamins were discovered in the late 19th century. Dried foods supplied nutrients to sailors on ocean voyages; on trips lasting longer than 2 mo. When sailors arrived on land, the disease disappeared rapidly (within 2 wk or less), which was associated with consumption of fresh fruit or salad greens (Carpenter, 2014). These foods supplied vitamin C.

Beriberi was described in Asian countries in earlier centuries and was associated with consumption of rice. The disease affected the nervous system and caused respiratory distress, heart failure, and death. Subsequently, Adolphe Vorderman, working in Java, described signs of beriberi in men serving in prisons where white rice was fed but not in prisons that fed brown rice. The missing nutrient was thiamin.

The term "vitamine" for vital amines was used for these discoveries because both vitamin C and thiamin were vital for life and contained an amine group in their structure. The name "vitamin" was used despite subsequent discoveries of additional vitamins without an amino group.

Fat-Soluble Vitamins. Vitamin A was the first identified fat-soluble vitamin. McCollum and Davis (1913) fed purified diets to rats and described a condition that caused xerophthalmia, an abnormal dryness of the conjunctiva and cornea. The affected rats recovered when milk, but not olive oil, was fed. Bloch (1923) described the presence of a factor in milk fat and cod liver oil that was not present in margarine or pork fat and that prevented xerophthalmia. The first fat-soluble vitamin, vitamin A, was discovered. Today, partial or total blindness associated with vitamin A–deficient diets is the most common metabolic disease in humans (WHO, 1995–2005).

Vitamin D is sometimes known as the sunshine vitamin because exposure of the skin to UV light produces vitamin D. Two forms of vitamin D exist: ergocalciferol (D_2), which is produced in plants, and cholecalciferol (D_3), which is produced in skin. Grazing cows wrapped in blankets made with materials impervious to sunlight were shown to have significantly lower blood vitamin D (Hymøller and Jensen, 2010).

Hibbs (1950) provided a historical review of futile attempts to prevent parturient paresis. Conditions such as anaphylaxis, circulatory dysfunction, infection, hypoglycemia and hypocalcemia were suggested to cause milk fever. That vitamin D was involved in calcium absorption and metabolism was demonstrated by Hibbs et al. (1946). They described the condition as being more prevalent in older cows (notably in >60% of older Jersey cows) and in winter months, when cows were maintained indoors.

Vitamin D is partially degraded in the rumen, conjugated with bile salts in the duodenum, and absorbed in the ileum of the small intestines (Sommerfeldt, 1982). Vitamin D_3 was toxic when large doses ($15.7–17.5 \times 10^6$ IU) were administered parenterally about 30 d before calving (Littledike and Horst, 1982).

The immune system represents a productive function in mammalian systems. It lies nascent until an outside threat such as a microbe threatens the well-being of the organism. Upon attack, the immune system releases cells that kill invading organisms by chemotaxis.

Vitamin E (α-tocopherol) supports neutrophils, basophils, and macrophages, especially during mastitis and expulsion of placental tissues during calving (Hogan et al., 1993). Like many other nutrients, vitamin E declines in blood during the transition period (Goff and Strabel, 1990). Many of the actions of vitamin E occur in conjunction with selenium.

Anecdotal evidence from publications cited by Asdell (1949) following injection of wheat germ oil as a source of vitamin E included the following: (1) of 12 cows that did not conceive readily, all conceived after treatment; (2) 49 of 70 cows conceived; (3) 17 of 25 infertile cows conceived; (4) 38 cows averaged 1.9 services per conception out of 41 cows that previously averaged 4.6 services per conception; and (5) "today the success is regular and everywhere one sees abortions, non deliveries, and mortality of the new-born disappear."

Ohio researchers observed an overall 38% incidence in retained placenta in an experiment testing amounts of protein, phosphorus, and selenium. Incidence was reduced to 20% in cattle fed a higher protein diet (Julien et al., 1976a). The higher protein diet also increased selenium in the total ration from 0.02 to 0.06 mg/d. In a follow-up multi-farm study, the incidence of retained placenta was 51.2% for control and 8.1% combined average for the cows receiving selenium and α-tocopherol at 40 and 20 d prepartum (Julien et al., 1976b).

Vitamin E serves as an antioxidant against the production of superoxides in muscle and other tissues (Chikunya et al., 2004). Oxidative stress increases the risk of infectious disease and reduces immune response during the transition period. The concentration of vitamin E in blood decreases prepartum (Goff and Strabel, 1990). Supplemental vitamin E prepartum does not appear to ameliorate oxidative stress but it plays a significant role in recovery from oxidative stress postpartum (Bouwstra et al., 2008). Results from a second field study (Bouwstra et al., 2010a) contradicted the results of the earlier controlled study. In a subsequent retrospective analysis of the field study (Bouwstra et al., 2010b), 1 of 8 groups failed in the regeneration of vitamin E radical and, as a result, failed to respond to vitamin E supplementation.

Vitamin E, but not selenium, reduced the duration of clinical mastitis in selenium-deficient diets (Smith et al., 1984). Fed together, vitamin E and selenium are complementary, in that both are more effective in reducing incidence of clinical mastitis than either alone. Vitamin E and Se increase the activity of glutathione peroxidase in erythrocytes and increase actions against mastitis infection. The proportion of quarters with new infections supplemented with 4,000 IU of vitamin E was 11.4% at 14 d before parturition compared with 32% for lower doses pre- and postpartum (Weiss et al., 1997). Clinical mastitis was 9.4 times more likely in cows treated with α-tocopherol at <3.0 μg/mL during the first 7 d postpartum than in cows treated with ≥ 3.0 μg/mL.

Doubling the ratio of oleic to palmitic acids increased oxidation of milk fat by 30 to 40% (Focant et al., 1998) in diets containing a combination of rapeseed and cottonseed. Oral vitamin E increased milk α-tocopherol and oxidative stability.

No effect of vitamin E supplementation was reported in heifers on enzymes responsible for destruction of reactive oxygen metabolites. Dobbelaar et al. (2010) suggested that heifers experience a low level of oxidative stress during parturition. Calves receiving vitamin E injection at 14 and 28 d of age had a 4-wk delay in increase of glutathione peroxidase activity to injection of selenium and vitamin E (Weiss et al., 1983). Supplementing vitamin E in the dry period increased α-tocopherol level in colostrum (Rajaraman et al., 1998).

Vitamin K is involved in blood clotting. Its presence was noted by Danish scientists in the early 1920s in a study involving newly hatched chicks (Norn et al., 2014). Its name was derived from the German word "Koagulationsvitamin" (clotting factor). Vitamin K acts to convert prothrombin to thrombin to initiate blood clotting. Prothrombin time is a clinical measure of blood clotting in affected animals. Coumarol, the toxic metabolite of dicoumarol, slows the conversion of prothrombin to thrombin.

Dicoumarol is a natural component of sweet vernal grass (*Anthoxanthum odoratum*) in Australia and sweet clover hay (*Melilotus alba*) in northern Canada, Minnesota, Wisconsin, and across northern Europe. Dicoumarol is converted to coumarol by molds and fungi in stored wet silages and wet wrapped round bales (Blakley, 1985; Runciman et al., 2002).

A dairy farmer in Wisconsin brought dead cows and calves to the School of Veterinary Medicine in the mid-1930s, along with a sample of moldy sweet clover hay of high moisture content that was being fed to the animals. Autopsy found large internal pools of blood in the abdominal cavities. The hay was sent to the biochemistry department, where after extensive research, the chemical structure of coumarol was determined and the chemical was subsequently synthesized. The Wisconsin Agriculture Research Foundation (WARF) received a patent for use of coumarin as a rodenticide in 1948. It was subsequently named "warfarin" when introduced into medical practice to prevent blood clots in individuals with heart valve problems. Warfarin was used to treat President Dwight D. Eisenhower while he was recovering from a heart attack. Warfarin remains the most widely used medicine in heart patients in the world. Today, medicines have been introduced into cardiology that are as effective as warfarin but do not require periodic checks of prothrombin time. At least 17 Nobel Prizes have been awarded to scientists based on their research with vitamins.

Feed Additives

Hutjens (1991) defined a feed additive "as a feed ingredient or group of feed compounds that produces a desirable animal response in a non-nutrient role." Feed offers the easiest avenue for delivering metabolic modifiers to dairy cattle. These are usually delivered as a premix or mineral package at a low inclusion rate in a TMR or in the grain mix for component fed herds. Desired consumption by a cow of an additive may range from milligrams to a few hundred grams. Antibiotics, ionophores, buffers, yeasts, microbial cultures, and antibiotics are discussed in this section.

Antibiotics. Sir Alexander Fleming went on vacation in 1928 and, upon returning to his laboratory, found an uncovered Petri dish with a circular zone on the plate with no bacterial growth. His discovery of antibiotics became one of most significant findings in medical history. He received the Nobel Prize in Medicine in 1945 for his discovery of penicillin (https://www.nobelprize.org/nobel_prizes/medicine/laureates/1945/).

In the late 1940s, fermentation end-products from production of vitamin B_{12} were fed as sources of water-soluble vitamins to chickens and pigs (Lassiter, 1955). At about the same time, a paper reported increased growth rate in chicks from a fermentation product of *Streptomyces*. Crystalline chlortetracycline (Aureomycin, Zoetis, Parsippany, NJ) was shown to increase growth in chicks in 1950. Improvements in growth rate of chicks and pigs were also noted for oxytetracycline, penicillin, bacitracin, and streptomycin.

Early research on feeding antibiotics to ruminants was contradictory. Positive, adverse, and no effects were noted when fermentation products from different pharmaceutical companies were fed. Bartley et al. (1953) fed 3 mg of chlortetracycline per 45.4 kg of BW to calves from birth to 42 d and noted a BW gain of 0.78 lb (group 1) and 0.83 lb (group 2) for chlortetracycline-fed calves compared with 0.52 lb/d for control. Chlortetracycline was removed from the diet after 7 wk from calves in group 1 and gain for the next 5 wk was 0.87 lb/d compared with 1.35 and 1.02 for group 2 and control. Chlortetracycline fed for 25 wk increased gain by 314% (15 mg/d) and 349% (45 mg/d) compared with 291% for control calves (Bartley et al., 1954). Feeding chlortetracycline increased BW gain in early weeks but BW of calves in control and treated groups were equal at 4 mo (Bartley et al., 1956).

Lassiter (1963) reported on 3 sets of field trials conducted on commercial dairies or state-owned dairy farms. Two studies were conducted on commercial dairies in Michigan. In the first trial conducted during the summer, 519 cows fed Aureomycin (0.1 mg/lb of BW) averaged 0.1 kg more milk than controls. The second study was conducted in winter months; cows fed Aureomycin averaged 0.82 kg/d more milk. Pooled data from both trials showed that cows fed Aureomycin averaged 0.81 kg/d more milk. Recent rulings by the FDA allow use of antibiotics in livestock only by prescription from an attending veterinarian.

Ionophores. Ionophores are polyether antibiotics that are not used in human or veterinary medicine. Antibiotic resistance to ionophores is not apparent in ruminants. Resistance to an antibiotic against a microbial population most often occurs with continued usage. Experiences in the broiler industry led to development of "shuttle programs" where a different ionophore is used when a new cycle of birds is first introduced into grower facilities. Two ionophores, monensin and lasalocid, are both approved by the FDA/CVM for control of coccidiosis and for increased growth rate of heifers.

For a complete description of actions of ionophores on ruminal microorganisms, see reviews by Pressman (1976) and McGuffey et al. (2001). Ionophores were approved initially for control of coccidiosis in avian species in 1971. Ionophores are the most widely used rumen fermentation modifier in the livestock industry. Seven ionophores are approved by the FDA for use in cattle (Table 1 in McGuffey et al., 2001). All except laidlomycin are used to control coccidiosis in 8 classes of livestock. Three are approved with claims for improved feed efficiency and increased rate of gain for growing and finishing cattle. Lasalocid and monensin are approved by the FDA for growing heifers, and lasalocid is approved for use in milk replacer for control of coccidiosis. Monensin was approved by the FDA for feeding to dry and lactating dairy cows in the United States in 2004. The claim, "for increased milk production efficiency" when fed in TMR at 11 to 22 mg/head per day was later amended in 2005 to185 to 660 mg/d for component-fed herds. Feeding to dry cows is at 115 to 410 mg/head per day. Monensin is also approved for use in lactating and dry cows in many countries outside the United States. Use of ionophores in dairy cattle is covered in the review by McGuffey et al. (2001).

Dr. Arthur P. Raun, an Iowa State University ruminant nutritionist, joined Lilly Research Laboratories in the early 1960s. He developed a plan to discover and develop a rumen fermentation modification product for the cattle industry based on stoichiometry and energetics of rumen fermentation from the theoretical calculations of rumen fermentation proposed by Wolin (1960):

$$57.5 \text{ hexose} \rightarrow 57.5 \text{ acetate} + 20 \text{ propionate} + 15 \text{ butyrate} + 60\ CO_2 + 35\ CH_4.$$

Energy yield is described as follows (Hungate, 1966):

$$1 \text{ hexose} + 2\ H_2O \rightarrow 2 \text{ acetate} + 2\ CO_2 + 4\ H_2,$$

$$1 \text{ hexose} + 2\ H_2 \rightarrow 2 \text{ propionate} + 2\ H_2O,$$

$$1 \text{ hexose} \rightarrow 1 \text{ butyrate} + 2\ CO_2 + 2\ H_2.$$

The heat of combustion (kcal/mol) for hexose is 673, for acetate is 209.4, for propionate is 362.7, for butyrate is 524, and for methane is 210.8. Thus, energy conversion efficiency from 1 mol (180 g) of hexose is 418.8 kcal for acetate 62.2%, for propionate 109.1% and 77.9%.

Samples of soil extracts and chemicals for the in vitro screen originated from the human medicine screening program in search of new and novel compounds. Lilly's corporate policy allowed testing of only failed compounds from the human medicine screen. Samples received were incubated for 6 h with test compounds identified only by a unique number in a corporate library of compounds. Samples were prepared for GLC analysis. In 1970, a technician observed a peak on the chromatogram that was "off scale" and that occurred at the time where propionic acid would appear. Dr. Raun initiated a study with beef steers with the fermentation product, and rumen samples exhibited the same peak as observed in the original screening. Large-scale field studies were initiated in feedlots and results submitted to the FDA. Approval for monensin was granted in December 1975. Dr. Raun was cited as one of the top 25 contributors to the beef industry for his discovery and developmental work on monensin.

Ruminal Actions of Ionophores. Bergen and Bates (1984) classified the benefits derived by the animal from feeding ionophores into 3 areas of effects: (1) increased efficiency of energy metabolism of rumen bacteria and/or animal; (2) improved nitrogen metabolism of rumen bacteria or animal; and (3) retardation of digestive disorders resulting from abnormal rumen fermentation. Each benefit provides a nutritional and metabolic advantage to the ionophore-supplemented animal over an unsupplemented animal.

Energy Metabolism. Increase in propionic acid represents the classical and much studied effect of ionophores. Richardson et al. (1976) reported increases of 54 and 36% in molar ruminal propionate in concentrate- and pasture-fed cattle, respectively, fed 200 mg of monensin. Isotope dilution studies showed that the increased rumen propionate was due to greater propionate production (Prange et al., 1978; Van Maanen et al., 1978; Rogers and Davis, 1982). Propionate production was increased 45 to 50% by monensin in 70% forage diets and increased 76% on 20% forage diets. Monensin in a 50:50 forage:concentrate ration produced more total moles of VFA per kilogram of DMI, and more moles of acetate and propionate than the control ration. These changes increased energy production by 33%.

Anaerobic ruminal fermentation dictates that substrate oxidation must be closely linked to reduction reactions. Volatile fatty acids and methane are terminal acceptors for metabolic H_2 (Hungate, 1966). Fermentation balance equations show that an increase in propionate production must be accompanied by reduced methane (Chalupa, 1977). Inhibition of growth occurs in some rumen bacteria with as little as 2.5 μg of monensin or lasalocid, whereas other rumen bacteria, and methanogens, are able to grow at 30 to 40 μg of either ionophore.

Protein. Ionophores have significant effects on nitrogen metabolism in the rumen. These include a reduction in protein degradation and reduction of ammonia and microbial protein (Van Nevel and Demeyer, 1977). Accumulation of α-amino nitrogen and peptides suggests a greater effect on deamination than on proteolysis (Russell et al., 1988). A greater proportion of protein intake reaches the abomasum when monensin is fed, and efficiency of protein synthesis is unchanged (Muntifering et al., 1980).

Spears (1990) summarized 20 experiments from the literature with monensin (n = 17) and lasalocid (n = 3) on apparent digestibility of energy in diets for cattle. Both ionophores showed about a 2% improvement in energy digestibility. Difference in digestibility in diets with lasalocid (+1.9 to 2.2) were statistically significant but, due to the high range of variability (−0.9 to +9.1) in monensin studies, differences were not significant.

Feeding of ionophores changes the site of digestion of dietary carbohydrate fractions but postruminal digestion of starch is increased such that total-tract digestibility is not different from control (Funk et al., 1986; McCarthy et al., 2015). Monensin increased efficiency of component-corrected milk at low (20.4%) compared with high (26.9%) starch rations. The authors noted a tendency for interaction of starch and monensin in that milk production tended to be greater for the higher starch monensin ration (Akins et al., 2014).

Fiber digestion is, for the most part, unaffected by ionophores (Allen and Harrison (1979). Reduced numbers of ruminococci may be offset by increased numbers of ionophore-insensitive fibrolytic bacteria. The bacteria *Fibrobacter succinogenes*, although gram-negative, is sensitive to ionophores probably because of the interference of glucose uptake (Franklund and Glass, 1987). Knowlton et al. (1996a) reported no differences in digestibility of DM, NDF, and starch by cows fed control or lasalocid. Feeding avoparcin decreased ruminal digestion of OM, ADF, and starch (Ali Haimoud et al., 1995). Total-tract digestibility was not different. Rumen fungi appear to be ionophore sensitive (Elliott et al., 1987).

Activity of phagocytes and monocytes in blood were increased in cows at 8 d postpartum in TMR with 26.2 versus 21.5% starch. Cows fed monensin had enhanced activity of phagocytes and monocytes (Yasui et al., 2016).

Ruminal hydrolysis of triglycerides and biohydrogenation of UFA in the rumen are inhibited by monensin (Van Nevel and Demeyer, 1977). Propionate was increased, methane production decreased, biohydrogenation of linoleic acid was reduced, and production of *trans*-octadecenoic isomers was increased in continuous culture rumen fermentors (Fellner et al., 1997). Jenkins et al. (2003), in a similar study, reported that monensin and soybean oil produced higher concentrations of *trans*-10 18:1 when barley (a more rapidly fermentable starch source) replaced corn as the starch source. The study suggested that grains with higher rates of ruminal degradation of starch in the presence of monensin and high soy oil diets resulted in incomplete biohydrogenation of linoleic acid. Reduction in milk fat was accentuated when monensin was fed with soybean oil (Al Zahal et al., 2008).

Grainger et al. (2008, 2010) concluded that monensin was not a solution to reduce methane emissions in grazing dairy cows. The effects of monensin supplementation in dairy cows and beef steers were evaluated in a meta-analysis of 22 controlled studies. Monensin reduced gross energy loss—methane ranged from 5.42 to 5.94%—and was greater for beef steers than dairy cows. However, total DMI, BW, and feed composition were not included in the statistical model. A sustained 7% reduction in methane production over a 6-mo period was obtained by feeding monensin in a TMR (Odongo et al., 2007).

Bovine pulmonary emphysema ("fog fever") is a condition that develops in cooler fall months, soon after cattle are turned out to pasture. Grazing cattle are affected within 5 to 10 d of turnout. Rumen bacteria convert tryptophan to 3-methyl indole, which, when absorbed, damages the lining of the air sacs of the lungs. The condition is irreversible and leads to death. Monensin and lasalocid inhibit the conversion of tryptophan to 3-methyl indole (Hammond et al., 1978).

In a study by Baile et al. (1982), monensin feeding at 0, 200, or 600 mg/head per day began in heifers weighing 196 kg and continued for 448 d, the last 120 d of which were after calving. There were no differences in feed intake but feed efficiency improved 8.1% overall, and heifers fed monensin at 200 and 600 mg/head per day calved 38 and 34 d earlier than controls (0 mg of monensin). Monensin decreased age at first breeding by 15 and 24 d in 2 starting weight groups (330 and 217 kg) by 36 and 61 d of age at first calving (Meinert et al., 1992). Cows fed monensin during 2 lactations had higher BW gain and BCS at the end of each lactation (Van der Werf et al., 1998).

Monensin in a controlled-release capsule administered prepartum reduced energy-associated metabolic diseases (displaced abomasum, ketosis, retained placenta) by 30% during the transition period (Duffield et al., 2002). First ovulation postpartum occurred 5 d earlier in cows fed monensin (Tallam et al., 2003). Loss of BCS and increased percent of first-service conception were reported for cows grazing and supplemented with a partial mixed ration (Gallardo et al., 2005).

Lasalocid with ground corn tended to increase feed intake, increased water intake and decreased body condition loss and milk fat (Knowlton et al., 1996a,b). Ionophore ingestion by humans is fatal. The median lethal dose (LD_{50}) for equines is about 400 mg.

β-Adrenergic Agonists

β-Adrenergic agonists serve as repartitioning agents and have been studied in multiple livestock species for more than 3 decades. The physiological effects of β-agonists are primarily on muscle resulting in muscle cell hypertrophy and secondarily on adipose tissue resulting in slightly reduced body fat through increased lipolysis and decreased lipogenesis (Anderson et al., 1991).

Research with numerous β-agonists (cimaterol, clenbuterol, ractopamine, salbutamol, and zilpaterol) began in the late 1970s and the first reports were published in 1984 (Ricks et al., 1984). An extensive review of this early work was assembled by Anderson and coworkers (1991). Following extensive safety and efficacy testing, ractopamine and zilpaterol received regulatory approval in Europe and the United States for use in swine, cattle, and turkeys starting in 1999. The physiological effect of clenbuterol in dairy cows was limited to the repartitioning effect on body composition with little effect on milk production (Stoffel and Meyer, 1993). Therefore, the primary use in dairy has been in dairy steers (Blum and Flueckiger, 1988; Haneklaus et al., 2011) and cull cows (Weber et al., 2013). The illegal use of clenbuterol, an efficacious but unsafe β-agonist, resulted in the ban of all β-agonists in the European Union (Kuiper et al., 1998).

Buffers and Acidosis

One sentence describes the importance of rumen fermentation to the cow: "Furthermore, ruminal OM (especially carbohydrate) digestibility has the greatest effect on microbial protein through the energy availability for protein synthesis or through (the) negative effects of reduced ruminal pH on microbial effects of reduced pH on fiber digestibility and microbial efficiency" (Firkins et al., 1998).

Five rations are prepared for the cow: (1) the one formulated by a nutritionist using the most up-to-date inputs on the cow and feeds; (2) the weight of feeds added to the mixer to prepare the ration; (3) the ration when ingredients are mixed; (4) the ration emptied into the feed bunk; and finally (5) the ration the cow eats. Errors challenge each step and the cow has final say in her consumption.

In order, feet, rumen health, and the mammary gland are the most important anatomical features for milk production. Cows must walk to the feed bunk and return to a comfortable site, lie down, rest, and ruminate. As a consulting nutritionist, my first 3 activities were (1) to observe cows walking; (2) to evaluate fecal consistency; and (3) to look for evidence of sorting at the feed bunk. These observations allowed a quick and accurate assessment of the feeding program past and present.

Walking, lying, and rising are dependent on healthy feet. If not, DMI and thus supply of nutrients for milk production are reduced. Cows experiencing severe lameness in early lactation lose about 350 kg of milk during lactation (Archer et al., 2010).

Most cows are at risk for some degree of acidosis. Risk factors are (1) forage source (grasses > legumes); (2) physically effective NDF (**peNDF** <30%); and (3) grain with pasture > grain at the bunk > TMR; and (4) level of intake. Intake of peNDF is defined by amount and particle length of NDF sources. Forage-to-concentrate ratio, forage particle length, and peNDF affect chewing, saliva quality, saliva quantity, and rumen pH (Yang and Beauchemin, 2006, 2007, 2009).

Increased frequency of feedings (1, 2, or 4 times) per day eliminate competition by parity and dominance and reduce sorting. Cows sort a TMR, seeking smaller feed particles, during eating but cows seek longer feed particles after an acidosis bout, apparently in an attempt to ameliorate acidosis (DeVries et al., 2005, 2008). Risk of acidosis increases as concentrate feeding increases and forage decreases. Balch et al. (1955) observed reduced milk fat content in cows when concentrate replaced a significant proportion of hay in the ration.

Buffers are salts of weak acids or bases. Buffers are water-soluble and possess a solubility factor known as the acid dissociation constant, pK_a, which is the pH at which the cation and anion concentrations are in equilibrium with the salt. The pK_a for $NaHCO_3$ is 6.4 and 10.3. At rumen pH of 6.4, the reaction is

$$[NaHCO_3] = [Na] + [HCO_3^-].$$

Concentrations of cation and anion increase as pH is reduced during rumen fermentation. Saliva is a rich source of carbonate and phosphate buffers and its release is stimulated by chewing, which enriches rumen buffering capacity. Viscosity decreases as pH decreases, which reduces lubrication during deglutition (Emery et al., 1960). As more VFA are produced, the equilibrium moves to the right and buffering capacity is reduced. Volatile fatty acids also serve as buffers: $VFA \rightarrow H^+ + VFA^-$, and have pK_a of 4.7 to 4.9. At pH of 5.5, the buffering capacity of bicarbonate is nil and lactic acid–producing bacteria begin to produce lactic acid. Lactate-utilizing bacteria (e.g., *Megasphaera* and

Selenomonas) are not sensitive to monensin, so risk of acidosis is attenuated as pH decreases.

Emery et al. (1960) initiated a research program at Michigan State University in the early 1960s directed at causes and relief of low fat milk when concentrate feeding increased. Cows spent less time chewing, secreted less saliva, had reduced rumen pH, and decreased acetate:propionate ratio as the percent of concentrate in the ration increased (Emery et al., 1960).

Sodium bicarbonate increased milk fat 0.81 to 0.86% with daily feeding of 907 g of roughage and grain ad libitum (Emery and Brown, 1961). Additive effects were observed when cows were fed sodium bicarbonate and MgO. Calcium carbonate feeding had no effect on milk fat secretion (Thomas and Emery, 1969). High grain rations increased the flux of long-chain fatty acids toward adipose tissue (Benson et al., 1972), decreased milk fat percent, and increased appearance of oleic and linoleic acids in milk fat (Askew et al., 1971). Dry matter intake and milk production were increased when $NaHCO_3$ was fed immediately postpartum (Kilmer et al., 1980; Erdman et al., 1982).

Calcareous marine algae (**CMA**, also known as Acid Buf) is a calcium carbonate source derived from the seaweed *Lithothamnium calcereum* that serves as a buffer for dairy cows (Bernard et al., 2014; Cruywagen et al., 2015). It contains 30% Ca as $CaCO_3$ and Mg (55 g/kg). Inclusion of CMA at 90 g/cow per day maintained rumen pH above 5.5 longer compared with $NaHCO_3$. Time below 5.5 was 13 h for $NaHCO_3$ (180 g/d) compared with 8.7 h for CMA over a 24-h period. Acetate was higher and propionate lower in cows fed CMA. Milk and 4% FCM yields were greater for CMA-fed cows.

Ruminal pH and E_h (Planck's constant) were determined in dairy cattle fed live yeast (*Saccharomyces cerevisiae*) or sodium bicarbonate (Marden et al., 2008). Total lactate concentration in the rumen was 5.4 and 12.2 m*M* for cows receiving yeast and bicarbonate, respectively. Ruminal digestibilities of OM, NDF, and ADF were higher ($P < 0.05$) for the yeast diet compared with sodium bicarbonate.

Erdman (1988) provided an extensive review on buffering requirements of the lactating dairy cow. Hu and Murphy (2005) provided an analysis of responses to sodium bicarbonate in early- and mid-lactation cows.

The buffering effect of sodium bicarbonate was questioned by Russell and Chow (1993). They reasoned that feeding mineral salts (Na and K) of strong acids would increase rumen fluid osmolarity, causing increased water consumption. Water flux into the rumen and drinking increased to reduce osmolarity. Increased fluidity of rumen fluid hastened passage of small feed particles associated with starch sources to the abomasum and beyond leaving a higher proportion of forage digestion in the rumen. Digestion of starch particles occurred in the small intestine. The effect is analogous to a high forage ration and results in increased acetate to propionate ratio and, increased milk fat.

Many published papers on $NaHCO_3$ cited the "osmolarity effect" but never attributed it to the movement of water and increased rate of passage of smaller fermentable feed particles from grains from the rumen and increased milk fat (Rogers and Davis 1982; Murphy et al., 1983; Okeke et al., 1983; Argyle and Baldwin, 1988).

Nocek (1997) provides a thorough review on the effects of reduced rumen pH on long-term health of the dairy cow. Daily bouts of some degree of acidosis occur following each meal. Lysis of bacteria releases histamines and endotoxins. These substances damage small blood vessels in the foot, resulting in ischemia in the corium. Sore feet and abnormal gait and precede lameness. Hooves of the weight-bearing rear legs are at the greatest risk of damage due to recurring acidosis insults.

Subacute ruminal acidosis likely occurs following a meal, especially in high-producing dairy cows. It is likely more prevalent during the transition period than recognized. Signs of subclinical acidosis in lactating cows include low BCS, lameness, laminitis, low butterfat test, and an inverted milk fat-to-protein ratio. Rumen pH was <5.5 for 13.8, 7.5, and 4.6 h for control, sodium bicarbonate, and Acid-Buf (a calcium carbonate), respectively. Rumen pH returned to 6.1 before the first feeding of the next day. Rumen pH <5.8 was found in 53% of cows grazing perennial ryegrass (O'Grady et al., 2008).

Monensin decreased noninfectious lameness by 31% in a study from Holland (Heuer et al., 2001). Lameness is second to mastitis as the leading cause of culling. Lameness was the top factor in a multi-factorial analysis of mortality in US dairy herds (McConnel et al., 2008).

Locomotion scoring is a clinical measure for detection of foot problems related to hoof disorders and lameness. Numerical scoring (1–4) is based on the angularity of the vertebral column and gait. A locomotion score of 1 indicates the cow walks with a normal gait and a straight top backline. A locomotion score of 2 indicates a cow with a slight arch and slightly compromised gait. An arched back and short steps define a score of 3. Finally, a cow with a score of 4 has a marked arch of the spinal column with rear feet tucked forward and walks unsteadily. Lameness compromises welfare, and cows consume feed faster and spend less time eating (Norring et al., 2014). Cows stand rather than lie down because of their inability to stand once lying down (Berry and Cook, 2007).

The prevalence of lameness is higher in multiparous than in primiparous cows. Cows on slatted floors in freestall barns had higher locomotion scores (more abnormal) than on solid concrete. Both concrete flooring types were inferior to rubber mats on hemorrhages in the hooves of the rear legs but sole ulcers were more prevalent for cows on rubber mats (Fjeldaas et al., 2011). Rubber mats reduced laminitis-related lesions compared with concrete.

Prevalence of lameness was positively correlated with time away from the pen and hoof trimming done by the owner compared with a professional trimmer. Risk of lameness was increased in freestall barns having brisket board height greater than 15 cm and stalls with concrete surfaces (Espejo and Endres, 2007). Higher locomotion scores, indicative of severity of lameness, occur most frequently in the first 70 d of lactation, and are associated with reduced risk of pregnancy and increased culling or death compared with cows with locomotion score $\leq$2.0 (Bicalho et al., 2007). Lameness compromises welfare of cows. Severely lame cows spend less time eating, consume feed faster, spend more time (h/d) lying, have more bouts of lying, and longer duration of lying in deep-bedded stalls (Ito et al., 2010).

Rubber versus concrete flooring in alleys of pens in a freestall barn was compared in heifers beginning before calving until 180 d into the second lactation. Hoof health and locomotion score were improved and required fewer therapies for cows housed on rubber surfaces.

Chronic inflammation, as indicated by higher lymphocyte counts and thus greater immune response, was greater in cows maintained on concrete flooring (Eicher et al., 2013). Infectious lesions of the foot occur more in early lactation and during the cooler months of the year. Noninfectious lesions occur more in the months following heat stress and follow the pattern of the lactation curve (DeFrain et al., 2013).

Two signs—gait and loose manure—are the first visible signs of borderline acidosis. Subacute ruminal acidosis (SARA) is a herd problem associated with feeding management. Cows experience low rates of rumination, reduced milk production, and a high removal rate from the herd. Laminitis is second only to mastitis as the most costly disease of dairy cattle (Esslemont and Kossaibati, 1996). Environmental conditions such as heat stress, walking surface (especially concrete), feed bunk space, overcrowding, pen layout, and poor stall design contribute to SARA (Cook et al., 2004; Stone, 2004).

Natural Products

Plants produce bioactive substances that affect the digestive system of mammals. Called phytonutrients, these bioactive substances have been used for productive and medicinal purposes over many centuries. Compounds include capsicum, curcuma, garlic oil, saccharin, neohesperidin dihydrochalcone, and eugenol. Phytonutrients enhance immunity, stimulate taste receptors, and possess antimicrobial activity in the small intestines. Gingko fruit extract has been shown to reduce methane production and increase propionate in vitro (Oh et al., 2017). Researchers have suggested that phytonutrients may serve as a potential alternative to ionophores in Europe where use of ionophores is limited.

Direct-fed microbial products (**DFM**) yeast and enzymes are GRAS substances with improved digestive health and increased DMI and milk production as claimed benefits. A DFM consisting of *Enterococcus faecium* and *Saccharomyces cerevisiae* improved total-tract digestibility of starch (AlZahal et al., 2014). Milk was increased by 2.3 kg/d but milk fat percent was reduced by 0.32 percentage points when a DFM containing yeast and *E. faecium* was fed from 21 d prepartum through 10 wk postpartum (Nocek and Kautz, 2006). Yeast culture and an enzymatically hydrolyzed yeast increased milk and fat-corrected milk (Nocek et al., 2011). Health and performance of a DFM were evaluated on 2 farms in Wisconsin. There were no differences in milk, milk components, or DMI but second-lactation cows on 1 farm required fewer antibiotic treatments for mastitis (enough so that the producer continued using the product; Oetzel et al., 2007). Redox potential and Clark's Exponent were reduced by addition of live yeast, suggesting that the yeast were oxygen scavengers in the rumen (Marden et al., 2008). No effect was reported with the addition of a cellulose enzyme preparation to alfalfa hay or bermudagrass haylage (Bernard et al., 2010).

An article on homeopathic treatment of mastitis was recently published in the *Journal of Dairy Science* (Ebert et al., 2017). The results indicated no additional effect of homeopathic treatments compared with placebo. Similar articles may appear in the future as the search continues for cures or supportive therapy of metabolic conditions. Publication will depend on scientific merit, even with acceptance of the null hypothesis.

GALACTOPOIETIC HORMONES

The anterior pituitary, located at the base of the brain, is known as the "master gland" of the body. It secretes 6 hormones: growth hormone (**GH**), thyrotropin-secreting hormone (**TSH**), prolactin (**PRL**), ACTH, FSH, and LH. Release of anterior pituitary hormones is controlled by the hypothalamus located above the pituitary gland. Hypothalamic hormones are released into portal blood and transported through the portal vein to the anterior pituitary. Release of hypothalamic hormones is regulated by feedback inhibition of circulating hormones released from target tissues; for example, thyroxine on thyrotropin-releasing hormone from the hypothalamus.

The thyroid hormones, thyroxine (T4) and triiodothyronine (T3), regulate metabolism of tissues. Thyrotropin-releasing hormone from the hypothalamus causes release of TSH into the blood. The thyroid gland responds to TSH with the release of T4 and T3. These hormones are involved in the uptake and nutrient utilization by body tissues. Iodinated casein is fed to cows as a mimic of T4.

Thyroprotein feeding causes a temporary increase in basal metabolic rate and milk production. Dr. J. W. Thomas began research with thyroprotein in the late 1940s at what is now the USDA Research Center in Beltsville, Maryland. Primiparous cows fed at 125% of Morrison's Feeding Standard and thyroprotein starting at 50 DIM had increased milk production compared with control for more than 200 d.

Thomas and Moore (1953) conducted a similar study with thyroprotein over multiple lactations, starting 20 heifers at 50 d in milk. Fifteen, 9, 5, 4, and 3 completed lactations 2 through 6, respectively. Eight heifers acted as controls and 6, 5, 3, 2, 1, and 2 lasted through 6 lactations. Milk production averaged 108% in the first month of feeding in each succeeding lactation compared with 92% for control. Milk fat test responded similarly to milk. Thomas (1953) recommended, in a National Research Council publication, that thyroprotein provided "no definite economic advantage of feeding under farm conditions."

Thyroprotein was not effective in hastening clearance of dichlorodiphenyltrichloroethane (DDT; Stull et al., 1968; Braund et al., 1969) or polychlorinated biphenyls (Willett and Liu, 1982).

Growth Hormone

Growth hormone—bovine somatotropin—regulates metabolism of all somatic cells in the body. Release from the anterior pituitary gland is regulated by growth hormone-releasing factor and somatostatin from the hypothalamus. Growth hormone stimulates production of IGF-1 by the liver, which mediates the action of GH on somatic cells throughout the body.

Russian scientists Asimov and Krouze (1937) collected bovine pituitary glands from cattle in abattoirs throughout Russia. The galactopoietic nature of aqueous extracts from these glands was demonstrated when extracts were injected in dairy cows. In multiple studies involving 600 cows (90 control; 510 injected) maintained in 4 barns, milk yield was increased by 3,872, 1,123, 1,562, and 1,118 L after 10, 7, 10, and 6 injections of the pituitary extract, respectively. The following quote is noteworthy: "The lactogenic preparations from the anterior pituitary made in our laboratory induce an increase of milk yield in lactating dairy cows. In certain series of tests this increase of the milk yield has reached seven or more liters of milk per day." Subsequent studies by Cotes et al. (1949), Brumby and Hancock (1955), Hutton (1957), Bullis et al. (1965), and Machlin (1973) demonstrated the galactopoietic nature of pituitary extracts.

Somatotropin Research

In the early 1970s, scientists were able to produce proteins of known AA sequence through a breakthrough technology called recombinant DNA. Scientists were able to produce DNA having the nucleotide sequence that corresponded to the genetic code of a specific protein. Such was the origin of recombinant bovine somatotropin (**rbST**). In 1982, Lilly Research Laboratories began research with rbST. I received a package from a company that contained 9 to 10 g of pure bST in two 2-L beakers. I stood in a walk-in cooler holding the containers and was in awe at what I had in my hands—more bST for research than all previous researchers had used in characterizing the response of cows to purified bovine pituitary growth hormone.

Commercialization of Somatotropin

The CVM is responsible for approval of all products fused in food-producing animals. Data must be generated to show that the candidate production-enhancing compound must be safe and efficacious for the animal, consumer, and environment.

Four companies, American Cyanamid, Eli Lilly and Company, Monsanto, and Upjohn, were interested in commercializing bST for use in lactating dairy cows. The first obstacle faced by these companies and by CVM was creating a framework of studies to demonstrate the efficacy and safety of use of rbST in lactating dairy cows.

Developing protocols to demonstrate safety and efficacy of a production-enhancing product was not something that CVM had done previously, and there were no scientists on the CVM staff with expertise in dairy cattle production. Therefore, CVM initiated a Dairy Advisory Committee to provide expertise in developing research requirements for a milk-enhancing product. Members of the committee included Carl Coppock, Jimmy Clark, and others. Dr. Susan Sechen, who studied with Dale Bauman, was ultimately hired by CVM to provide expertise in dairy cattle. The 4 company representatives, CVM staff, and the advisory committee set out to develop protocols to determine safety and efficacy of rbST in lactating dairy cows.

Biology of Somatotropin

Research from 1980 to 2005 focused on understanding the biology of somatotropin in the dairy cow. In a normal lactation, peak milk production occurs between 50 and 60 d and begins to decline at the rate of about 4% per month. Cows are in negative energy balance in early lactation and depend on mobilization of body fat to provide energy for maintenance and milk production.

Bauman (1985) injected bovine pituitary-derived growth hormone (bGH; 27 mg/d) and rbST at 0, 13.5, 27, and 40.5 mg/d for 188 d in dairy cows beginning at 84 ± 10 DIM. Milk (3.5% FCM) was increased by 16% with bGH and 23 to 41% by rbST (control group = 27.9). Fat-corrected milk (kg/d) at the 27 mg/d dose was 32.5 and 37.0 ($P < 0.05$) for bGH and rbST, respectively. Dry matter intake lagged the milk response but, by 9 to 11 wk, DMI (% of BW) was 4.0 for control cows and 4.6 for cows at the 2 highest doses of rbST.

Sechen et al. (1989) reported an 11% increase in milk yield with daily injections of somatotropin for 21 d but no effect on DMI, which suggested a partitioning of consumed calories for milk at the expense of deposition to adipose tissue.

Four rations in a 2 × 2 arrangement: low (14%) or high (17%) CP × low (33%) or high (40%) rumen-undegradable intake protein (UIP) for cows were assigned to control or 640 mg of bST injected at 28-d intervals (McGuffey et al., 1990). Nine cows with no bST and fed the low–low ration served as negative controls. Milk yield was not different ($P > 0.1$) for CP percent. On the low–low ration, rbST increased milk yield ($P < 0.05$) by 2.3 kg/d. Milk and 3.5% FCM were increased in cows receiving the 40% UIP ration. Net energy intake decreased as forage increased in the TMR. Milk fat percentage was reduced by feeding the 40:60 TMR but it was determined that sodium bicarbonate was not incorporated into the grain mix, which may have contributed to reduced fat percent. Milk and 3.5% FCM yields were increased by rbST.

Soderholm et al. (1988) used deuterium oxide dilution to determine body composition in cows receiving daily injections of bST for 38 wk. Body fat (kg) and BCS were reduced by increasing doses of bST. Body fat (kg) determined at 0, 12, 24, and 36 wk was lowest at wk 12 and increased thereafter but was 131 kg less at 36 wk compared with start of bST.

McGuffey et al. (1991) fed 78 cows 40:60, 50:50, and 60:40 forage-to-concentrate ratios and treated cows with rbST at either 0 or 640 mg every 28 d. Whole-body chemical composition was determined in 12 cows at 35.9 DIM (T_0) and in 35 cows after either 84 or 168 d of rbST. Body composition in the cows at T_0 was 76.8 kg of fat, 88.1 kg of protein, and 278 kg of water. Body fat and total body energy were less ($P < 0.05$) in cows receiving rbST. Milk yield of cows used to determine body condition was 3.5 kg/d more ($P < 0.05$) than in controls. The study showed that administration of rbST partitioned energy into milk synthesis at the expense of energy deposition into adipose tissue. Tauer (2016) estimated that use of bST reduced the cost of producing milk by $2.67 per 100 kg or 5.5%.

Milk Fat Depression

Griinari et al. (1998) proposed that milk fat depression required 2 conditions in the rumen: (1) presence of dietary linoleic acid, and (2) altered rumen environment. Biohydrogenation competes with propionate for metabolic hydrogen disposal.

Ionophores reduce the acetate:propionate ratio, and logic would imply that ionophores reduce milk fat. In a 9-trial summary of monensin registration trials, milk fat depression did not occur at sites that had 2% linoleic acid with NDF at ≥31% in the diet. Lower milk fat occurred at sites with dietary NDF ≤29%. Milk fat depression is not singly caused by ionophores (McGuffey et al., 1991). Similar results were reported by Dubuc et al. (2009). Other factors such as amount of fermentable substrate, amount and quality of dietary NDF, and grain processing must be considered when feeding dairy cattle, with or without ionophores. Milk fat percent was maintained with monensin at NDF in TMR ≥6% on the top screen of the Penn State Particle Size Separator and in rations with ≥40.2% NSC (Duffield et al., 2003).

Grain Processing

Corn, sorghum, and cereal grains contain 70 to 80% of DM as starch. Starch availability for rumen fermentation from cereal grains is wheat > barley > corn > sorghum (Knowlton et al., 1998). Starch in the total ration may be 25 to 30% of DM in rations for high-producing cows. Increasing ruminal starch fermentability promotes higher milk and milk protein yields. Cereal grains need processing by cracking, grinding, rolling, or flaking or stored as high moisture to improve rumen fermentation. Application of steam during rolling or flaking to these feed grains increases fermentation of starch, production of propionate, and flow of microbial protein. Total-tract digestibility of corn and sorghum is improved by steam flaking versus steam rolling and other methods. Net energy of lactation for corn and sorghum is increased about 20% compared with dry rolling (Theurer et al., 1999).

Barley is the predominant cereal grain fed to cattle in northern areas of Canada and Europe. Yang et al. (2000) determined that the processing index (vol/wt), a reciprocal measure to flake density, was 64%. Milk (kg/d) was 25.6, 28.1, 30.8, and 29.0 for diets with a processing index (%) of 81.0, 72.5, 64.0, and 55.5, respectively.

TOXIC SUBSTANCES IN FEEDS

An array of toxic compounds can be found in feedstuffs offered to dairy cattle. Macy (1921) provided a history on cottonseed as a feed, noting that toxicity from cottonseed was reported as early as 1859. Experiments revealed that swine and preruminant calves were most sensitive among animals to cottonseed toxicity. Gossypol was the first toxic substance in feeds described in the *Journal of Dairy Science* (Gallup, 1926). Consumption of 2 to 4 kg/d of cottonseed, meal or whole, for an extended period may cause gossypol toxicity, which results in debilitating conditions and death.

Biological toxins such as dicoumarol (discussed previously) are produced by molds and fungi on feedstuffs in the field or during storage. Fescue (*Festuca arundinacea*), a cool-season grass, causes a disease in grazing cattle called “Fescue foot” that is caused by the endophyte fungus *Acremonium coenophialum.* Over a 3-yr period of study, feed intake by dairy cattle grazing infected pastures was 10% lower than in cattle grazing other cool-season grasses (Lassiter et al., 1956). Julien et al. (1974) isolated an ethanol-soluble product from fescue hay that produced toxic signs in calves when infused intraperitoneally. Increased respiration rate, open-mouth breathing, and elevated rectal temperature were observed. Cattle with the disease exhibit sore feet and walk with a limp. Vitamin E supplementation had no effect on signs of toxicity.

In 1960, young turkey poults were dying from unknown cause(s) in multiple locations in southeast England during late spring and early summer. Investigators found peanut meal to be a common feed ingredient in feeds of affected flocks. The condition was named turkey X disease (Wannop, 1961).

Mycotoxins are a family of compounds produced by the fungi *Aspergillus*, *Fusarium*, and *Penicillium* (Ward and de Ondarza, 2010). These compounds are toxic and carcinogenic, and the FDA has set a limit of 0.5 μg/L in milk. Major toxins are deoxynivalenol, zearalenone, T-2 toxin, fumonisin, and ochratoxin. The molds infect corn grain standing in the field or in storage. Moisture and temperature are important factors for growth of the molds, and wind and insects are vectors for transfer to other plants. Monogastric animals are more sensitive to mycotoxicosis than ruminants because of rumen degradation.

Mycotoxin binders are added to feeds to reduce the risk of transfer to milk. California imports much of its corn for use in dairy cattle feeding. Government and University of California–Davis scientists analyzed samples (n = 50) of imported (n = 43) and locally grown (n = 7) corn for the presence of 6 different aflatoxins. Fourteen samples tested positive, 1 of which contained 41.3 μg/kg (Krout-Greenberg et al., 2013).

Mycotoxins may suppress or stimulate the immune system (Sharma, 1993). Suppression weakens the immune response to stimuli, whereas stimulation produces hypersensitive allergic reactions.

Factors Affecting Butter Quality and Taste

Butter is one of many tasty products made from milk. Nutritionists must be aware of any feedstuff that may contribute to or cause an off-flavor in milk or milk products. Composition of the ration fed to cows has a major effect on flavor and stability of butter. Nevens and Tracy (1928) described butter produced from cows fed ground soybeans as being “gummy,” and the conditioned worsened as the proportion of soybeans increased. They noted an increase in iodine number, a measure of unsaturation, as soybeans were fed in larger amounts. Similar responses were reported for fish oil (Brown and Sutton, 1931) and corn oil (Sutton et al., 1932).

Fatty acid composition of butter reflects the source of milk used to make butter. Softness is a quality of butter reflective of its degree of unsaturation. Plant and fish oils contain relatively high concentrations of PUFA, which may affect flavor in butter when they exceed 3 to 4% of the diet (Middaugh et al., 1988; Stegeman et al., 1992). Butters made with milk from cows fed oilseeds were softer at 4 and 20°C. Ramaswamy et al. (2001) reported a decrease in milk fat percent from control of 0.82 and 0.46 percentage units when added fat from fish oil (2%) or fish oil (1%), respectively, plus extruded soybeans (1%) was fed. Butter made from milk produced by cows fed a rumen-protected canola-based lipid source was slightly softer than milk from normally fed cows (Cadden et al., 1984). No differences in flavor were detected in butters made from high-PUFA milks. Oral vitamin E increased milk α-tocopherol and oxidative stability of butter from milk of supplemented cows fed a mixture of extruded rapeseed and linseed (Bobe et al., 2007).

CLIMATE

Environmental temperature and relative humidity have significant effects on milk production, composition, health, and well-being of the dairy animal. Milk composition, especially fat percent, changes between seasons, as first described by Eckles (1909; cited by Ragsdale and Brody, 1922). Ragsdale and Brody (1922) estimated a 0.2% increase in milk fat for each 10°F decrease in environmental temperature.

Brody (1956) described the effect of environmental temperature for 3 types of cattle: very cold tolerant, wooly (yaks, Scottish Highlander), cold-tolerant, heat-intolerant northern European breeds (*Bos taurus*), and cold-intolerant humped-back cattle Zebu and Brahman (*Bos indicus*). *Bos taurus* expend 2% more energy to maintain body temperature from 7°F to 50°F compared with *B. indicus* (60% at 50°F). Thermo-regulatory mechanisms include open-mouth respiration with excess salivation and vaporization through the skin.

Milk production and feed intake are reduced during heat stress in a likely attempt to reduce heat of metabolism. Heat-stressed cows shift acid–base balance to a more alkalotic state. Panting increases the rate of loss of CO_2 by shifting the equilibrium of the innate bicarbonate buffering system to produce water and carbon dioxide. Heat stress decreases libido, fertility, embryonic survival, and, during late gestation, fetal growth (Collier et al., 1982). Successful cooling strategies incorporate conduction, convection, evaporation, and radiation (Collier et al., 2006).

Feeding a positive DCAD diet improved protein utilization and higher milk fat percentage during hot weather in Georgia, United States (Wildman et al., 2007). West (2003) provides an excellent review on the effects of the hot, humid climate of the southeastern United States on the dairy cow. Increased precipitation regardless of form adversely affects milk production (Qi et al., 2015).

Dry matter intake was reduced 28% during heat stress compared with thermoneutral conditions in environmental chambers. Response of glucose to an epinephrine challenge was similar in normal and heat-stress conditions but lipolysis from adipose tissue was reduced by 56% during heat stress. Feeding monensin likely increased gluconeogenesis and possibly glycogenolysis during heat stress. Milk production was reduced, likely because of reduced mammary synthesis of lactose (Baumgard et al., 2011).

Temperature-humidity index best describes the environmental conditions of the cow. Ambient temperature with high humidity, as in the southeastern United States, affects milk production and well-being more than in the Desert Southwest, where humidity is low. Thermoneutral conditions occur at THI $\leq$72. Dry matter intake and milk production decrease as THI exceeds 72. Radiant energy and heat production by the cow affect DMI and milk production. Fertility and fetal growth are compromised during late gestation. Heifers born to heat-stressed cows weighed less (−4.8 kg) at birth and lower efficiency of IgG absorption (Monteiro et al., 2014). Similarly, calves born to heat-stressed cows weighed less at birth and, at 12 mo of age, had compromised immune system and less milk in the ensuing lactation (Dahl et al., 2016).

Amelioration of heat stress is accomplished by cooling systems that enhance heat dissipation by convection, conduction, radiation, and evaporation. These include fans, shade, and sprinkler systems at the feed bunk, and misters in corral shades and exit lanes from milking parlors.

Significant changes occur in metabolism during heat stress. Glucose is used for other bodily functions instead of for milk production. Monensin continues to supply more glucose from feed intake. Adipose tissue fails to recognize catabolic signals (Baumgard et al., 2011). Jersey cows are more tolerant than Holsteins when THI $\geq$72. Feeding encapsulated niacin during heat stress increased evaporative heat loss and reduced rectal and vaginal temperatures (Zimbelman et al., 2010). A study was initiated in summer in the Midwestern United States to demonstrate the effectiveness of bST. High temperature and humidity forced stoppage of the study in the summer because of the small, highly variable milk response (Mollett et al., 1986). Public outcry by a small group of scientists and consumer groups led the assault on commercial use of bST based on the results of the study.

Mineral loss, especially potassium, through sweating must be replaced. A high positive DCAD diet (>40 mEq) and fat in the diet take on added importance during heat stress. High concentrate rations lessen impact of heat of rumen fermentation.

Significant behavioral changes occur in cows during periods of heat stress (Cook et al., 2007; Allen et al., 2015). Cows spend less time lying in freestalls, more time standing in alleyways, and have lower locomotion scores during periods of heat stress. Milk yield was decreased by 9.6 kg/d during heat stress compared with 4.8 kg/d in thermal-neutral conditions in pair-fed cows. Increased time spent standing was suggested as a behavioral change in cows that promoted heat loss (Allen et al., 2015). Economic loss from heat stress was $897 million in the United States (St-Pierre et al., 2003).

CARBON FOOTPRINT

Global warming is a significant concern in the scientific community. Methane is labeled as the major greenhouse gas and ruminant animals are considered a major contributor to total production. Entering "methane" as an "article title" search term on the *Journal of Dairy Science* website produced 328 papers. Topics covered were confined versus pasture feeding, forage source and amount, effect of carbohydrate source and processing, ionophores, fat type, fat source, and fat amount for H_2 disposal by rumen fermentation. Enhanced propionate production is the major route of disposal of H_2. Other sources of disposal include NO_3, 3-nitro-oxypropanol, and unsaturated fat (Olijhoek et al., 2016). Most of these articles were published in the last 10 years, demonstrating the response of the dairy science community to new and pressing issues.

Dairy cattle moved into the Central Valley of California in the 1980s because of the availability of byproducts from the fruit and nut industries. Digestion of by-products serves as a source of energy for ruminants; these by-products would otherwise decompose to CO_2. Dairy cows convert these inedible products into milk, thus reducing substrate for atmospheric greenhouse gas production.

Knapp et al. (2014) published a thorough review on cattle contributions to methane emissions, and technologies (bST, ionophores, buffers, fat feeding) introduced for enhanced production have reduced the contribution to greenhouse gases from dairy cows. Additionally, on-farm anaerobic fermentors utilize manure for production of methane, which is used as a power source for electricity generators and engines to power motors for transportation. Fair Oaks Dairy in northwestern Indiana uses much of its manure for such purposes. Methane can be used to power vehicles, the ash residue can be applied as fertilizer for crops, and recovered water can be used for irrigation.

SUMMARY AND FUTURE DIRECTIONS

Improvements in efficiency drive innovation. Efficiency is simply the ratio of output to input, and all of the variance of efficiency is in the denominator. In 100 years, dairy scientists have introduced many techniques, processes, and products to improve efficiency of the dairy cow. This review has considered the mechanisms by which metabolic modifiers affect metabolism in the rumen and its microbes, bone, liver, adipose, and mammary tissue.

It has been suggested that milk per day of life is an excellent measure of efficiency of the dairy cow. Our search for increasing milk per day of life begins at conception and applies to the epigenetics of the future calf. Questions such as, why are genetically identical twins occasionally different in phenotypic expression? Are stem cells a possibility?

A symposium titled "The Rumen and Beyond," (Bravo and Wall, 2016) published in volume 99 of the *Journal of Dairy Science* (pages 4939–4996) featured papers that examined the role of genetics (VandeHaar et al., 2016), gut health (Steele et al., 2016) of the rumen and lower gut, immunity (Sordillo, 2016), and communications between organs and systems (Bradford et al., 2015) to improve health and productivity of the dairy cow in the future. The topics covered in this symposium illustrate that scientists have many fruitful avenues for discovery and further improving the productivity of the dairy cow in the next 100 years.

The scientific community of the American Dairy Science Association has made significant contributions to all phases of dairy cattle production. Genetics has provided a cow with great potential for milk production. Much has been learned in nutrition and feeding methods to provide the optimal diet to the meet the production potential of the cow. New technologies continue to provide nutritional products that allow nutritionists to increase the limits of a well-balanced ration for production and improved well-being for cows and the environment. Walter Isaacson (2017) recently published a biography on Albert Einstein called "Einstein: His Life and Universe." Isaacson notes that, "Einstein also came to symbolize the perception that modern physics was something that ordinary laymen could not comprehend" and that Einstein believed that, "Imagination is more important than knowledge."

Dairy scientists must strive to interpret their research in the lay press for consumers to understand. We must also continue to imagine, discuss, propose, experiment, and share ideas to enhance our industry and welfare of all people throughout the world. There is no worse human condition than an empty stomach!

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APPENDIX

Table A1. Timeline of key events in the use of metabolic modifiers

Date	Milestone	Reference
1913	Lipids are required in feed for growth.	McCollum and Davis, 1913
1918	Salt is recognized as the first metabolic modifier.	Joffe, 1918
1919	Water requirement for milk production is established.	McCandless and Gaessler, 1919
1922	Effects of temperature on milk fat percentage are first reported.	Ragsdale and Brody, 1922
1923	Vitamin A deficiency first linked to blindness.	Bloch, 1923
1926	Methods to eliminate the toxicity of gossypol in cottonseed meal are published.	Gallup, 1926
1928	Effects of feeding soybean hay or ground soybeans on flavor of milk are reported.	Nevens and Tracy, 1928
1928	Alexander Fleming discovers penicillin.	
1937	Pituitary extracts increase milk production when injected into cows.	Asimov and Krouze, 1937
1945	Requirement of choline for protein metabolism is identified.	Supplee et al., 1945
1945	A. I. Virtanen is awarded Nobel Prize in Chemistry for inventions in agricultural chemistry and fodder preservation method.	Virtanen, 1945
1950	Historical review of parturient paresis is published in JDS.	Hibbs, 1950
1953	Thyroprotein feeding in dairy cows is reported.	Thomas and Moore, 1953
1955	Antibiotics first used as growth stimulants in feeds.	Lassiter, 1955
1961	Effect of buffers shown for cows fed high-grain rations.	Emery and Brown, 1961
1961	Mycotoxin poisoning shown in turkey poults.	Wannop, 1961
1974	Relationship established between ration composition and displaced abomasum.	Coppock, 1974
1975	Relationship between ruminal ammonia and nonprotein N (NPN) utilization shown.	Roffler and Satter, 1975a,b
1976	Role of vitamin E and selenium in reducing incidence of retained placenta is demonstrated.	Julien et al., 1976a,b
1976	Monensin shown improve feed efficiency.	Richardson et al., 1976

Continued

Table A1 (Continued). Timeline of key events in the use of metabolic modifiers

Date	**Milestone**	**Reference**
1982	Climate change shown to affect cow welfare.	Collier et al., 1982
1985	Response of cows to long-term administration of bovine somatotropin is shown.	Bauman, 1985
1992	Dry matter intake is shown to decrease in transition period.	Bertics et al., 1992