A 100-Year Review: From ascorbic acid to zinc—Mineral and vitamin nutrition of dairy cows¹

W. P. Weiss²

Department of Animal Science, Ohio Agricultural Research and Development Center, The Ohio State University, Wooster 44691

ABSTRACT

Mineral and vitamin nutrition of dairy cows was studied before the first volume of the *Journal of Dairy Science* was published and is still actively researched today. The initial studies on mineral nutrition of dairy cows were simple balance experiments (although the methods available at the time for measuring minerals were anything but simple). Output of Ca and P in feces, urine, and milk was subtracted from intake of Ca and P, and if values were negative it was often assumed that cows were lacking in the particular mineral. As analytical methods improved, more minerals were found to be required by dairy cows, and blood and tissue concentrations became primary response variables. Those measures often were poorly related to cow health, leading to the use of disease prevalence and immune function as a measure of mineral adequacy. As data were generated, mineral requirements became more accurate and included more sources of variation. In addition to milk yield and body weight inputs, bioavailability coefficients of minerals from different sources are used to formulate diets that can meet the needs of the cow without excessive excretion of minerals in manure, which negatively affects the environment. Milk, or more accurately the lack of milk in human diets, was central to the discovery of vitamins, but research into vitamin nutrition of cows developed slowly. For many decades bioassays were the only available method for measuring vitamin concentrations, which greatly limited research. The history of vitamin nutrition mirrors that of mineral nutrition. Among the first experiments conducted on vitamin nutrition of cows were those examining the factors affecting vitamin concentrations of milk. This was followed by determining the amount of vitamins needed to prevent deficiency diseases, which evolved into research to determine the amount of vitamins required to

promote overall good health. The majority of research was conducted on vitamins A, D, and E because these vitamins have a dietary requirement, and clinical and marginal deficiencies became common as diets for cows changed from pasture and full exposure to the sun to stored forage and limited sun exposure. As researchers learned new functions of fat-soluble vitamins, requirements generally increased over time. Diets generally contain substantial amounts of B vitamins, and rumen bacteria can synthesize large quantities of many B vitamins; hence, research on water-soluble vitamins lagged behind. We now know that supplementation of specific water-soluble vitamins can enhance cow health and increase milk production in certain situations. Additional research is needed to define specific requirements for many water-soluble vitamins. Both mineral and vitamin research is hampered by the lack of sensitive biomarkers of status, but advanced molecular techniques may provide measures that respond to altered supply of minerals and vitamins and that are related to health or productive responses of the cow. The overall importance of proper mineral and vitamin nutrition is known, but as we discover new and more diverse functions, better supplementation strategies should lead to even better cow health and higher production.

Key words: vitamin, mineral, requirements, health

INTRODUCTION

By the mid to late 19th century we knew that animals needed to consume certain minerals to live and be productive, but we did not know which minerals and how much was needed. Investigation into the mineral nutrition of dairy cattle soon followed (Appendix Table A1). However, the science and application of mineral and vitamin nutrition of dairy cattle did not advance as quickly as other areas of nutrition. Advances were limited by (1) analytical difficulties in measuring minerals and vitamins, (2) the lack of sensitive response measures for several vitamins and minerals, (3) the fact that the often-subtle responses to changes in supply of minerals and vitamins require large number of animals to be used in experiments, (4) diet dependency of responses (e.g., mineral antagonists, concentrations and

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²Corresponding author: weiss.6@osu.edu

availability of vitamins and minerals in basal ingredients), and (5) the long experimental duration required to observe responses. Many of these difficulties were pointed out in the first paper published in the *Journal of Dairy Science* that addressed mineral nutrition of dairy cows:

“[Investigation is] difficult because the environment of the animal is composed of such a complication of influences that it is impossible to determine the proportionate contribution of each of them, especially of the obscure and intricate facts of mineral metabolism; and also because, on account of the supreme importance of mineral metabolism, the animal is so wonderfully protected by mineral reserves and other safety provisions that unfavorable effects of treatment are slow to appear and are difficult to demonstrate in a clear-cut manner.” (Forbes, 1919)

Although mineral nutrition was difficult to study when the journal was founded, the importance of developing mineral-adequate diets was discussed during the fifth year of the journal by Meigs (1923). Only Ca and P were discussed in that paper because, as Meigs stated, “There is little reason to think that deficiencies of any other mineral elements play a very large or general practical role under ordinary conditions.” The state of the art at that time is reflected in how the Ca requirement was expressed in that paper: “1 pound of alfalfa hay for every 3 or 4 pounds of milk.”

The vitamin theory was developing around the same time we recognized that animals needed certain minerals. In 1871, noting that death rates of children increased dramatically when milk became unavailable to citizens of Paris, Jean Baptiste Dumas (as quoted by Semba, 2012) hypothesized that milk contained “indefinite substances employed in the sustenance of life, in which the smallest and most insignificant traces of matter may prove to be not only efficacious but even indispensable.” Vitamins A, B, and C were discovered in 1912, but the first studies on vitamins that appeared in the journal were not published until the seventh volume; these papers dealt with the nutritional value of milk and vitamin requirements of calves. As with minerals, requirements were expressed on a feedstuff basis (e.g., “2 ounces of cod liver oil” or “the juice of 2 oranges”). Progress in vitamin nutrition of dairy cattle has arguably been slower than that in mineral nutrition (Appendix Table A1). Vitamins can be extremely difficult to analyze. Concentrations are often in nanograms per kilogram, many are extensively metabolized or synthesized within the rumen, and clinical responses are often generic and subtle. Vitamins requirements

were based on avoidance of classical deficiency diseases (e.g., rickets for vitamin D); if deficiency diseases were not observed, diets were assumed to be adequate in the vitamin.

ADVANCES IN MINERAL NUTRITION

Dairy cattle likely require at least 22 minerals (Table 1), and other minerals may be added to that list as our analytical abilities become more sensitive. Calcium and P nutrition have been studied longer than any other mineral, probably because they are major constituents of milk and because concentrations in biological samples were great enough to be measured using the analytical procedures available at the time. The initial studies on Ca and P nutrition were balance experiments (intake – fecal – urine – milk), and surprisingly Ca balance was negative in almost all experiments (Forbes et al., 1922). Phosphorus balances were also negative in several but not all experiments. The Ca concentrations of the diets were not presented, but most diets contained more than 50% alfalfa and some diets contained supplemental Ca; negative Ca balances would not be expected. Nonetheless, this led to the development of quantitative requirements for Ca and P (NRC, 1945).

1917–1945

During this period mineral research was limited mostly to Ca and P, and primary response variables were balance (intake – output of the mineral), blood concentrations, and milk production. However, one study (Huffman et al., 1933) evaluated the P requirement for reproduction using 14 heifers. Titration-type studies were being used to quantify requirements, and proper experimental protocols for evaluating mineral requirements were being developed. Also during this time the importance of interactions among minerals and other nutrients was being recognized. The dietary Ca:P ratio was often discussed and assumed to be important (although more recent experiments have shown that the ratio is not a major factor affecting absorption of either mineral). Vitamin D had been discovered, and studies with both calves and cows showed that Ca and P balances were greatly improved when vitamin D was provided (Wallis, 1938). Vitamin D status likely explains the data from Forbes et al. (1922) and illustrates the complexities of mineral nutrition and that establishing mineral requirements depends on the diet as well as the cow. The quantitative studies conducted during this period culminated in the first NRC nutrient requirement publication (NRC, 1945), in which 27 pages were dedicated to dairy cattle (NRC, 2001 was 381 pages). Requirements for maintenance, growth, and

Table 1. Essential or potentially essential minerals for dairy cattle

Mineral	NRC requirement ¹	Brief overview of functions and responses
Macrominerals (needed in gram amounts)		
Calcium	1945	Skeleton, major milk component, cell signaling, muscle and nerve functioning, enzyme activation and control
Chloride	1971	Acid–base balance, water homeostasis, gastric secretion, oxygen transfer to cells
Magnesium	1945 ²	Enzyme activation and binding to substrate, skeleton, muscle and nerve functioning, cell membrane stability
Phosphorus	1945	Skeleton, acid–base balance, energy metabolism, major milk component, cell membranes, nucleic acids, fiber digestion (microbial requirement)
Potassium	1971	Acid–base balance, water homeostasis, muscle and nerve functioning, enzyme cofactor, nutrient transport, major milk component
Sodium	1971	Acid–base balance, water homeostasis, muscle and nerve functioning, nutrient transport, rumen pH control
Sulfur	1971	AA and vitamin synthesis (microbial and animal), cartilage synthesis, acid–base balance, rumen fermentation and fiber digestion (microbial)
Trace minerals (needed in milligram amounts)		
Chromium	ND ³	Potential activity of insulin, lipid mobilization, immune function, thyroid hormone synthesis
Cobalt	1971	Vitamin B ₁₂ synthesis (microbial); may be involved with hemopoiesis
Copper	1971	Cofactor for numerous enzymes (redox, antioxidant, iron metabolism), erythropoiesis, collagen formation, immune function, gene regulation
Iodine	1950 ⁴	Component of thyroid hormones; may have independent effects on immune function
Iron	1971	Oxygen transport, cofactor for cytochromes and enzymes involved in energy metabolism, antioxidant enzymes
Manganese	1966	Cartilage synthesis; cofactor for enzymes involved with lipid, AA, and carbohydrate metabolism; antioxidant enzymes
Molybdenum	ND ³	Cofactor for redox enzymes
Selenium	1971	Antioxidant enzyme, arachidonic acid metabolism, immune function
Zinc	1971	Cofactor for numerous enzymes, protein synthesis, gene regulation, immune function
Potentially essential to dairy cattle		
Arsenic		Unknown but may be cofactor in enzymes; has increased milk yield in goats
Fluorine		Skeletal and teeth development
Silicon		Cartilage development
Nickel		Cofactor for some microbial enzymes; enhanced growth has been observed in cattle, but mode of action is unknown
Vanadium		Glucose metabolism, may be involved with insulin activity; supplementation has increased milk production in cows

¹Year that the requirement was established by the NRC. The need for a specific mineral may have been recognized earlier.

²Requirement established for calves (not adult cattle).

³Recognized as essential but requirement has not been quantified.

⁴Allowance recommended only for specific geographic areas.

milk production for Ca and P were presented in that book. Over the past approximately 100 yr, the NRC requirements for Ca and P for a standard cow (625 kg of BW producing 32 kg of milk) have increased by approximately 48 and 22%, respectively (Figure 1). These changes over time reflect changes in diets, cows, and analytical and statistical techniques.

During this period, data on the concentrations of several minerals in milk were published, but studies did not examine how diet affected milk composition. The only trace mineral that received attention during this time was Co (Neal and Ahmann, 1937). This study introduced some principles and concepts that have

guided trace mineral research through the years. Cows were on treatments for more than 1 yr (responses to trace minerals require very long experiments). The authors took a vast array of measurements and commented on the extreme difficulty of quantifying trace minerals and how the lack of analytical sensitivity can be misleading. They specifically stated that the amount of Co needed was so low that it could not be measured accurately and that biological response should be used to assess adequacy. Last, and perhaps most important, they evaluated multiple minerals (Cu, Fe, and Co) and found interactions among them, and they emphasized the importance of mineral interactions: “The specific

symptoms that may be expected with a deficiency, or excess, of any element or compound are dependent on the ratio of that element or compound to all others in the ration" (Neal and Ahmann, 1937).

1946–1971

Research on mineral nutrition of dairy cattle accelerated during this time, primarily led by the development of flame spectroscopy, which simplified mineral assays and greatly increased analytical sensitivity. The effect of improved analytical techniques on research is clearly demonstrated by the study of milk fever. At the time of the first major review on milk fever (Hibbs, 1950), hypocalcemia was considered just one of many different theories explaining the etiology of milk fever. In that review, it was stated that diet may be a factor, but current understanding did not favor that concept. However, when assaying blood for Ca became routine with the advent of flame spectroscopy, hypocalcemia was quickly identified as the cause of clinical signs of milk fever and led to numerous studies on the effects of Ca, P, and vitamin D. During this time, the low dietary Ca approach was developed as a way to control milk fever. It had some success, but hypocalcemia remained a problem. A few studies (Visek et al., 1953) using radioactive Ca were conducted to better quantify absorption and body distribution of Ca, but little progress was made in improving the accuracy of our Ca requirement estimates. Other than research on milk fever, P nutrition did not receive much attention during

this time. The value of ruminal buffers (e.g., sodium bicarbonate) to reduce milk fat depression in low-forage diets was first explored during this period (Emery and Brown, 1961). Results were promising enough that over the following decades this became an extensively researched area. Hypomagnesemia was suggested to be the primary cause of signs associated with grass tetany, and of practical importance the antagonism of dietary K on serum Mg was shown (Kunkel et al., 1953).

Publications on trace mineral nutrition became more common during this time, which resulted in a trace mineral symposium at the 1969 American Dairy Science Association national meeting. Review papers on Co, Cu, Fe, Mn, Se, I, and Zn were subsequently published in the journal (Ammerman, 1970; Hemken, 1970; Hogue, 1970; Miller, 1970; Thomas, 1970). Information on some trace minerals (e.g., Se) was rudimentary at best; however, some broad foundations regarding trace mineral nutrition were formed and are still relevant today. Several studies were conducted to determine whether trace mineral supply altered the mineral composition of milk. One objective was to determine whether we could improve the nutritional value of milk (e.g., increase I concentration to reduce deficiencies in humans), and another objective was to prevent detrimental effects of excess trace minerals. For many years it was known that increased concentrations of Cu in milk increased the risk of developing oxidized flavor in milk. Studies during this period showed that dietary Cu influenced the Cu concentration in milk (Dunkley et al., 1968). Because the inclusion rate for supplemental

Figure 1. Progression of requirements (NRC, 1945, 1950, 1956, 1966, 1971, 1978, 1989, 2001) for total dietary Ca and P. Requirements were calculated for a 625-kg cow producing 32 kg of milk with 3.5% fat. For 2001, the absorption coefficient for Ca and P was set at 0.55 and 0.70, respectively. Color version available online.

Cu was high in that study (~80 mg/kg), results were not extremely practical, but an often overlooked result from that study was that feeding very high concentrations of Cu did not alter plasma Cu concentrations. This was among the first studies to show that plasma concentrations of many trace minerals do not reflect supply and are an unreliable or insensitive measure of trace mineral status. Although this has been known for decades, plasma or serum concentrations of trace minerals are still often measured in trace mineral experiments. The need for biomarkers of trace mineral status other than deficiency signs or production measures was often expressed. Proposed status measures included mineral concentrations in blood, milk, hair, and tissues and activity of certain enzymes. By 1970, liver Cu concentration was identified as the most sensitive marker for Cu status, and it remains the gold standard today.

Differences in bioavailability among sources of trace minerals were discussed, but methods for measuring availability were lacking; this still remains an issue for many trace minerals. One of the most important contributions made during this time is the clear demonstration of interactions among minerals and that some of these interactions are unique to ruminants. An antagonist relationship between Mo and Cu in ruminants was suggested as early as 1945 (Dick and Bull, 1945), and in 1964 (Vanderveen and Keener, 1964) the effects of excess Mo and S on liver Cu concentrations were clearly demonstrated in dairy cows. Because of the practical importance of this relationship, efforts to quantify this antagonism continue today. This antagonism is unique to ruminants and raised questions regarding the use of rodent models for mineral metabolism in cows. Antagonistic effects of Ca and P on Mn and of Zn on Cu were demonstrated.

Experiments designed to quantify requirements for Cu, I, Mn, and Zn were conducted during this time. However, advancements in developing definitive requirements were slow, mostly because of inadequate knowledge regarding proper response variables. During this period, the value of dietary Se to dairy cattle was demonstrated (Maplesden and Loosli, 1960). Selenium would become one of the most, if not the most, researched trace mineral for dairy cattle, and that research would lead to a major change in the way we evaluated trace mineral adequacy (discussed later). The mineral research conducted during this period culminated in the first major change in NRC mineral requirements. Requirements (NRC, 1971)—or, more correctly, allowances—were established for all macro and trace minerals that were deemed essential. For the first time, the publication included maximum tolerable concentrations for a few minerals.

1972–1989

Formulating diets to meet mineral requirements expanded during this period because of research that better defined mineral requirements, widespread analysis of feeds for minerals (due in large part to increased use of flame spectroscopy), and improvement in computers. Health outcomes were increasingly used in research designed to evaluate mineral requirements.

By this time, hypocalcemia was known to be the cause of clinical signs associated with milk fever, and major research efforts were underway to understand Ca and P metabolism in dry and lactating cows. A review by Horst (1986) outlined the current state of knowledge on Ca and P homeostasis and discussed the involvement of vitamin D in great detail. Over the years since that review was published, additional details have been added to our understanding of Ca, P, and vitamin D metabolism in dairy cows, but otherwise the review has stood the test of time. Research continued on dietary means to reduce clinical milk fever, and the Ca-deficient diet approach showed promise (Goings et al., 1974). However, a different approach to mitigating milk fever started to be developed during this time and would arguably become the predominant milk fever control method. Inducing metabolic acidosis via feeding strong anions was known to increase urinary excretion of Ca caused by increased mobilization from the bone and enhanced Ca absorption from the gut (Horst and Jorgensen, 1974). Norwegian scientists discovered that cows fed AIV silage (grass silage treated with sulfuric and hydrochloric acid) had less milk fever than cows fed other types of forages (Ender et al., 1971). This was followed by a study by Block (1984) in which cows were fed a control diet or a diet with excess (relative to K and Na) S and Cl (i.e., a negative anion-cation balance). No milk fever was observed in cows fed anionic diet, whereas incidence in control cows was 47%. This paper was followed by numerous studies that determined the optimal degree of acidification, determined requirements for other minerals when anionic diets were fed, compared different sources of anions, and provided other data that allowed the development of effective and practical diets based on the negative anion difference principle. Eventually, concentrations of dietary K and Mg rather than Ca were identified as major factors affecting prevalence of milk fever. The negative anion approach has had widespread field acceptance and has reduced the prevalence of clinical milk fever in dairy cows.

With the advent of the personal computer, software was being developed to formulate diets, including meeting requirements for many macrominerals (Stallings et

al., 1985). Rather than supplying a specific amount of mineral in a balanced diet, free choice supply of minerals was widely recommended based on the assumption that cows had "nutritional wisdom" and would self-select the minerals they needed in approximately the correct amounts. Although this nutritional lore is still espoused by some today, 2 studies conducted during this period showed that cows will not balance their own diet when given mineral choices (Coppock et al., 1972; Muller et al., 1977).

Ruminal buffers, mostly sodium bicarbonate, potassium carbonate, and magnesium oxide, received significant research attention during this time (see review by Erdman, 1988). This review was among the first to quantify the relationship between dietary fiber supply, amount of grain feeding, and buffer requirements. This review and the extensive primary literature published on buffers, ranging from more fundamental studies to very applied trials, were followed by widespread adoption of buffer supplementation of diets for lactating dairy cows. The primary response variable was milk fat concentration and yield, but some studies included measures of acid-base balance in the cow and ruminal fermentation. The interest in buffers also led to more research on requirements of electrolytes and interactions among electrolytes. Potassium requirements and the effect heat stress had on those requirements were quantified (Dennis and Hemken, 1978; Schneider et al., 1986), and attempts were made to quantify interactions among Na, K, Mg, and other minerals. These attempts were largely unsuccessful because statistical analysis and computing power were not advanced enough to handle the multifactor experiments that were required. Sulfur requirements of lactating cows were quantified (Bouchard and Conrad, 1973), and the value determined in 1979 (0.18% of diet DM) is almost unchanged (0.20%) in NRC (2001). The effects of excess S were also described (Kandylis, 1984).

The major advances made in trace mineral research during this period were (1) greatly expanded knowledge regarding the metabolism, functions, and requirements of Se; (2) use of health outcomes other than deficiency diseases to establish requirements; and (3) evaluation of organic sources of trace minerals (e.g., chelates). White muscle disease had been established as a manifestation of Se and vitamin E deficiency, and some data suggested a link between Se and retained placenta (Trinder et al., 1969). The link was clearly established in 1976 (Julien et al., 1976). This research and other studies published in the journal and elsewhere were pivotal in obtaining US Food and Drug Administration approval to add supplemental inorganic Se to diets of dairy cows in 1979 at the rate of 0.1 mg/kg of diet DM (which was increased to 0.3 mg/kg of diet DM in

1987). More papers appeared in the journal on Se than any other trace mineral during this time. In addition to studies on retained placenta, objectives of the research included effects of diet on Se concentrations in meat and milk, factors affecting Se absorption, effect of Se on reproductive efficiency, transfer of Se from dam to fetus, and effects of Se on calf health.

A study that had a wide-ranging effect on trace mineral (and vitamin) research and requirements found that Se and vitamin E reduced the severity and prevalence of clinical mastitis (Smith et al., 1984). Because mastitis was a major health problem, results of this study were rapidly adopted by dairy nutritionists to improve milk quality and animal welfare. More important, however, this study showed that health outcomes can be used to quantify requirements and led to studies on the effects of dietary Cu, Zn, vitamin A, and β -carotene on mastitis. Results from studies measuring mastitis response to supplemental trace nutrients would be used to establish requirements for Cu, Zn, vitamin E, and vitamin A by future NRC committees.

Studies had been published evaluating different sources of supplemental trace minerals such as copper chloride versus copper sulfate; however, in 1986 the first paper evaluating organic trace minerals appeared in the journal (Kincaid et al., 1986). This paper showed that organic Cu was less affected by antagonists than Cu from copper sulfate. This would lead to studies evaluating source by antagonist interactions. Numerous studies evaluating effects of organic trace minerals on mineral status, health, and mineral excretion would follow. Over time, the use of organic trace minerals in dairy diets would be commonplace. These types of studies clearly demonstrated the need to uncover sensitive biomarkers of mineral status. Liver concentration was a good status indicator for some minerals, but liver biopsies are invasive and not amenable to widespread application. Using clinical responses (e.g., mastitis) to titrate requirements or compare biopotency of different sources was too insensitive and required very large and cost-prohibitive experiments. Activity of glutathione peroxidase in blood was used as a status indicator for Se, but no easily applied marker existed for Cu, Mn, and Zn. Even today, trace mineral research is hindered by the lack of good biomarkers for dairy cows.

Discovering and quantifying relationships between minerals was a major research thrust (see reviews by (Jacobson et al., 1972; Miller, 1975, 1981), and studies evaluating effects of mineral nutrition on health and reproduction rather than milk production were becoming common (see reviews by Hidirolou, 1979; Hurley and Doane, 1989). Advances in mineral nutrition during this time were incorporated into the sixth revised edition of the NRC requirements (NRC, 1989), and several

changes were made from the version published in 1971. Requirements for Ca and P continued to increase (Figure 1), K and especially Mg requirements were increased substantially, the Zn requirement doubled (from 20 to 40 mg/kg of diet DM), and the Se requirement tripled (from 0.1 to 0.3 mg/kg of diet DM).

1990–2001

Much of the mineral research published during this time was more in line with fine-tuning mineral requirements. Although no real breakthroughs with respect to mineral nutrition occurred in this time frame, applied mineral nutrition changed markedly with the publication of the seventh revised edition of the NRC requirements (NRC, 2001).

Research continued on the use of negative DCAD to prevent hypocalcemia. The mode of action was better understood (Block, 1994; Goff et al., 1995), and optimal supplementation strategies for macromineral with DCAD diets were developed. Phosphorus nutrition was extensively researched during this period because of environmental issues. Phosphorus from manure runoff from agricultural animal units, including dairy farms, was identified as a major pollutant of surface waters and a cause of eutrophication. A series of simple yet highly impactful studies led by Larry Satter clearly determined how much P was needed by dairy cows and that overfeeding P had no benefit to the cow but significantly increased P in manure (e.g., Wu and Satter, 2000). These studies had adequate statistical power and lasted long enough (in some studies cows were on treatments for more than 2 yr) to produce unequivocal results and likely convinced many dairy nutritionists to re-evaluate their P supplementation strategies and reduce the degree of overfeeding. These studies also added environmental impact to the list of response variables when conducting mineral nutrition research.

The use of Mg as a ruminal buffer and concerns over adequate tissue supply of Mg led to increased research on Mg. The high concentration of K in some haycrop forages (often caused by excess application of manure) was recognized as a major factor reducing bioavailability of dietary Mg (Schonewille et al., 1999). Diets with negative DCAD were beneficial to dry cows, but some research was starting to suggest that positive DCAD diets were beneficial to lactating cows (Sanchez et al., 1994).

Source of dietary Cu and Zn (mostly organic vs. inorganic sources) did not have great effects on most response measures that were used in dairy cattle studies, whereas source of Se (selenized yeast vs. inorganic Se) affected blood, milk, and tissue concentrations of Se (Knowles et al., 1999). The difference in response

between minerals reflected the differences in the chemical form of the trace minerals. Both supplemental Cu and Se were shown to enhance neutrophil function (Hogan et al., 1990; Xin et al., 1991), and these studies led to more studies that used immune function as a response variable when assessing mineral nutrition of cows. Breed was shown to significantly affect metabolism of Cu (Du et al., 1996). This study showed that Jersey cattle accumulate liver Cu more efficiently than do Holsteins, which could increase the risk of Cu toxicity by Jersey cows. In addition, it raised the question of whether results on mineral studies using Holsteins could be extrapolated without concern to Jerseys.

The seventh revised edition of the NRC guidelines (NRC, 2001) incorporated the data generated during this period and for the first time developed factorial requirements for almost all minerals (exceptions were Co, I, S, and Se). In addition to factorial requirements, feed-specific (especially for minerals supplements) absorption coefficients were used to estimate supply of available, not total, minerals. For example, a diet with a high concentration of alfalfa (which has a low availability coefficient for Ca) would require a higher concentration of Ca to meet a cow's requirement than a diet with a high concentration of corn silage that included calcium carbonate. This approach incorporated an important source of variation (i.e., bioavailability of mineral), but for average diets it did not change requirements very much with the exception of an approximately 20% increase in Zn requirement and a 65% decrease in Mn requirement.

2001–2017 and Beyond

In 2009, the US Food and Drug Administration approved the supplementation of Cr (as Cr propionate) to dairy cow diets. This was the first new trace mineral for dairy cow diets since Se was approved in 1979. A review published by NRC (1997) identified major benefits and risks of Cr supplementation, but several follow-up papers published in the journal (e.g., McNamara and Valdez, 2005; Lloyd et al., 2010) provided essential data regarding the efficacy and safety of Cr supplementation.

Molecular techniques started being used to evaluate effects of mineral nutrition on cows during this time, and increased availability of inductively coupled plasma MS greatly increased the analytical sensitivity for measuring many trace minerals in biological samples. Expression of specific genes and proteins is being evaluated as a potential biomarker for mineral adequacy, but results have been equivocal (Hansen et al., 2010; Sinclair et al., 2013). Basic information will be required so that target genes and proteins can be identified, and

this likely will be an active area of research in mineral nutrition. Source of trace minerals was shown to affect the fecal microbiome of cows (Faulkner et al., 2017) in a way that might help explain some clinical responses that have been observed when different sources of zinc are fed. Changes in ruminal and intestinal microbiomes could have substantial implications for digestion and immune function, and studies in this area are likely to continue.

Several studies were conducted to determine absorption of minerals and factors affecting absorption. For precision feeding of minerals to be accomplished, these data are needed. The effect of erroneous estimates of mineral absorption is illustrated by studies (Weiss and Socha, 2005; Hansen et al., 2006) showing that the NRC (2001) requirement for Mn was substantially underestimated, probably because Mn absorption was overestimated. Whereas effects of inadequate mineral intake have been known for the past 100 yr, detrimental effects of overfeeding specific minerals are still being uncovered (NRC, 2005). Overfeeding minerals can cause adverse animal responses, reduction in water quality, and negative effects on plant growth. Overfeeding P can affect water quality, and overfeeding Cu can affect animal health and may affect plant health when the manure is applied to crops. Similar issues occur for many minerals when they are overfed. A more holistic, whole-farm approach to mineral supplementation is needed. Bioavailability coefficients for more minerals and more feeds are needed, laboratory techniques for estimating bioavailability are needed, and known interactions and antagonism among minerals and other nutrients must be better quantified so that more accurate models can be developed to estimate mineral requirements (Hill et al., 2008) and improve whole-farm mineral balance (Arriaga et al., 2009).

Over the past 100 yr we have greatly increased our understanding of mineral nutrition of dairy cattle, especially with regards to requirements. However, because the cost of mineral experiments on large ruminants is high, basic information on mineral metabolism by cattle will likely always be limited. Increased application of molecular techniques and newer statistical methods should increase both our understanding of mineral metabolism of cows and our application of that information in developing healthy, productive, and efficient (both economically and environmentally) diets.

ADVANCES IN VITAMIN NUTRITION

A vitamin is an organic compound required in minute amounts that cannot be synthesized in adequate quantities to meet the animal's needs. Currently 14 compounds (choline is considered a vitamin in this

paper) are considered vitamins; however, not all those compounds are vitamins for all species. Healthy adult cattle synthesize adequate amounts of ascorbic acid (vitamin C); hence, it is not a vitamin for a cow but it is a vitamin for a human. Ruminants, because of bacterial synthesis, do not have strict dietary requirements for many B vitamins; hence, these vitamins received little attention from dairy nutritionists for most of the past 100 yr. With increasing production and changes in diet and management, metabolic and production responses are now being observed for some B vitamins. Only 10 vitamins have been studied in adequate detail to evaluate metabolic, clinical, and production responses by dairy cows (Table 2). Most early research on vitamins with dairy cows involved the nutritional value of milk. Milk was a major supplier of vitamins to the human diet, and vitamin concentrations in milk and factors affecting those concentrations were important research topics. Later came studies evaluating animal responses to vitamin nutrition. For several decades, the only response factor used when studying vitamin nutrition was prevention of classical deficiency signs. If deficiency signs were not observed, diets were assumed to be adequate in the vitamin. That view changed in the 1980s, and currently a wide array of responses are evaluated. Analytical difficulties, especially for many B vitamins, limited the rate of progress in understanding vitamin nutrition and to this day limits our ability to quantify requirements for some vitamins.

1917–1945

The first papers appearing in the journal that directly addressed vitamins discussed the vitamin content of milk. Dairy products were key to the discovery of vitamins, and an early paper (Lindquist, 1924) discussed the concentrations in dairy products of the 3 known vitamins (A, B, and C). Quantification methods were limited at that time; whole milk was listed as being “abundant” in vitamin B but having only a “relatively large amount” of vitamin C. Butter had a “very plentiful” concentration of vitamin A. Factors affecting vitamin concentrations in milk and dairy products were the primary research thrust into the 1930s. By then diet was shown to influence concentrations of vitamins A and D in milk, and effects of processing (e.g., pasteurization) on vitamin concentrations in milk were known. Publications evaluating the effects of vitamins on responses by dairy cattle started to appear in earnest in the 1930s. By then it was known that calves (and presumably cows) did not have a dietary requirement for vitamin C (Thurston et al., 1929). Vitamin D (e.g., sun-cured hay) was shown to affect requirements for Ca and P as measured in balance studies (Wallis et al., 1935). Metabolic

Table 2. Vitamins that have been studied adequately using dairy cows to evaluate metabolic, clinical, or productive responses

Vitamin	NRC requirement ¹	Brief overview of functions and responses
Fat-soluble vitamins		
Vitamin A	1945	Vision, gene regulation, cell development
β-Carotene ²		Vitamin A synthesis, lipid-soluble antioxidant
Vitamin D	1971	Ca and P metabolism, gene regulation, immune cell regulation
Vitamin E	1989	Lipid-soluble antioxidant, cell membrane stability, arachidonic acid metabolism
Vitamin K		Blood coagulation, bone formation
Water-soluble vitamins		
Ascorbic acid		Water-soluble antioxidant, collagen synthesis
Biotin		Cofactor for several enzymes (propionate, lipid, AA metabolism, gluconeogenesis), hoof health
Choline		Nerve function, cell membrane formation, cell signaling, lipid transport, methyl group metabolism
Folic acid		Methyl group, nucleic acid, and AA metabolism
Niacin		Carbohydrate, lipid, and AA metabolism as a component of NAD(H) and NADP(H); inhibits triglyceride synthesis; may be involved with inflammatory response
Vitamin B ₁₂		Methyl group metabolism, methionine synthesis, synthesis of succinyl-CoA (energy metabolism, hemoglobin synthesis)

¹Year that a definitive requirement was first expressed by the NRC.

²Not currently defined as a vitamin.

and functional relationships between vitamin D, Ca, and P are still being studied to this day. In 1938, Wallis (1938) unequivocally determined that adult dairy cows required vitamin D. Vitamin A (most of the early research actually involved β -carotene rather than vitamin A) was known to be required by preweaned calves, but it was not until 1940 that increasing supply of vitamin A via feeding hays with different β -carotene concentrations increased growth in dairy heifers (Ward et al., 1940), and in 1941, Moore (1941) produced vitamin A deficiency in adult dairy cows. That paper also established the value of measuring β -carotene concentrations in blood to estimate vitamin A status in cows. During this time, we learned that β -carotene concentrations in fresh forages were quite high but decreased rapidly when stored as hay and that silage usually had less β -carotene than fresh forage but more than hay. This knowledge was used to explain problems that occurred during winter feeding when cows did not have access to pasture. Today, the information on factors affecting β -carotene concentrations in forages is used to define requirements and explain response differences among studies. The last major finding that occurred during this time was the effect of diet on ruminal synthesis of B vitamins (Lardinois et al., 1944). Essentially, the study showed that feeding diets that stimulated rumen fermentation (i.e., adequate N when readily fermentable carbohydrates were fed) increased synthesis rate.

Although quantitative data on vitamin A were extremely limited, the first edition of the dairy NRC requirements (NRC, 1945) included requirements for vitamins A (given as milligrams of β -carotene) and D. Requirements were provided for growth (vitamins A and D), maintenance (vitamin A), and late gestation

(vitamin A). The NRC assumed that if adequate vitamin A was provided to maintain the cow, no additional vitamin A was needed for lactation. The vitamin A requirement for pregnancy (approximately the last 12 wk of gestation) was more than 50% greater than maintenance requirements; however, no justification was given for this difference. The vitamin A requirement was based on prevention of deficiency disease (as measured by eye abnormalities) but included a substantial (almost 4 $\times$) safety margin. Very little supplemental vitamin A was fed, and the requirement included β -carotene found in basal feedstuffs (essentially forages). Enough data had been generated to know that the concentration of β -carotene in forages was highly variable, and because forages were not routinely assayed, actual supply of β -carotene (i.e., vitamin A) was not known. This could explain the wide safety margin that was used. The NRC stated that vitamin D was required, but adequate data were not available to give a specific requirement.

1945–1971

During this period, research emphasis shifted from studying factors affecting vitamin concentrations of milk to studying vitamin metabolism and nutrition of cows. Vitamin A (and β -carotene) concentrations in milk and blood could be assayed using colorimetric methods, and studies were conducted to determine whether these concentrations could be used as status indicators. Serum concentrations of β -carotene were strongly correlated with β -carotene intake, whereas the relationship was weaker for vitamin A. Concentrations of both vitamin A and β -carotene in plasma were found to decrease markedly as cows approached parturition

(Sutton et al., 1945). This was rediscovered more than 4 decades later, which led to the practice of extra vitamin supplementation during the prepartum period. Vitamin status and supplementation were shown to affect health, production, and reproductive outcomes, and these rather than prevention of classical deficiency disease were being used to establish requirements. Based on prevalence of diarrhea and mortality, vitamin A requirements for newborn calves was set at 10,000 IU/d (Hansen et al., 1946). The β -carotene requirement for efficient reproduction of cows was set at 0.2 mg/kg of BW or 79 IU of vitamin A/kg of BW (Ronning et al., 1959). That experiment was essentially the basis for the NRC vitamin A requirement until 2001.

Vitamin D research was limited to its effects on milk fever, and the studies concentrated on using massive (>1,000,000 IU/d and in some studies >20,000,000 IU/d) doses of vitamin D (see review by Hibbs, 1950). Cows fed several million units per day for 3 to 8 d prepartum had less milk fever, but practical application of that protocol was limited because timing of supplementation was critical. Research on vitamin D was likely constrained by analytical methodology. The rat bioassay was the only method available to assay concentrations of vitamin D in blood and feeds. No vitamin D requirement had been established by 1971; however, the NRC (1971) recommended an intake of approximately 3,000 IU/d for dry cows and 5,400 IU/d for lactating cows. Sun-cured hay remained the primary source of dietary vitamin D.

An attempt to establish vitamin E requirements based on reproduction was made (Gullickson et al., 1949). Diets that did not support reproduction of rats (the only assay available for vitamin E was a rat bioassay) did not affect reproductive efficiency of cows; however, almost 50% of the cows died after more than 1 yr on a diet severely deficient in vitamin E. Up to this point, the only benefit of feeding additional vitamin E was to prevent oxidized flavor in milk (Dunkley et al., 1967), a practice still used occasionally today, and hence no vitamin E requirement (or even recommendation) was established when the fourth revised edition of the NRC guidelines (NRC, 1971) was published.

Because of ruminal synthesis and concentrations found in basal feeds, B vitamins received little attention during this time. Daily oral supplementation of a B vitamin cocktail (including 1.2 g/d of niacin) did not reduce concentrations of blood ketones or prevalence of ketosis (Shaw, 1946). Research in the following decade would show that higher doses of niacin can reduce blood ketones in some situations. By this time, Co deficiency was known to be alleviated by vitamin B₁₂ administration, and requirements for Co (i.e., 0.1 mg/kg of diet DM) rather than B₁₂ were established. Factors affecting

concentrations of B₁₂ in liver and blood were evaluated as status indicators without success, partly because some of the microbiological methods used to assay B₁₂ were difficult and lacked specificity.

1972–1989

Pharmacological doses of niacin were being evaluated to prevent and treat ketosis (Schultz, 1971), but otherwise almost no research on B vitamin nutrition in dairy cows was published in the journal during this time. Choline was shown to be extensively degraded in the rumen (Atkins et al., 1988), but later studies showed that marked increases in milk yield often occurred if choline was protected from degradation (Erdman and Sharma, 1991). Advances in analytical methods for fat-soluble vitamins were a likely reason for the substantial amount of research conducted on those vitamins during this period. Vitamins A and E and β -carotene could be assayed routinely using HPLC, and binding assay and chromatographic methods for metabolites of vitamin D were available. Another reason for the increased interest in fat-soluble vitamin nutrition was the paradigm shift that was occurring on dairy farms. Pasture (which is rich in β -carotene and tocopherol) was largely replaced with silage and hay (which can be low in both of those nutrients). This change also reduced the amount of sun exposure cows received. Cows fed diets based on stored forages and housed inside were more likely to be deficient in vitamin D, vitamin E, and β -carotene, which increased the likelihood of observing positive responses to supplementation.

The amount of vitamin A needed to maintain proper cerebrospinal fluid pressure (a longtime indicator of vitamin A status) in calves was re-evaluated using different analytical and statistical techniques (Eaton et al., 1972). This re-evaluation plus data published later was a primary reason why vitamin A requirements were increased in the seventh revised dairy requirements (NRC, 2001). A major change in vitamin nutrition research occurred in the early 1980s, when immune function and mastitis severity and prevalence became response variables in vitamin experiments. Cows with low concentrations of vitamin A and β -carotene in blood (Chew et al., 1982) and cows not supplemented with vitamin E (Smith et al., 1984) had more mastitis than cows with better vitamin A (or β -carotene) or vitamin E status. Supplemental vitamin A, β -carotene, or vitamin E were later shown to enhance immune cell function (neutrophil or lymphocytes), which likely was a reason for the clinical responses that were observed. Additional research defined blood concentrations of those vitamins that were considered adequate (i.e., status indicators). The studies on vitamin A (conducted

Figure 2. Progression of requirements (NRC, 1945, 1950, 1956, 1966, 1971, 1978, 1989, 2001) for vitamins (Vit) A, D, and E. Requirements were calculated for a 625-kg cow (milk yield was not considered in establishing requirements). For all years other than 2001, requirements are for total diet (basal plus supplemental), but for 2001, requirements are for supplemental vitamins. Prior to 1971 the vitamin A requirement for late-gestating cows (last 60 d) differed from the requirement for lactating cows. When only β -carotene requirements were presented they were converted to vitamin A (1 mg = 400 IU). Color version available online.

mostly at Washington State University) and vitamin E (mostly at The Ohio State University) had a direct effect on applied nutrition and were at the forefront of studies evaluating effects of nutrition on immune function. Vitamin D, which up to this point was studied almost exclusively relative to its effects on Ca and P metabolism, was shown to influence immune function (Reinhardt and Hustmyer, 1987).

Reproductive efficiency and reproductive disorders were shown to be affected by fat-soluble vitamins. Vitamin E supplementation of stored forage-based diets reduced incidence of retained fetal membranes (Harrison et al., 1984). Bovine corpora lutea have high concentrations of β -carotene, which has led to a substantial number of studies evaluating its effects on reproduction (see review by Hurley and Doane, 1989). Although enough studies show positive effects to indicate a relationship, often studies lack adequate statistical power to make definitive conclusions. Vitamin D supplementation may enhance some measures of reproductive efficiency (Ward et al., 1971), but because of inadequate statistical power, vitamin requirements for reproduction remain poorly defined.

Although substantial progress was made in vitamin nutrition of dairy cows during this period, the sixth revised edition of the dairy requirements (NRC, 1989) did not make marked changes in vitamin requirements (Figure 2). Vitamin A requirements did not change. A vitamin E allowance was presented for the first time, but it was for total dietary vitamin E and it was so

low that almost all unsupplemented diets would be considered adequate. The vitamin D requirement was increased substantially based on the amount needed to maintain blood Ca concentrations in late-gestation cows.

1990–2001

Immune cell function was a primary response factor for research on vitamins A, D, and E during this time, and the research generally supported and expanded on previous results (i.e., that adequate vitamins A, D, and E enhanced immune cell function). A major “new” discovery (actually a rediscovery and expansion of results from Sutton et al., 1945) was the dramatic decrease in plasma concentrations of β -carotene, retinol, and tocopherol that occurred in the peripartum period (Goff and Stabel, 1990; Weiss et al., 1990). By this time, peripartum immunosuppression was known to occur, and the decrease in fat-soluble vitamins mirrored the normal decrease in immune function that occurred around parturition. Because of the connection between immune function and vitamins A and E, an obvious hypothesis was that the decrease in fat-soluble vitamin status was partially responsible for immunosuppression. This hypothesis was tested, and increased supplementation of vitamin E during the prefresh period maintained blood concentrations of tocopherol, prevented the depression in neutrophil function, and reduced mastitis in fresh cows (Hogan et al., 1992; Weiss et al., 1997).

The metabolism and nutrition of water-soluble vitamins, especially niacin, biotin, and choline, received substantial attention during this time. Outcomes related to health and production were used to evaluate water-soluble vitamins. Some, but not all, studies reported increased milk and milk component yields when cows were supplemented with niacin. Effect of stage of lactation, type and amount of dietary fat, and concentrations of starch and protein were evaluated in an attempt to determine when a response to niacin supplementation was likely (e.g., Driver et al., 1990; Drackley et al., 1998; Minor et al., 1998). These types of studies have not definitively identified situations in which responses to supplementation are likely. Biotin supplementation was shown to reduce hoof lesions, decrease lameness, and increase milk yields (the milk yield response was not in response to improved hoof health) in dairy cows (Hedges et al., 2001; Zimmerly and Weiss, 2001).

The largely positive responses observed when vitamins A and E were supplemented led the NRC (2001) to greatly increase the vitamin A requirement for adult cattle and establish a requirement (not an allowance) for vitamin E (Figure 2). In addition, requirements for vitamins A, D, and E were set for supplemental vitamins, not total vitamins. Because of the variation in response, no requirement was established for β -carotene or any water-soluble vitamin.

2001–2017 and Beyond

Metabolism of B vitamins by dairy cows, mostly from Christiane Girard's group at Agriculture and Agri-Food Canada, led vitamin research during the first 17 yr of the 21st century. That group showed that essentially all the supplemental niacin fed disappeared before the duodenum and that substantial amounts of other B vitamins also disappeared (Santschi et al., 2005). These findings could partially explain the variable responses observed when niacin was supplemented. However production responses to rumen-protected niacin have been as variable as responses to niacin. Additional studies by that group evaluated factors (e.g., type of forage, starch concentrations, and protein concentrations) that may affect ruminal synthesis of B vitamins (e.g., Schwab et al., 2006). The increased interest in B vitamin nutrition of dairy cows is a function of their ever-increasing milk yields. However, production responses to supplemental B vitamins are still inconsistent even with high-producing cows. Clearly, additional studies are needed to clarify factors affecting response to supplemental B vitamins.

Antioxidant vitamins (vitamin E, β -carotene, and ascorbic acid) and immune function and health continued to be studied. The preponderance of data support a link between improved antioxidant status and improved health, especially during the peripartum period (e.g., LeBlanc et al., 2004). The naturally lower antioxidant status that occurs around calving is likely a reason why supplementation of antioxidants is often beneficial to these cows. In a pioneering study using mastectomized cows, colostrum synthesis was shown to be a major reason why plasma retinol concentrations decreased at calving; however, the decrease in β -carotene and tocopherol was caused by more than just colostralgenesis (Goff et al., 2002). Excess consumption (3–8 times the requirement of NRC, 2001) of vitamins A or E, at least during the dry period, was shown to be detrimental (Puvogel et al., 2005; Bouwstra et al., 2010). Research, mostly with rodent models, is identifying new functions of vitamins, especially fat-soluble vitamins. These functions include regulation of gene expression and cellular function. Research on vitamin D has expanded far beyond Ca metabolism and will likely receive increased interest. As with minerals, progress in vitamin nutrition of dairy cows is restrained by the lack of good biomarkers. Current response variables, such as disease prevalence, immune cell function, and blood and tissue concentrations of the vitamin, lack sensitivity or are poorly correlated with status.

CONCLUSIONS

The *Journal of Dairy Science* has reported many of the major advances made in mineral and vitamin nutrition of dairy cows. Initial studies concentrated on mineral balance and prevention of classical deficiency diseases. The nutritional value of milk with respect to minerals and vitamins and how the cow's diet influenced concentrations of those nutrients in milk was also a major research thrust when the journal was in its infancy. As analytical methods for measuring minerals and vitamins improved, the amount of research increased, as did its complexity. Research evolved into determining requirements and optimal supplementation strategies for minerals and vitamins to promote good health and reduce diseases. Now the effects of minerals and vitamins on cell regulation, immune function, and gene expression are being studied actively. Discovery of unknown functions and responses to vitamins and minerals will open up new fields of study, which should eventually result in improved cow health and productivity and enhanced nutritional value of milk and other dairy products.

REFERENCES

- Ammerman, C. B. 1970. Recent developments in cobalt and copper in ruminant nutrition: A review. *J. Dairy Sci.* 53:1097–1107.
- Arriaga, H., M. Pinto, S. Calsamiglia, and P. Merino. 2009. Nutritional and management strategies on nitrogen and phosphorus use efficiency of lactating dairy cattle on commercial farms: An environmental perspective. *J. Dairy Sci.* 92:204–215.
- Atkins, K. B., R. A. Erdman, and J. H. Vandersall. 1988. Dietary choline effects on milk yield and duodenal choline flow in dairy cattle. *J. Dairy Sci.* 71:109–116.
- Bechdel, S. I., R. A. Dutcher, and H. H. Tucker. 1928a. The deposition of minerals in the bones of calves fed rachitic and antirachitic rations. *PA Agric. Exp. Sta. Bul.* 230.
- Bechdel, S. I., H. E. Honeywell, R. A. Dutcher, and M. H. Knutsen. 1928b. Synthesis of vitamin B in the rumen of the cow. *J. Biol. Chem.* 80:231.
- Block, E. 1984. Manipulating dietary anions and cations for prepartum dairy cows to reduce incidence of milk fever. *J. Dairy Sci.* 67:2939–2948.
- Block, E. 1994. Manipulation of dietary cation-anion difference on nutritionally related production diseases, productivity, and metabolic responses of dairy cows. *J. Dairy Sci.* 77:1437–1450.
- Bouchard, R., and H. R. Conrad. 1973. Sulfur requirement of lactating dairy cows. I. Sulfur balance and dietary supplementation. *J. Dairy Sci.* 56:1276–1282.
- Bouwstra, R. J., M. Nielen, J. A. Stegeman, P. Dobbelaar, J. R. Newbold, E. H. J. M. Jansen, and T. van Werven. 2010. Vitamin E supplementation during the dry period in dairy cattle. Part I: Adverse effect on incidence of mastitis postpartum in a double-blind randomized field trial. *J. Dairy Sci.* 93:5684–5695.
- Chew, B. P., L. L. Hollen, J. K. Hillers, and M. L. Herlugsen. 1982. Relationship between vitamin A and β -carotene in blood plasma and milk and mastitis in Holsteins. *J. Dairy Sci.* 65:2111–2118.
- Coppock, C. E., R. W. Everett, and W. G. Merrill. 1972. Effect of ration on free choice consumption of calcium-phosphorus supplements by dairy cattle. *J. Dairy Sci.* 55:245–256.
- Dennis, R. J., and R. W. Hemken. 1978. Potassium requirements of dairy cows in early and midlactation. *J. Dairy Sci.* 61:757–761.
- Dick, A. T. 1953. The control of copper storage in the liver of sheep by inorganic sulphate and molybdenum. *Aust. Vet. J.* 29:233–239.
- Dick, A. T., and L. B. Bull. 1945. Some preliminary observations on the effect of molybdenum on copper metabolism in herbivorous animals. *Aust. Vet. J.* 21:70–72.
- Drackley, J. K., D. W. LaCount, J. P. Elliott, T. H. Klusmeyer, T. R. Overton, J. H. Clark, and S. A. Blum. 1998. Supplemental fat and nicotinic acid for Holstein cows during an entire lactation. *J. Dairy Sci.* 81:201–214.
- Draize, J. H., and O. A. Beath. 1935. Observations on the pathology of blind staggers and alkali disease. *J. Am. Vet. Med. Assoc.* 39:753–763.
- Driver, L. S., R. R. Grummer, and L. H. Schultz. 1990. Effects of feeding heat-treated soybeans and niacin to high producing cows in early lactation. *J. Dairy Sci.* 73:463–469.
- Du, Z., R. W. Hemken, and R. J. Harmon. 1996. Copper metabolism of Holstein and Jersey cows and heifers fed diets high in cupric sulfate or copper proteinate. *J. Dairy Sci.* 79:1873–1880.
- Dunkley, W. L., A. A. Franke, J. Robb, and M. Ronning. 1968. Influence of dietary copper and ethylenediaminetetraacetate on copper concentration and oxidative stability of milk. *J. Dairy Sci.* 51:863–866.
- Dunkley, W. L., M. Ronning, A. A. Franke, and J. Robb. 1967. Supplementing rations with tocopherol and ethoxyquin to increase oxidative stability of milk. *J. Dairy Sci.* 50:492–499.
- Eaton, H. D., J. J. E. Rousseau, J. R. C. Hall, H. I. Frier, and J. J. Lucas. 1972. Reevaluation of the minimum vitamin A requirement of Holstein male calves based upon elevated cerebrospinal fluid pressure. *J. Dairy Sci.* 55:232–237.
- Emery, R. S., and L. D. Brown. 1961. Effect of feeding sodium and potassium bicarbonate on milk fat, rumen pH, and volatile fatty acid production. *J. Dairy Sci.* 44:1899–1902.
- Ender, F., I. W. Dishington, and A. Helgebostad. 1971. Calcium balance studies in dairy cows under experimental induction and prevention of hypocalcaemic paresis puerperalis. *Z. Tierphysiol. Tierernährg. Futtermittelk.* 28:233–256.
- Erdman, R. A. 1988. Dietary buffering requirements of the lactating dairy cow: A review. *J. Dairy Sci.* 71:3246–3266.
- Erdman, R. A., and B. K. Sharma. 1991. Effect of dietary rumen-protected choline in lactating dairy cows. *J. Dairy Sci.* 74:1641–1647.
- Faulkner, M. J., B. A. Wenner, L. M. Solden, and W. P. Weiss. 2017. Source of supplemental dietary copper, zinc, and manganese affects fecal microbial relative abundance in lactating dairy cows. *J. Dairy Sci.* 100:1037–1044.
- Forbes, E. B. 1919. The mineral metabolism of the milch cow. *J. Dairy Sci.* 2:9–18.
- Forbes, E. B., J. A. Schulz, C. H. Hunt, A. R. Winter, and R. F. Remler. 1922. The mineral metabolism of the milch cow. *J. Biol. Chem.* 52:281–315.
- Goff, J. P., K. Kimura, and R. L. Horst. 2002. Effect of mastectomy on milk fever, energy, and vitamins A, E, and β -carotene status at parturition. *J. Dairy Sci.* 85:1427–1436.
- Goff, J. P., T. A. Reinhardt, and R. L. Horst. 1995. Milk fever and dietary cation-anion balance effects on concentration of vitamin D receptor in tissue of periparturient dairy cows. *J. Dairy Sci.* 78:2388–2394.
- Goff, J. P., and J. R. Stabel. 1990. Decreased plasma retinol, α -tocopherol, and zinc concentration during the periparturient period: Effect of milk fever. *J. Dairy Sci.* 73:3195–3199.
- Goings, R. L., N. L. Jacobson, D. C. Beitz, E. T. Littledike, and K. D. Wiggers. 1974. Prevention of parturient paresis by a prepartum, calcium-deficient diet. *J. Dairy Sci.* 57:1184–1188.
- Gullickson, T. W., L. S. Palmer, W. L. Boyd, J. W. Nelson, F. C. Olson, C. E. Calverley, and P. D. Boyer. 1949. Vitamin E in the nutrition of cattle. I. Effect of feeding vitamin E poor rations on reproduction, health, milk production, and growth. *J. Dairy Sci.* 32:495–508.
- Hansen, R. G., P. H. Phillips, and I. W. Rupel. 1946. The effect of vitamin supplements upon survival of new-born calves. *J. Dairy Sci.* 29:761–766.
- Hansen, S. L., M. S. Ashwell, A. J. Moeser, R. S. Fry, M. D. Knutson, and J. W. Spears. 2010. High dietary iron reduces transporters involved in iron and manganese metabolism and increases intestinal permeability in calves. *J. Dairy Sci.* 93:656–665.
- Hansen, S. L., J. W. Spears, K. E. Lloyd, and C. S. Whisnant. 2006. Feeding a low manganese diet to heifers during gestation impairs fetal growth and development. *J. Dairy Sci.* 89:4305–4311.
- Harrison, J. H., D. D. Hancock, and H. R. Conrad. 1984. Vitamin E and selenium for reproduction of the dairy cow. *J. Dairy Sci.* 67:123–132.
- Hedges, J., R. W. Blowey, A. J. Packington, C. J. O. Callaghan, and L. E. Green. 2001. A longitudinal field trial of the effect of biotin on lameness in dairy cows. *J. Dairy Sci.* 84:1969–1975.
- Hemken, R. W. 1970. Iodine. *J. Dairy Sci.* 53:1138–1143.
- Hibbs, J. W. 1950. Milk fever (parturient paresis) in dairy cows; A review. *J. Dairy Sci.* 33:758–789.
- Hidiroglou, M. 1979. Trace element deficiencies and fertility in ruminants: A review. *J. Dairy Sci.* 62:1195–1206.
- Hill, S. R., K. F. Knowlton, E. Kebreab, J. France, and M. D. Hanigan. 2008. A model of phosphorus digestion and metabolism in the lactating dairy cow. *J. Dairy Sci.* 91:2021–2032.
- Hilton, J. H., S. M. Hauge, and J. W. Wilbur. 1935. The vitamin A activity of butter produced by cows fed alfalfa hay and soybean hay cut in different stages of maturity. *J. Dairy Sci.* 18:795–800.
- Hogan, J. S., K. L. Smith, W. P. Weiss, D. A. Todhunter, and W. L. Shockley. 1990. Relationships among vitamin E, selenium, and bovine blood neutrophils. *J. Dairy Sci.* 73:2372–2378.
- Hogan, J. S., W. P. Weiss, D. A. Todhunter, K. L. Smith, and P. S. Schoenberg. 1992. Bovine neutrophil responses to parenteral vitamin E. *J. Dairy Sci.* 75:399–405.
- Hogue, D. E. 1970. Selenium. *J. Dairy Sci.* 53:1135–1137.
- Horst, R. L. 1986. Regulation of calcium and phosphorus homeostasis in the dairy cow. *J. Dairy Sci.* 69:604–616.

- Horst, R. L., and N. A. Jorgensen. 1974. Effect of ammonium chloride on nitrogen and mineral balance in lactating and nonlactating goats. *J. Dairy Sci.* 57:683–688.
- Huffman, C. F., C. S. Robinson, C. W. Duncan, L. W. Lamb, and M. F. Mason. 1933. A study of the phosphorus requirement of dairy cattle. *J. Dairy Sci.* 16:203–223.
- Hurley, W. L., and R. M. Doane. 1989. Recent developments in the roles of vitamins and minerals in reproduction. *J. Dairy Sci.* 72:784–804.
- Jacobson, D. R., R. W. Hemken, F. S. Button, and R. H. Hatton. 1972. Mineral nutrition, calcium, phosphorus, magnesium, and potassium interrelationships. *J. Dairy Sci.* 55:935–944.
- Julien, W. E., H. R. Conrad, and A. L. Moxon. 1976. Selenium and vitamin E and incidence of retained placenta in parturient dairy cows. II. Prevention in commercial herds with prepartum treatment. *J. Dairy Sci.* 59:1960–1962.
- Kandylis, K. 1984. Toxicology of sulfur in ruminants. *J. Dairy Sci.* 67:2179–2187.
- Kincaid, R. L., R. M. Blauwikel, and J. D. Cronrath. 1986. Supplementation of copper as copper sulfate or copper proteinate for growing calves fed forages containing molybdenum. *J. Dairy Sci.* 69:160–163.
- Knowles, S. O., N. D. Grace, K. Wurms, and J. Lee. 1999. Significance of amount and form of dietary selenium on blood, milk, and casein selenium concentrations in grazing cows. *J. Dairy Sci.* 82:429–437.
- Kunkel, H. O., K. H. Burns, and B. J. Camp. 1953. A study of sheep fed high levels of potassium bicarbonate with particular reference to induced hypomagnesemia. *J. Anim. Sci.* 12:451–458.
- Lardinois, C. C., R. C. Mills, C. A. Elvehjem, and E. B. Hart. 1944. Rumen synthesis of the vitamin B complex as influenced by ration composition. *J. Dairy Sci.* 27:579–583.
- LeBlanc, S. J., T. H. Herdt, W. M. Seymour, T. F. Duffield, and K. E. Leslie. 2004. Peripartum serum vitamin E, retinol, and β -carotene in dairy cattle and their associations with disease. *J. Dairy Sci.* 87:609–619.
- Lindquist, H. G. 1924. Vitamines in dairy products. *J. Dairy Sci.* 7:294–305.
- Lloyd, K. E., V. Fellner, S. J. McLeod, R. S. Fry, K. Krafka, A. Lamptey, and J. W. Spears. 2010. Effects of supplementing dairy cows with chromium propionate on milk and tissue chromium concentrations. *J. Dairy Sci.* 93:4774–4780.
- Maplesden, D. C., and J. K. Loosli. 1960. Nutritional muscular dystrophy in calves. II. Addition of selenium and tocopherol to a basal, dystrophogenic diet containing cod-liver oil. *J. Dairy Sci.* 43:645–653.
- McNamara, J. P., and F. Valdez. 2005. Adipose tissue metabolism and production responses to calcium propionate and chromium propionate. *J. Dairy Sci.* 88:2498–2507.
- Meigs, E. B. 1923. The mineral requirements of dairy cows. *J. Dairy Sci.* 6:46–53.
- Miller, W. J. 1970. Zinc nutrition of cattle: A review. *J. Dairy Sci.* 53:1123–1135.
- Miller, W. J. 1975. New concepts and developments in metabolism and homeostasis of inorganic elements in dairy cattle: A review. *J. Dairy Sci.* 58:1549–1560.
- Miller, W. J. 1981. Mineral and vitamin nutrition of dairy cattle. *J. Dairy Sci.* 64:1196–1206.
- Minor, D. J., S. L. Trower, B. D. Strang, R. D. Shaver, and R. R. Grummer. 1998. Effects of nonfiber carbohydrate and niacin on periparturient metabolic status and lactation of dairy cows. *J. Dairy Sci.* 81:189–200.
- Moore, L. A. 1941. Some ocular changes and deficiency manifestations in mature cows fed a ration deficient in vitamin A. *J. Dairy Sci.* 24:894–902.
- Muller, L. D., L. V. Schaffer, L. C. Ham, and M. J. Owens. 1977. Cafeteria style free-choice mineral feeder for lactating dairy cows. *J. Dairy Sci.* 60:1574–1582.
- NRC (National Research Council). 1945. Recommended Nutrient Allowances for Domestic Animals. No. III. Recommended Nutrient Allowances for Dairy Cattle. NRC, Washington, DC.
- NRC (National Research Council). 1950. Recommended Nutrient Allowances for Dairy Cattle. 2nd rev. ed. NRC, Washington, DC.
- NRC (National Research Council). 1956. Nutrient Requirements of Dairy Cattle. 3rd rev. ed. Natl. Acad. Sci., Washington, DC.
- NRC (National Research Council). 1966. Nutrient Requirements of Dairy Cattle. 3rd rev. ed. Natl. Acad. Sci., Washington, DC.
- NRC (National Research Council). 1971. Nutrient Requirements of Dairy Cattle. 4th rev. ed. Natl. Acad. Sci., Washington, DC.
- NRC (National Research Council). 1978. Nutrient Requirements of Dairy Cattle. 5th rev. ed. Natl. Acad. Sci., Washington, DC.
- NRC (National Research Council). 1989. Nutrient Requirements of Dairy Cattle. 6th rev. ed. Natl. Acad. Sci., Washington, DC.
- NRC (National Research Council). 1997. The Role of Chromium in Animal Nutrition. Natl. Acad. Press, Washington, DC.
- NRC (National Research Council). 2001. Nutrient Requirements of Dairy Cattle. 7th rev. ed. Natl. Acad. Press, Washington, DC.
- NRC (National Research Council). 2005. Mineral Tolerance of Animals. 2nd rev. ed. Natl. Acad. Press, Washington, DC.
- Neal, W. M., and C. F. Ahmann. 1937. The essentiality of cobalt in bovine nutrition. *J. Dairy Sci.* 20:741–753.
- Puvogel, G., C. R. Baumrucker, H. Sauerwein, R. Ruhl, E. Ontsouka, H. M. Hammon, and J. W. Blum. 2005. Effects of an enhanced vitamin A intake during the dry period on retinoids, lactoferrin, IGF system, mammary gland epithelial cell apoptosis, and subsequent lactation in dairy cows. *J. Dairy Sci.* 88:1785–1800.
- Reinhardt, T. A., and F. G. Hustmyer. 1987. Role of vitamin D in the immune system. *J. Dairy Sci.* 70:952–962.
- Ronning, M., E. R. Berousek, A. H. Kuhlman, and W. D. Gallup. 1959. The carotene requirements for reproduction in Guernsey cattle. *J. Dairy Sci.* 36:52–56.
- Sanchez, W. K., D. K. Beede, and J. A. Cornell. 1994. Interactions of sodium, potassium, and chloride on lactation, acid-base status, and mineral concentrations. *J. Dairy Sci.* 77:1661–1675.
- Santschi, D. E., R. Berthiaume, J. J. Matte, A. F. Mustafa, and C. L. Girard. 2005. Fate of supplementary B-vitamins in the gastrointestinal tract of dairy cows. *J. Dairy Sci.* 88:2043–2054.
- Schneider, P. L., D. K. Beede, and C. J. Wilcox. 1986. Responses of lactating cows to dietary sodium source and quantity and potassium quantity during heat stress. *J. Dairy Sci.* 69:99–110.
- Schonewille, J. T., A. T. Van't Klooster, H. Wouterse, and A. C. Beynen. 1999. Effects of intrinsic potassium in artificially dried grass and supplemental potassium bicarbonate on apparent magnesium absorption in dry cows. *J. Dairy Sci.* 82:1824–1830.
- Schultz, L. H. 1971. Management and nutritional aspects of ketosis. *J. Dairy Sci.* 54:962–973.
- Schwab, E. C., C. G. Schwab, R. D. Shaver, C. L. Girard, and D. E. Putnam. 2006. Dietary forage and nonfiber carbohydrate contents influence B-vitamin intake, duodenal flow, and apparent ruminal synthesis in lactating dairy cows. *J. Dairy Sci.* 89:174–187.
- Semba, R. D. 2012. The discovery of the vitamins. *Int. J. Vitam. Nutr. Res.* 82:310–315.
- Shaw, J. C. 1946. Studies on ketosis in dairy cattle. VII. The efficacy of B vitamins and methionine in the treatment of ketosis. *J. Dairy Sci.* 29:131–139.
- Sinclair, L. A., K. J. Hart, D. Johnson, and A. M. Mackenzie. 2013. Effect of inorganic or organic copper fed without or with added sulfur and molybdenum on the performance, indicators of copper status, and hepatic mRNA in dairy cows. *J. Dairy Sci.* 96:4355–4367.
- Smith, K. L., J. H. Harrison, D. D. Hancock, D. A. Todhunter, and H. R. Conrad. 1984. Effect of vitamin E and selenium supplementation on incidence of clinical mastitis and duration of clinical symptoms. *J. Dairy Sci.* 67:1293–1300.
- Stallings, C. C., G. Kroll, J. C. Kelley, and M. L. McGilliard. 1985. A computer ration evaluation program for heifers, dry cows, and lactating cows. *J. Dairy Sci.* 68:1015–1019.
- Sutton, T. S., H. E. Kaeser, and P. A. Soldner. 1945. Changes in the level of vitamin A and carotene in the blood plasma of dairy cows associated with parturition and beginning lactation. *J. Dairy Sci.* 28:933–939.
- Thomas, J. W. 1970. Metabolism of iron and manganese. *J. Dairy Sci.* 53:1107–1123.

- Thurston, L. M., L. S. Palmer, and C. H. Eckles. 1929. Further studies of the role of vitamin C in the nutrition of calves. *J. Dairy Sci.* 12:394–404.
- Trinder, N., C. Woodhouse, and C. Renton. 1969. The effect of vitamin E and selenium on the incidence of retained placentae in dairy cows. *Vet. Rec.* 85:550–553.
- Vanderveen, J. B., and H. A. Keener. 1964. Effects of molybdenum and sulfate sulfur on metabolism of copper in dairy cattle. *J. Dairy Sci.* 47:1224–1230.
- Visek, W. J., R. A. Monroe, E. W. Swanson, and C. L. Comar. 1953. Calcium metabolism in dairy cows as studied with Ca^{45} . *J. Dairy Sci.* 36:373–384.
- Wallis, C. G., L. S. Palmer, and T. W. Gullickson. 1935. The relation of vitamin D to calcium and phosphorus retention in cattle as shown by balance trials. *J. Dairy Sci.* 18:213–228.
- Wallis, G. C. 1938. Some effects of a vitamin D deficiency on mature dairy cows. *J. Dairy Sci.* 21:315–333.
- Ward, G., G. B. Marion, C. W. Campbell, and J. R. Dunham. 1971. Influences of calcium intake and vitamin D supplementation on reproductive performance of dairy cows. *J. Dairy Sci.* 54:204–206.
- Ward, R. E., S. I. Bechdel, and N. B. Guerrant. 1940. Carotene and vitamin A in the nutrition of growing dairy cattle. *J. Dairy Sci.* 23:115–124.
- Weiss, W. P., J. S. Hogan, K. L. Smith, and K. H. Hoblet. 1990. Relationships among selenium, vitamin E, and mammary gland health in commercial dairy herds. *J. Dairy Sci.* 73:381–390.
- Weiss, W. P., J. S. Hogan, D. A. Todhunter, and K. L. Smith. 1997. Effect of vitamin E supplementation in diets with a low concentration of selenium on mammary gland health of dairy cows. *J. Dairy Sci.* 80:1728–1737.
- Weiss, W. P., and M. T. Socha. 2005. Dietary manganese for dry and lactating Holstein cows. *J. Dairy Sci.* 88:2517–2523.
- Wu, Z., and L. D. Satter. 2000. Milk production and reproductive performance of dairy cows fed two concentrations of phosphorus for two years. *J. Dairy Sci.* 83:1052–1063.
- Xin, Z., D. F. Waterman, R. W. Hemken, and R. J. Harmon. 1991. Effects of copper status on neutrophil function, superoxide dismutase, and copper distribution in steers. *J. Dairy Sci.* 74:3078–3085.
- Zimmerly, C. A., and W. P. Weiss. 2001. Effects of supplemental biotin on performance of Holstein cows in early lactation. *J. Dairy Sci.* 84:498–506.

APPENDIX

Table A1. Timeline for advances in mineral and vitamin nutrition of dairy cattle

Date	Milestone	Reference
1917	Need for NaCl by dairy cattle is known, and some information on Ca, P, and Mg is available.	
1919	Forbes publishes the first paper in the <i>Journal of Dairy Science</i> (JDS) on mineral nutrition of the “milch” cow.	Forbes, 1919
1922	Variation in vitamin A concentration in milk is related to the inclusion of specific feedstuffs in diets fed to cows.	e.g., Hilton et al., 1935
1923	Meigs publishes a paper in JDS on the need to establish Ca and P requirements. Only Ca and P are discussed because “there is little reason to think that deficiencies of any other mineral elements play a very large ... role.”	Meigs, 1923
1928	Link between vitamin D and rickets in calves is clearly established. Ruminant synthesis of B vitamins is demonstrated.	Bechdel et al., 1928a, b
1935	Selenium is identified as an agent in alkaline staggers.	Draize and Beath, 1935
1945	First National Research Council (NRC) requirements are published. Allowances are provided for Ca, P, NaCl, Mg, I, carotene, and vitamin D, and the dietary need for K, S, Co, Cu, Fe, and Mn is recognized.	NRC, 1945
1950	Second revised dairy NRC requirements are published. Factorial allowances are provided for Ca and P, and the allowance for vitamin A for adult cattle is presented. Other vitamins and minerals are discussed.	NRC, 1950

Continued

Table A1 (Continued). Timeline for advances in mineral and vitamin nutrition of dairy cattle

Date	Milestone	Reference
1953	Antagonism between K and Mg is demonstrated in ruminants. Antagonism between Cu, S, and Mo is demonstrated.	Dick, 1953; Kunkle et al., 1953
1966	Third revised dairy NRC requirements are published. Factorial allowances are presented for Ca, P, and vitamins A and D. Other minerals and vitamins are discussed.	NRC, 1966
1971	Finding show that negative DCAD diets can prevent milk fever. Fourth revised dairy NRC requirements are published; first time that allowances for vitamin E and minerals other than Ca and P are included.	NRC, 1971
1978	Fifth revised dairy NRC requirements are published. Allowances for Mg and Mn are doubled and allowance for Fe is halved.	NRC, 1978
1979	The US Food and Drug Administration approves the addition of supplemental Se to dairy diets.	
1984	Direct link between mineral and vitamin supplementation and mastitis in dairy cattle is established.	Smith et al., 1984
1986	Studies evaluating organic trace minerals start being published.	e.g., Kincaid et al., 1986
1988	Substantial research on the use of ruminal buffers leads to widespread industry adoption of the practice.	e.g., Erdman, 1988
1989	Sixth revised dairy NRC requirements are published. Only small changes are made for most minerals and vitamins, except the vitamin E requirement is given for adult cattle for the first time and Se allowance is increased 3-fold.	NRC, 1989
1990–1996	Several studies demonstrate production and health benefits when dairy cows are supplemented with B vitamins. Reduced fat-soluble vitamin status during the peripartum period is related to increased disease.	e.g., Driver et al., 1990; Goff and Stabel, 1990; Weiss et al., 1990
2001	Seventh revised dairy NRC requirements are published. Factorial requirements are established for absorbed minerals. Health is used to establish requirements for some vitamins.	NRC, 2001
~2010	Molecular biology is used to identify indicators of mineral status.	e.g., Hansen et al., 2010
2017	Eighth revised dairy NRC requirements are being prepared.	