VITAMINS IN ANIMAL NUTRITION

Comparative Aspects to Human Nutrition

Lee Russell McDowell

VITAMINS IN ANIMAL NUTRITION

ANIMAL FEEDING AND NUTRITION

A Series of Monographs and Treatises

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This book is dedicated with appreciation
to my parents,
to my wife, Lorraine,
and to my daughters,
Suzannah, Jody, and Teresa

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Foreword

This is the tenth in a series of books about animal feeding and nutrition. The books in this series are designed to keep the reader abreast of the rapid developments that have occurred in this field in recent years. As the volume of scientific literature expands, interpretation becomes more complex, and a continuing need exists for summation and for up-to-date books.

This book on vitamins is written by Dr. Lee R. McDowell, a distinguished scientist in animal nutrition, who was also editor of *Nutrition of Grazing Ruminants in Warm Climates* (Academic Press, 1985). For the past 23 years, he has been working on animal nutrition studies at the University of Florida and with numerous collaborating animal scientists in Latin America, Africa, Asia, and other areas. He has lectured throughout the world and has collected research data, photographs, and other materials of value for this book. His expertise and knowledge have been greatly enriched by contact with many of the world's leading nutrition scientists.

For many years, there has been a great need for a single book on vitamins covering both animals and humans. Dr. McDowell has done a magnificent job of reviewing the vitamin literature and condensing it into one textbook. He covers the basic chemical, metabolic, and functional role of vitamins. Moreover, he devotes proper consideration to vitamin supplementation. The book is well illustrated with a wealth of valuable photographs depicting vitamin deficiencies in livestock, laboratory animals, and humans.

In addition to worldwide use as a textbook, this book should also be of considerable value to research and extension specialists, teachers, students, feed manufacturers, farmers, and others dealing with the livestock industry. Animal industry personnel, veterinarians, and those interested in comparative nutrition will find this book very useful. It should be valuable for anyone concerned with vitamin nutrition.

New feed and food crops, improved methods of production and processing, increased productivity of animals and crops, changes in animal products including more lean and less fat in meat and less fat in milk, longer shelf life requirements of food products, and a myriad of new technological developments have resulted in a need to reevaluate vitamin supplementation. This book is timely and valuable in bringing the vitamin field up-to-date and in discussing supplementation needs.

Tony J. Cunha

Preface

Vitamins in Animal Nutrition contains 18 chapters of concise, up-to-date information on vitamin nutrition for both animals and humans. The first chapter deals with the definition of vitamins, general considerations, and the fascinating history of these nutrients. Chapters 2 through 15 discuss the 14 established vitamins in relation to history; chemical structure, properties, and antagonists; analytical procedures; metabolism; functions; requirements; sources; deficiency; supplementation; and toxicity. Chapter 16 deals with other vitamin-like substances, and Chapter 17 reviews the importance of essential fatty acids. The final chapter discusses vitamin supplementation considerations.

It is hoped that this book will be of worldwide use as a textbook and as an authoritative reference book for use by research and extension specialists, feed manufacturers, teachers, students, and others. An attempt has been made to provide a balance between animal nutrition and clinical human nutrition. Likewise, a comparison between the balance of chemical, metabolic, and functional aspects of vitamins and their practical and applied considerations has been made.

A unique feature is the description of the practical implications of vitamin deficiencies and excesses and the conditions that might occur with various animal species and humans. A large number of photographs illustrate vitamin deficiencies in farm livestock, laboratory animals, and humans. Unlike other textbooks, this one places strong emphasis on vitamin supplementation in each chapter and devotes the last chapter to this subject.

In preparing this book, I have obtained numerous suggestions from eminent scientists both in the United States and in other countries of the world. I wish to express my sincere appreciation to them and to those who supplied photographs and other material used. I am especially grateful to the following: C. B. Ammerman, L. B. Bailey, R. B. Becker, D. K. Beede, B. J. Bock, H. L. Chapman, J. H. Conrad, G. L. Ellis, R. H. Harms, J. F. Hentges, J. K. Loosli, R. M. Mason, R. Miles, R. L. Shirley, R. R. Streiff, and W. B. Weaver (Florida); R. T. Lovell and H. E. Sauberlich (Alabama); O. Balbuena, B. J. Carrillo, and B. Ruksan (Argentina); H. Heitman (California); J. M. Bell, M. Hidiroglou, and N. Hidiroglou (Canada); N. Ruiz (Colombia); N. Comben (England); M. Sandholm (Finland); L. S. Jensen (Georgia); T. B. Keith (deceased) (Idaho); A. H. Jensen (Illinois); V. Ramadas Murthy (India); A. Prabowo (Indonesia); V. Catron (deceased), and V. C. Speer (Iowa); G. L. Cromwell (Kentucky); G. F. Combs (Maryland); F. J. Stare (Massachusetts); R. W. Luecke, E. R. Miller, R. C. Piper, J. W. Thomas, and D. E. Ullrey (Michigan); R. T. Holman and T. W. Sullivan (Minnesota); V. Herbert, L. E. Kook, M. C. Latham, and M. L. Scott (New York); A. Helgebostad and H. Rimeslatten (Norway); D. E. Becker (Ohio); P. R. Cheeke, D. C. Church, O. H. Muth, and J. E. Oldfield (Oregon); D. S. McLaren (Scotland); J. R. Couch and T. M. Ferguson (deceased) (Texas); D. C. Dobson (Utah); J. P. Fontenot, M. D. Lindemann, and L. M. Potter (Virginia); J. R. Carlson, J. A. Froseth, and L. L. Madsen (deceased) (Washington); and M. L. Sunde (Wisconsin). Appreciation is expressed to company representatives, including G. Patterson (Chas. Pfizer Co); J. C. Bauernfeind, T. M. Fry, E. L. MacDonald, L. A. Peterson, and S. N. Williams (Hoffmann–LaRoche, Inc.); C. H. McGinnis (Rhône–Poulenc, Inc.); and A. T. Forrester (The Upjohn Co.). Special thanks go to J. P. Fontenot for the preliminary planning of this book, and to P. R. Cheeke and J. E. Oldfield for editing and providing useful suggestions for the entire publication.

I am particularly grateful to Nancy Wilkinson and Lorraine M. McDowell for their useful suggestions and assistance in the editing of the entire book. Likewise, I wish to acknowledge with thanks and appreciation the skill and care of Patricia French for overseeing the typing and proofreading of chapters, and also thank Vanessa Carbia for her valuable assistance. Also, I am indebted to the Animal Science Department of the University of Florida for providing the opportunity and support for this undertaking. Finally, I thank Tony J. Cunha for encouraging me to undertake the responsibility of writing this book, and for the experience of his expertise on this subject.

Lee Russell McDowell

1

Introduction and Historical Considerations

I. DEFINITION OF VITAMINS

Vitamins are defined as a group of complex organic compounds present in minute amounts in natural foodstuffs that are essential to normal metabolism and lack of which in the diet causes deficiency diseases. Vitamins consist of a mixed group of chemical compounds and are not related to each other as are proteins, carbohydrates, and fats. Their classification together depends not on chemical characteristics but on function. Vitamins are differentiated from the trace elements, also present in the diet in small quantities, by their organic nature.

Vitamins are required in trace amounts (micrograms to milligrams per day) in the diet for health, growth, and reproduction. Omission of a single vitamin from the diet of a species that requires it will produce deficiency signs and symptoms. Many of the vitamins function as coenzymes (metabolic catalysts); others have no such role, but perform certain essential functions.

Some vitamins deviate from the preceding definition in that they do not always need to be constituents of food. Certain substances that are considered to be vitamins are synthesized by intestinal tract bacteria in quantities that are often adequate for body needs. However, a clear distinction is made between vitamins and substances that are synthesized in tissues of the body. Ascorbic acid, for example, can be synthesized by most species of animals, except when they are young or under stress conditions. Likewise, niacin can be synthesized from the amino acid tryptophan and vitamin D from action of ultraviolet light on precursor compounds in the skin. Thus, under certain conditions and for specific species, vitamin C, niacin, and vitamin D would not always fit the classic definition of a vitamin.

II. CLASSIFICATION OF VITAMINS

Classically, vitamins have been divided into two groups based on their solubilities in fat solvents or in water. Thus, fat-soluble vitamins include A, D, E, and K, while vitamins of the B complex, C, and others are classified as water soluble. Fat-soluble vitamins are found in feedstuffs in association with lipids.

The fat-soluble vitamins are absorbed along with dietary fats, apparently by mechanisms similar to those involved in fat absorption. Conditions favorable to fat absorption, such as adequate bile flow and good micelle formation, also favor absorption of the fat-soluble vitamins (Scott *et al.*, 1982). Conversely, their absorption is impaired when conditions are unfavorable for normal fat absorption. Water-soluble vitamins are not associated with fats and alterations in fat absorption do not affect their absorption. Fat-soluble vitamins are stored in appreciable amounts in the animal body. Except for vitamin B_{12}, water-soluble vitamins are not stored and excesses are rapidly excreted. A continual dietary supply of the water-soluble vitamins is needed to avoid deficiencies. Fat-soluble vitamins are primarily excreted in the feces via the bile, whereas water-soluble vitamins are mainly excreted in urine. Water-soluble vitamins are relatively nontoxic but excesses of fat-soluble vitamins A and D can cause serious problems. Fat-soluble vitamins consist only of carbon, hydrogen, and oxygen, whereas some of the water-soluble vitamins also contain nitrogen, sulfur, or cobalt.

Table 1.1 lists 14 vitamins classified as either fat or water soluble. The number of compounds justifiably classified as vitamins is controversial. The term vitamin has been applied to many substances that do not meet the definition or criteria for vitamin status. Of the 14 vitamins listed, choline is only tentatively classified

TABLE 1.1

Fat- and Water-Soluble Vitamins with Synonym Names

Vitamin	Synonym
Fat soluble	
Vitamin A_1	Retinol
Vitamin A_2	Dehydroretinol
Vitamin D_2	Ergocalciferol
Vitamin D_3	Cholecalciferol
Vitamin E	Tocopherol
Vitamin K_1	Phylloquinone
Vitamin K_2	Menaquinone
Vitamin K_3	Menadione
Water soluble	
Thiamin	Vitamin B_1
Riboflavin	Vitamin B_2
Niacin	Vitamin pp, vitamin B_3
Vitamin B_6	Pyridoxol, pyridoxal, pyridoxamine
Pantothenic acid	Vitamin B_5
Biotin	Vitamin H
Folacin	Vitamin M, vitamin B_c
Vitamin B_{12}	Cobalamin
Choline	Gossypine
Vitamin C	Ascorbic acid

as one of the B-complex vitamins. Unlike other B vitamins, choline can be synthesized in the body, is required in larger amounts, and apparently functions as a structural constituent rather than as a coenzyme. *Myo*-inositol and carnitine are not listed in Table 1.1 even though they could fit the vitamin category but apparently for only several species. Chapters 2–15 in this book concern the 14 vitamins listed in Table 1.1, while Chapter 16 concerns vitamin-like substances and Chapter 17 considers essential fatty acids. The essential fatty acids are not vitamins, but a deficiency disease does result that is similar to vitamin deficiency. The final chapter deals with vitamin supplementation considerations.

III. VITAMIN NOMENCLATURE

When the vitamins were originally discovered, they were isolated from certain foods. During these early years, the chemical composition of the essential factors was unknown, therefore, these factors were assigned letters of the alphabet. The system of alphabetizing became complicated when it was discovered that activity attributed to a single vitamin was instead the result of several of the essential factors. In this way, the designation of groups of vitamins appeared (e.g., the vitamin "B" group). Additional chemical studies showed that variations in chemical structure occurred within compounds having the same vitamin activity but in different species. To overcome this, a system of suffixes was adopted (e.g., vitamin D_2 and D_3). The original letter system of designation thus became excessively complicated.

With the determination of the chemical structure of the individual vitamins, letter designations were sometimes replaced with chemical-structure names (e.g., thiamin, riboflavin, and niacin). Vitamins have also been identified by describing a function or its source. The term vitamin H (biotin) was used because the factor protected the "haut," the German word for "skin." Likewise, vitamin K was derived from the Danish word "koagulation" (coagulation). The vitamin pantothenic acid refers to its source, as it is derived from the Greek work "pantos," meaning "found everywhere."

The Committee on Nomenclature of the American Institute of Nutrition (CNAIN, 1981) has provided definite rules for the nomenclature of the vitamins. This nomenclature is used in this book. The official and major synonym names of vitamins are given in Table 1.1 and also in the respective vitamin chapters.

IV. VITAMIN REQUIREMENTS

Vitamin requirements for animals and humans are listed in the Appendix tables at the end of this book and in the appropriate chapter. While metabolic needs are similar, dietary needs for vitamins differ widely among species. Some vitamins are metabolic essentials, but not dietary essentials, for certain species, because they can be synthesized readily from other food or metabolic constituents.

Poultry, swine, and other monogastric animals are dependent on their diet for vitamins to a much greater degree than are ruminants. Tradition has it that ruminants in which the rumen is fully functioning cannot suffer from a deficiency of B vitamins. It is generally assumed that ruminants can always satisfy their needs from the B vitamins naturally present in their feed, plus that synthesized by symbiotic microorganisms. However, under specific conditions relating to stress and high productivity, ruminants have more recently been shown to have requirements, particularly for the B vitamins thiamin (see Chapter 6) and niacin (see Chapter 8).

The rumen does not become functional with respect to vitamin synthesis for some time after birth. For the first few days of life the young ruminant resembles a nonruminant in requiring dietary sources of the B vitamins. Beginning as early as 8 days and certainly by 2 months of age, ruminal flora have developed to the point of contributing significant amounts of the B vitamins (Smith, 1970). Production of these vitamins at the proximal end of the gastrointestinal tract is indeed fortunate for they become available to the host as they pass down the tract through areas of efficient digestion and absorption.

In monogastric animals, including humans, intestinal synthesis of many B vitamins is considerable (Mickelsen, 1956) though not as extensive or as efficiently utilized as in ruminants. Low efficiency of utilization is probably related to several factors. Intestinal synthesis in nonruminants occurs in the lower intestinal tract, an area of poor absorption. The horse, with a large production of B vitamins in the large intestine, is apparently able to meet most of its requirements for these vitamins in spite of the poor absorption from this area. Intestinally produced vitamins are more available to those animals (rabbit, rat, and others) that habitually practice coprophagy and thus recycle products of the lower gut. This behavior yields significant amounts of B vitamins to the host animal.

V. VITAMIN OCCURRENCE

Vitamins originate primarily in plant tissues and are present in animal tissue only as a consequence of consumption of plants, or because the animal harbors microorganisms that synthesize them. Vitamin B_{12} is unique in that it occurs in plant tissues as a result of microbial synthesis. Two of the four fat-soluble vitamins, vitamins A and D, differ from the water-soluble B vitamins in that they occur in plant tissue in the form of a provitamin (a precursor of the vitamin), which can be converted into a vitamin in the animal body. No provitamins are known for any water-soluble vitamin. Tryptophan, which can be converted into niacin, is usually known as an amino acid. In addition, fat- and water-soluble vitamins differ in that water-soluble B vitamins are universally distributed in all living tissues, whereas fat-soluble vitamins are completely absent from some tissues.

VI. HISTORY OF THE VITAMINS

The history of the discovery of the vitamins is an inspirational and exciting reflection of the ingenuity, dedication, and self-sacrifice of many individuals. Excellent reviews of vitamin history with appropriate references include Wagner and Folkers (1962), Marks (1975), Maynard *et al.* (1979), Scott *et al.* (1982), Widdowson (1986), and Loosli (1988). A brief sketch of important events emphasizing early history of vitamins is outlined in Table 1.2.

The existence of nutritive factors, such as vitamins, was not recognized until about the start of the twentieth century. The word "vitamin" had not been coined yet. However, what were to be later known as vitamin deficiency diseases, such as scurvy, beriberi, night blindness, xerophthalmia, and pellagra, had plagued the world at least since the existence of written records. Records of medical science from antiquity attesting to human association of certain foods with either the cause or prevention of disease and infirmity are considered the nebulous beginnings of the concept of essential nutrients (Wagner and Folkers, 1962). Even so, at the beginning of the twentieth century the value of food in human nutrition was expressed solely in terms of its ability to provide energy and basic building units necessary for life.

In the late 1800s and early 1900s some scientists believed that life could be supported with chemically defined diets. In 1860 Louis Pasteur reported that yeast could grow on a medium of sugar, ammonium salts, and ash of yeast. Justus von Liebig observed that certain yeasts were unable to grow at all under these conditions, while others grew only very slowly. The ensuing arguments between Liebig and Pasteur did not solve the question. Pasteur's (1822–1895) research showing that bacteria caused disease led scientists trained in medicine to be reluctant to believe the "vitamin theory" that certain diseases resulted from a shortage of specific nutrients in foods (Loosli, 1988).

The first phase leading to the "vitamin hypothesis" began with gradual recognition that cause of diseases such as night blindness, scurvy, beriberi, and rickets could be related to diet. Although the true cause, nutritional deficiency, was not suspected, these results marked the first uncertainty in the germ and infection theories of origin for these diseases. Finally, in the early 1900s many scientists in the field of nutrition almost simultaneously began to realize that a diet could not be adequately defined in terms of carbohydrate, fat, protein, and salts. At that time it became evident that other organic compounds had to be present in the diet if health was to be maintained.

TABLE 1.2

Brief History of Vitamins (Ancient History—1951)

2600 B.C.	Beriberi was recognized in China and is probably the earliest documented deficiency disorder.
1500 B.C.	Scurvy, night blindness, and xerophthalmia were described in ancient Egypt. Liver consumption was found to be curative for night blindness and xerophthalmia.
A.D. 130–200	Soranus Ephesius provided classical descriptions of rickets.
1492–1600	World exploration threatened by scurvy: Magellan lost four-fifths of his crew Vasco da Gama lost 100 of his 160 men
1747	Lind performed controlled shipboard experiments on the preventive effect of oranges and lemons on scurvy. Also developed method of preserving citrus juice by evaporation and conserving in acid form.
1768–1771	Captain Cook demonstrated that prolonged sea voyages were possible without ravages of scurvy.
1816	Magendie described xerophthalmia in dogs fed carbohydrate and olive oil.
1824	Combe described a fatal anemia, pernicious anemia, and suggested that it could be related to a disorder of the digestive tract.
1849	Choline was isolated by Streker from the bile of pigs.
1881	Lunin reported that animals did not survive on diets composed solely of purified fat, protein, carbohydrate, salts, and water.
1880s	Japanese physician Takaki prevented beriberi in Japanese Navy by substituting other foods for polished rice.
1897	Eijkman showed that beriberi (thiamin deficiency) from polished rice consumption could be cured by adding rice polishings back into the diet.
1906	Hopkins suggested substances in natural foods, termed "accessory food factors," were indispensable and did not fall into the categories of carbohydrate, fat, protein, and mineral.
1907	Holst and Frolich produced experimental scurvy in guinea pigs by feeding a deficient diet, with pathological changes resembling those in humans.
1909	Hopkins reported a rat growth factor in some fats.
1912	The term "vitamine" was first used by the Polish biochemist Funk to describe an accessory food factor.
1913	McCollum and Davis discovered fat-soluble A in butter that was associated with growth.
1919	Steenbock reported that the yellow color (carotene) of vegetables was vitamin A.
1919	Mellanby produced rickets in dogs, which responded to a fat-soluble vitamin in cod liver oil.
1920	Goldberger reported that pellagra was not caused by bacterial infection, but rather was an ill-balanced diet high in corn.
1922	McCollum established vitamin D as independent of vitamin A by preventing rickets after destroying vitamin A activity when bubbling oxygen through cod liver oil.
1923	Evans and Bishop discovered vitamin E. The deficiency caused female rats to abort, while male rats became sterile.
1926	Jansen and Donath isolated thiamin in crystalline form from rice bran.
1926	Minot and Murphy showed that large amounts of raw liver given by mouth daily would alleviate pernicious anemia.

(continued)

TABLE 1.2 *(Continued)*

1926	Steenbock showed that irradiation of foods as well as animals produced vitamin D_2.
1926	Goldberger and Lillie described a rat syndrome, later shown to be riboflavin deficiency.
1928	Bechtel and co-workers established that rumen bacteria of cattle synthesized B vitamins.
1928	Szent-Györgyi isolated hexuronic acid (ascorbic acid, vitamin C) from orange juice, cabbage juice, and cattle adrenal glands.
1929	Moore proved that the animal body converts carotene to vitamin A.
1929	Norris and co-workers reported a curled toe paralysis (riboflavin deficiency) in chicks.
1929	Castle showed that pernicious anemia resulted from the interaction of a dietary (extrinsic) factor and an intrinsic factor produced by the stomach.
1930	Norris and Ringrose described a pellagra-like dermatitis in the chick, later established as a pantothenic acid deficiency.
1931	Pappenheimer and Goettsch showed that vitamin E is required for prevention of encephalomalacia of chicks and nutritional muscular dystrophy in rabbits and guinea pigs.
1931	Willis demonstrated that a factor from yeast was active in treating a tropical macrocytic anemia seen in women of India.
1932	Choline was discovered to be the active component of pure lecithin previously shown to prevent fatty livers in rats.
1933	R. J. Williams and associates fractionated a growth factor from yeast and named it pantothenic acid.
1934	Szent-György named a factor that would cure dermatitis in young rats, vitamin B_6.
1934	Dam and Schönheyder described a nutritional disease of chickens characterized by bleeding, thus a new fat-soluble vitamin was discovered.
1935	Wald demonstrated the relation of vitamin A to night blindness and vision.
1935	Kuhn in Germany and Karrer in Switzerland synthesized riboflavin.
1935	Warburg and co-workers first demonstrated a biochemical function for nicotinic acid when they isolated it from an enzyme (NADP).
1935–1937	Cobalt, the central ion in vitamin B_{12}, was shown to be a dietary essential for cattle and sheep by Underwood and co-workers in Australia and in Florida by Becker and associates.
1936	Biotin was the name given to a substance isolated from egg yolk by Kogl and Tonnis that was necessary for the growth of yeast.
1936	R. R. Williams and colleagues determined the structure of thiamin and synthesized the vitamin.
1937	Elvehjem and associates found that nicotinic acid cured black tongue in dogs. It was quickly shown to be effective for pellagra in humans.
1939	Vitamin K was isolated by Dam and Karrer of Europe and a few months later in the U.S. from three different laboratories.
1940	Harris and associates completed the first synthesis of biotin.
1942	Baxter and Robeson crystallized vitamin A.
1943–1946	Chemists from the Lederle group crystallized and later synthesized folacin.
1948	Rickes and co-workers in the U.S. and Smith in England isolated vitamin B_{12}.
1951	Smith and co-workers showed that cobalt deficiency in sheep could be prevented by vitamin B_{12} injection.

Beriberi was probably the earliest documented deficiency disorder, being recognized in China as early as 2600 B.C. Scurvy, night blindness, and xerophthalmia were described in the ancient Egyptian literature around 1500 B.C. Substances rich in vitamin A as remedies for night blindness were used very early by the Chinese, and livers were recommended as curative agents for night blindness and xerophthalmia by Hippocrates around 400 B.C. In 1536 Canadian Indians cured Jacques Cartier's men of scurvy with a broth of evergreen needles. In 1747 James Lind, a British naval surgeon, showed that the juice of citrus fruits was a cure for scurvy, but its routine use was not started in the British Navy until 1795. Cod liver oil was used as a specific treatment for rickets long before anything was known about the cause of this disease, and was fed to farm animals as early as 1824. In the 1880s, the Japanese physician Takaki recognized the cause of beriberi in the Japanese Navy as stemming from an unbalanced white rice diet, and virtually eliminated this condition by increasing the consumption of vegetables, fish, and meat and by substituting barley for rice.

The period before the close of the nineteenth century was characterized by the discovery of diseases of nutritional origin in animals, which opened the way for controlled experimental studies of nutritional causes and cures for such diseases that were common to both humans and the lower animals. The rat undoubtedly contributed most to the discovery of vitamins from 1900 through the 1920s, although chickens, pigeons, guinea pigs, mice, and dogs also played their part (Widdowson, 1986). In 1890 Christiaan Eijkman, a Dutch physician working in a military hospital in Java, found that chickens fed almost exclusively on polished rice developed polyneuritic signs bearing a marked resemblance to those of beriberi in humans. A new head cook at the hospital discontinued the supply of "military" rice (polished) and thereafter the birds were fed on whole grain "civilian" rice with the result that they recovered. He also noted that beriberi in prisoners eating polished rice tended to disappear when a less highly milled product was fed. Many great advances in science have started from such chance observations pursued by men and women of inspiration.

In 1881 the Swiss biochemist N. Lunin reported that animals did not survive on synthetic diets composed solely of purified fat, protein, carbohydrate, salts, and water. Lunin proposed that natural foods such as milk contain small quantities of as yet unknown substances essential to life. In 1906 Frederick Hopkins in England suggested that unknown nutrients were essential for animal life and used the term "accessory growth factors." Hopkins was responsible for opening up a new field of discovery that largely depended on the use of the rat. When Hopkins later discovered that he was not the first to suggest that unknown nutrients were essential, or to conduct animal experiments, he was anxious to share his Nobel prize with Eijkman in 1929.

In 1912 Casimir Funk proposed the "vitamine theory." He had reviewed the literature and made the important conclusion that beriberi could be prevented or cured by a protective factor present in natural food. Funk named the distinct factor that prevented beriberi as a "vitamine." This word was derived from "vital amine." Later, when it became evident that not all "vitamines" contained nitrogen (amine), the term became vitamin.

After reviewing the literature between 1873 and 1906, in which small animals had been fed restricted diets of isolated proteins, fats, and carbohydrates, E. V. McCollum of the United States noted that the animals rapidly failed in health and concluded that the most important problem in nutrition was to discover what was lacking in such diets. By 1915, McCollum and M. Davis at Wisconsin discovered that the rat required at least two essential growth factors, a "fat-soluble A" factor and a "water-soluble B" factor. In addition to being required as factors for normal growth, the "fat-soluble A" factor was found to cure xerophthalmia and the "water-soluble B" factor cured beriberi. At the same time as their work in Wisconsin, T. B. Osborne and L. B. Mendel of Connecticut also established the importance of vitamin A.

With the pioneer work of Eijkman, Hopkins, Funk, McCollum, and others, scientists began to seriously consider the new class of essential nutrients. The brilliant research of scientists in the first half of this century led to the isolation of more than a dozen vitamins as pure chemical substances. The golden age of vitamin research was mainly in the 1930s and 1940s. For vitamin discovery, the general procedure employed was first to study the effects of a deficient diet on a laboratory animal and then to find a food that would prevent the deficiency. Using a variety of chemical manipulations, the particular nutrient involved was gradually concentrated from the food, and its potency was tested at each stage of concentration on further groups of animals (Wagner and Folkers, 1962). This laborious procedure has been simplified in recent years by the discovery that several vitamins are also growth factors for microorganisms that can therefore replace animals for potency testing. By such methods it is now possible to isolate vitamins and subsequently to identify them chemically. A remarkable achievement has been the direct synthesis by chemists of at least ten vitamins identified in this way. The last vitamin to be discovered was vitamin B_{12} in 1948, which brought the period of vitamin discovery to a close. On the other hand, the possibility that there are still undiscovered vitamins must be recognized (see Chapter 16). More detailed historical considerations for each vitamin are presented in the respective chapters (Chapters 2–15).