History of Nutrition

Early Research into the Vitamins: The Work of Wilhelm Stepp

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Wilhelm Stepp has been described in Germany as the "founder of the science of vitamins" (Schröder 1964). The purpose of this article is to reexamine his work first in the context of the knowledge and beliefs in 1907, the time at which he began his experiments, and then in the light of present-day knowledge. For the 50 years previous to 1907, German scientists had been recognized as the leaders in the field of nutrition, and their laboratories were the places to which many Americans and other Europeans would go for postgraduate training.

THE BACKGROUND

It had become a dogma in Germany, since the time of Liebig, that nutritional requirements could be completely expressed in terms of protein and total energy apart from the need for a few minerals that were in any case in ample supply in normal diets. Hopkins (1930) comments: "The minds of the leaders of thought in nutritional science were obsessed by a sense of the overwhelming importance of calorimetric studies."

Professor von Bunge at the German university in Dorpat, Estonia, and then at Basel had his graduate students experiment with the use of purified diets for small animals. N. Lunin, a student working in von Bunge's laboratory, published a paper entitled "The significance of inorganic salts for the nutrition of animals" (Lunin 1881). He described feeding mice a diet of protein, sugar, fat and salts; the animals died after 16–36 d. However, when a small amount of milk was added to the diet, they lived and grew for 2.5 mo. He states: "A natural food such as milk must, therefore, contain besides the known principal ingredients small quantities of other and unknown substances essential to life"; also "it would be of great interest to investigate the significance of these substances for human nutrition." However, he did nothing further in this type of research but went on to a distinguished career in Russia as a pediatrician (Voss 1956).

Von Bunge explained away, instead of following up Lunin's revolutionary conclusion. Why? F. G. Hopkins, in his Nobel prize lecture (1930), reveals from personal knowledge that von Bunge "was inclined to disbelieve [the existence of unknown nutritional factors]. He thought that the real error in the synthetic diets used by his pupils (which was, so to speak "dissected milk"), was that the method of its preparation had involved the separation of inorganic constituents from certain organic combinations in which latter form alone could they adequately subserve the purposes of metabolism." Von Bunge believed in particular that the iron and phosphorus in foods had to be present in pre-formed organic combinations, because the animal kingdom had such limited powers of synthesis that it could not, for example, utilize inorganic iron for synthesis of hemoglobin or inorganic phosphate for the synthesis of lecithin (Ihde and Becker 1971, Carpenter 1990).

Curiously, the dogma had such a strong hold that C. A. Socin (1891) and W. S. Hall (1896) from von Bunge's school, who had essentially the same results as Lunin, were not encouraged to investigate what the active factor in milk might be. Others under the influence of von Bunge were W. Falta and C. T. Noeggerath (1906), who fed purified protein (casein or ovalbumin), fat, starch and salts to rats and made similar observations. They supposed that the animals' precipitous decline in weight and early death, unless supplemental milk was provided, were caused by lack of calories due to the unpalatability of the diet. P. Knapp (1909), an ophthalmologist who was also in the orbit of von Bunge (now in Basel), noted the comment of Falta and Noeggerath that the rats fed their purified diet had shown an abnormality of the eyes prior to their sudden decline in weight and death after 6–10 wk. He repeated the study and saw that in all of his nine animals death was preceded by severe conjunctivitis and corneal ulcers (Knapp 1909). The rats were also light sensitive, and the corneal lesions were so severe that the animals could not keep their eyes open. Knapp was therefore one of the first scientists to recognize xerophthalmia and keratomalacia in experimental animals fed a synthetic diet that, as we now know, was deficient in vitamin A. He also cautiously voiced the suspicion that lack of food could not be the cause of the eye lesions but rather that there must have been a factor missing in the diet that was present in milk. One should note that almost 100 years earlier, F. Magendie (1816) had observed ulceration of the corneas of dogs nourished only with water and sugar.

A late believer in the Liebig-von Bunge view was the famous nutritional biochemist E. Abderhalden. He wrote: "we arrive at the conclusion that at present there is no compelling proof for the hypothesis that there exist totally unknown substances essential for survival" (Abderhalden and Lampe 1913). How can one explain this tenacious adherence to a theory in the face of a multitude of contradicting evidence? K. Guggenheim (1995) cogently argues that the immensely successful germ theory of disease with the related toxin theory, and the accompanying practices of antisepsis and vaccination, filled the thoughts of scientists at that time with the idea that only a positive agent could cause a disease. The notion that a deficiency, the lack of an agent, could bring about a disease or death seemed wrong-headed.

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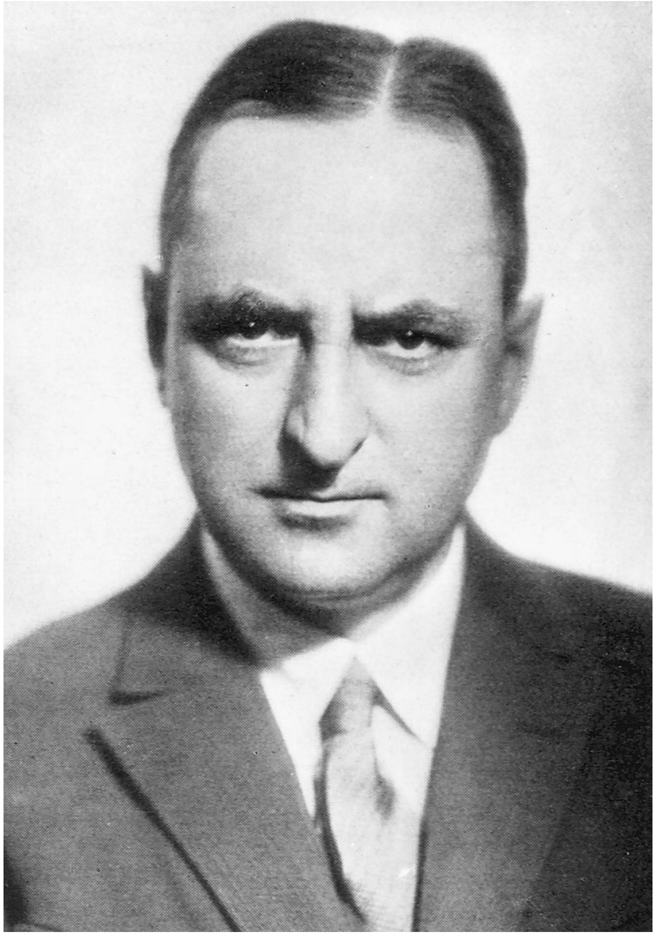
0022-3166/97 $3.00 © 1997 American Society for Nutritional Sciences. J. Nutr. 127: 1255–1259, 1997
Manuscript received 7 March 1997. Accepted 14 March 1997.



Wilhelm Stepp (1882–1964)

Two other workers in Holland and England repeated Lunin's type of experiment with the same result. But each was reluctant to publish their data until they had identified the factor in milk and only referred to their work in passing in lectures mainly on other topics. The first was the Dutch physiologist C. A. Pekelharing (1905), who fed mice protein, carbohydrate, fat and salts and found that the animals died within 4 wk. He could keep them alive only by adding milk to their diet, noting that the quantity of milk necessary was "quite negligible" compared with the amount of food consumed. "My intention is only to point out that there is a still unknown substance in milk which, even in very small quantities, is of paramount importance to nourishment. This substance occurs not only in milk, but in all sorts of foodstuffs, animal and vegetable." He added that he would be doing nothing further on the subject. A year later, F. G. Hopkins (1906), on the basis of his own unpublished experiments, similarly concluded: "no animal can live upon a mixture of pure protein, fat and carbohydrate; even when the necessary inorganic material is carefully supplied, the animal still cannot flourish. The animal body is adjusted to live either on plant tissues or on other animals and these contain countless substances other than proteins, carbohydrates and fats. Physiological evolution, I believe, has made some of these well-nigh as essential as the basal constituents of the diet. In diseases such as rickets and particularly in scurvy, we have had for long years knowledge of a dietetic factor; but though we know how to benefit these conditions empirically, the real errors in the diet are to this day quite obscure. They are, however, certainly of the kind which comprise these minimal qualitative factors that I am considering." Hopkins waited a further six years to publish his actual data (Hopkins 1912) and was then stimulated to do so by the claim of Funk (1911) to have isolated a vitamin.

Meanwhile, in 1907–1908 two other young men began to reexamine the subject. One was 28-year-old Elmer McCollum, working independently as an assistant professor in the Wisconsin College of Agriculture, and his career and achievements have been fully recorded (McCollum 1957). The other was Wilhelm Stepp, a 25-year-old medical school graduate working in the laboratory of the physiological chemist F. Hofmeister in Strasbourg (now in France but then in German territory). Stepp's idea, or hypothesis, was that the essential dietary factor(s) in milk might be a "lipoid," by which he meant a substance associated with fat and soluble in ether or alcohol.

STEPP'S FIRST EXPERIMENTS

As an experimental approach, Stepp (1909) had the original idea of using an adequate diet and removing particular substances rather than using a synthetic, clearly inadequate diet to which known substances were added. By extracting a complete (survival) diet with specific solvents and thus making it inadequate, Stepp hoped to characterize the unknown essential components.

In his first experiments, Stepp (1909) prepared a diet adequate for survival from wheatbread baked with milk (milkbread). In later work (1911–1912, 1912–1913, 1913), his basic diet was a proprietary protein-rich rice flour (100 g) mixed with milk (75 mL) and then air-dried to a hard dough (henceforth called milkdough). In his final studies (1918–1919) he started with commercial dog chow. On all three of these diets his young mice grew and thrived.

He extracted the milkbread for 12 h with boiling alcohol and for 12 h with boiling ether and fed the extracted diet to nine weanling albino mice in two separate experiments. All the mice died within 3 wk, after first growing normally but then losing weight precipitously in the last few days of life. In a control experiment, he mixed the alcohol-ether extract (after solvent removal) with some of the alcohol-ether–extracted (AEEX) milkbread and gave this reconstituted diet to three mice. They all survived normally. He concluded that a fat-soluble substance, perhaps even fat itself, was essential for survival.

To exclude the possibility that the solvents had removed essential minerals, he added the salts obtained from ashing the milkbread diet to the AEEX-milkbread. Mice fed this mixture all died in less than 3 wk. He dismissed the possibility that the deaths were caused by lack of energy by observing that, except for the last few days before death, the animals fed the AEEX-milkbread diet ate as much as the controls. He reported a peculiar paralysis of the hind legs and roughness of fur in the depleted animals, which, as we now know, are characteristic signs of a deficiency of a number of vitamins.

In later work (1911–1912), Stepp fed mice the AEEX-milkdough diet to which an extract of the same diet had been added that had been obtained by prolonged (3-d) extraction with boiling alcohol and observed that the mice still all died in 3 wk. He concluded that the extracted factor essential for survival was heat sensitive.

SOLUBILITY OF THE FACTOR

To understand Stepp's conclusions as to the solubility of the lipoid, it is important to note exactly Stepp's method of extraction, because the survival factor clearly was contained in the extract (Stepp 1911–1912). He stirred the milkdough with alcohol at 50°C and then filtered it. The filtrate was dried in vacuo and dissolved in ether (ether extract I); the residue on the filter was Soxhlet-extracted with ether for 1 d (ether extract II). The two ether extracts were combined and added to the AEEX-milkdough diet, the ether was then evaporated from the mixture in vacuo, and the residue was softened with water and fed to the mice. All survived with normal weight gains that he reports in his paper. Clearly, whatever was being extracted must have been soluble in ether, though Stepp does not comment on this fact.

To explore the solubility of the survival factor further, Stepp (1913) then fed mice not the usual fatal AEEX-milkdough diet but one that was extracted only with ether. Unexpectedly, survival was 100%, whereas when the extraction process used only alcohol, survival was zero. His conclusion was that the survival factor was insoluble in ether, which seems to be in direct contradiction to his previous finding.

In later work (1916c), Stepp used an alcohol-extracted (AEX) dog chow diet on which mice survived for an average of only 23.2 d ± 3.4 SD; when this diet was supplemented with an ether extract of egg yolk the survival was 43.2 d ± 12.3 SD. He therefore revised his previous view regarding the extractability of the factor and surmised that ether could partially extract the factor from yolk but not from milkdough. His final conclusion, then, was that the factor was ether soluble, though whether or not it could be obtained by ether extraction depended on the foodstuff from which it was being extracted.

The possibility that the milkbread, milkdough or dog chow might have contained both an ether-soluble factor and a factor soluble in alcohol but not ether seems not to have occurred to Stepp at that time. Much later, however, he wrote that the extracts could have contained both a water- and a fat-soluble vitamin (Stepp and György 1927).

HEAT SENSITIVITY OF THE FACTOR

To explore the heat sensitivity of the factor further, Stepp then thought of egg yolk as a rich source of lipoids that could be extracted at a lower temperature than those from the milkdough. He first confirmed that egg yolk, mixed with the AEEX-milkdough diet, kept the mice alive normally (Stepp 1911–1912). He then extracted egg yolk with ether and alcohol at 40–50°C. By adding the yolk extract to AEEX-milkdough, a normal survival diet was generated. As a control, Stepp (1911–1912) heated an alcohol extract of egg yolk in boiling alcohol for 48 h and added the heated extract (after solvent removal) to the AEEX-milkbread diet; in contrast to results using the egg yolk extract made at 40°C, the heated extract failed to prevent rapid death of the mice fed that diet. Similar experiments were performed with fractions extracted with alcohol from calf brain, heated or unheated, with equivalent results. In another experiment, milk was added to AEEX-milkdough and the mixture heated, with stirring, to 100°C until dry (30 min); fed this diet, seven out of 12 mice died within 4 wk. Unheated milk, of course, when added to the AEEX-milkdough supported longer survival. When the unextracted milkbread diet (by itself) was suspended in water, heated to 100°C, then air-dried and fed to mice, the following observations were made (Stepp 1912–1913): unheated, no mortality; 6 h heated, no mortality; 24 h heated, 50% mortality; 48 h heated, 86% mortality.

Stepp (1912–1913) also looked at recovery: mice fed the heated egg yolk extract, added to the AEEX-milkdough diet, lost weight (28% by the 12th d). When fed unheated egg yolk extract starting on that day, they resumed normal weight gain and survived for 2 mo.

TABLE 1

Basal diet for mice

Supplement	Alcohol-extracted dog chow	Polished rice
None	(a) All died in 3 wk	(b) All died in 3 wk
Alcohol extract of egg yolk	(c) All survived 2 mo	(d) All died in 3–5 wk (no weight gain)
Orypan	(e) All died in 3 wk	(f) All survived for at least 6 wk (some weight loss)

EXPERIMENTS WITH BUTTER AND MILK

It was, of course, necessary to show that the essential factor missing in the AEEX-milkdough diet was not simply fat. Stepp demonstrated that tristearin, tripalmitin or triolein added separately to the AEEX-milkdough diet could not keep his mice alive, nor could added lecithin, cholesterol or cerebroside. Adding butter was also ineffective. This last finding was in contrast to later work by McCollum and Davis (1913), who noted that butter contained a fat-soluble factor essential for the growth of rats.

Milk, on the other hand (Stepp 1911–1912), had proved effective when added to the AEEX-milkdough diet, provided it was unheated and the amount was sufficient: with 200 mL of milk mixed with 100 g of dry AEEX-milkdough diet, all six mice survived satisfactorily, whereas 75 mL/100 g AEEX-milkdough fed to six mice led to deaths of three mice in 21 d and three mice in 41 d. Stepp remarks that this experiment illustrated a dose-dependency relationship, concluding that 75 mL of milk contained less than the minimum amount of the essential lipid.

THE ANTI-BERIBERI FACTOR

In 1911, C. Funk described a water-soluble substance he called "vitamine" present in yeast and whole grains, particularly in rice bran. A dietary deficiency of "vitamine" caused a fatal polyneuritis in pigeons, a condition he believed to be analogous to beriberi (Funk 1911). We now know that "vitamine" is the B-vitamin thiamin.

Stepp (1916a) knew by that time that the anti-beriberi factor was soluble in alcohol as well as water. He therefore decided to test whether or not the alcohol-ether extractable substance in milkbread or dog chow that he had found to be essential for survival in mice was identical with the anti-beriberi factor.

Stepp used two basal diets: AEX-dog chow or thoroughly water-washed polished rice, each with a mineral supplement (0.5% of the diet). He also used two test supplements: a proprietary anti-beriberi product consisting of a concentrated rice bran extract called "Orypan" (given as 2% of the diet) or a supplement made by cold-alcohol extraction of approximately 180 g of egg yolk added to 300 g of each basal diet. The latter would have provided about 4 μg thiamin as well as about 70 IU of vitamin A per day per mouse, if they ate some 4 g of dry diet per day. His results are summarized in **Table 1.**

A REEXAMINATION OF THE MOUSE EXPERIMENTS

We now know that of the fat-soluble vitamins A, D, E and K, it is only a deficiency of vitamin A that can cause weight loss and death in weanling mice after a period of about 10 wk (McCarthy and Ceredo 1952). However, we know of no experiments in which a vitamin A deficiency has resulted in consistent deaths within 3 wk, as was Stepp's experience. And if, by chance, the breeding stock had been fed a diet deficient in vitamin A they would have failed to produce live young. Furthermore, if Stepp's mice were exceptional in dying in 3 wk if deprived of vitamin A, one would have expected them to die when fed white rice, minerals and rice bran extract, which contribute neither retinol nor carotenoids (Table 1f).

Secondly, we know that alcohol extraction would have removed the thiamin from Stepp's basal diets, and it has been shown that deficiency of this vitamin can result in the death of young mice within 3 wk (Hauschildt 1942). The paralysis of the hind legs and rough fur of the sick mice could be due to deficiency of either vitamin A or thiamin.

Thirdly, Stepp's observation (1911–1912) that butter, when added to the AEEX-milkdough diet, did not support survival would support the idea that his mice died of thiamin rather than vitamin A deficiency. McCollum and Davis (1913) used butter as their first source of the lipid-soluble survival factor.

Stepp's experiment, as set out in Table 1, was certainly well designed to answer his question, and the results were just those needed to show that Funk's and Stepp's factors were different. However, in the light of modern knowledge they pose serious problems. One aspect, the survival of the mice receiving treatment "f" [rice + Orypan], has already been mentioned. Another is that the mice receiving treatment "e" [AEEX-dog chow + Orypan] died even though they were receiving adequate thiamin. This diet could hardly have had less vitamin A than the rice in treatment "f."

Another unexpected finding is the failure of 75 mL of milk added to 100 g of diet to prevent deaths. This quantity of milk would contribute about 20 μg of vitamin A, and Slanetz (1943) has reported that 15 μg/100 g diet is enough to keep mice alive; 75 mL of milk would also contribute about 27 μg of thiamin to 100 g of diet. Assuming that the mice ate some 4 g of dry diet per day, they would obtain only about 1 μg of thiamin per day, an insufficient amount for their survival (Hauschildt 1942).

On the other hand, Stepp also reported that an ether extract of egg yolk was active for his mice, and this could not have been a source of thiamin.

LATER WORK

In later experiments, Stepp (1918–1919) extended his findings to other species. Rats fed the AEX-dog chow diet died in 6–14 wk; dogs survived only 2–3 mo on that diet plus rice bran. Pigeons, on the other hand, grew well and survived on AEX-milkbread, provided they also received a rice bran supplement (Stepp 1916b). He thought that birds, though requiring the anti-beriberi factor, had no need for the lipid-soluble factor—a wrong conclusion, as we now know. It just takes them longer to be depleted of vitamin A.

In any case, it was the work done with purified diets by McCollum and by Osborne and Mendel that led to the discoveries of the various fat-soluble and water-soluble vitamins. However, McCollum (1964) somewhat overstates his claims when he writes, "Our first great pioneering discovery came in 1912. We had a certain diet on which little rats grew for a time and appeared to be in a fair state of health when either butter fat or fat extracted by ether from egg yolk was included. The same diet containing lard or olive oil as the source of fat was a failure. This was the first discovery of a fat-soluble vitamin." Already in 1911 Stepp had stated that "certain lipid substances present in milk, soluble in alcohol-ether, are indispensable for the survival of mice" and added that these substances are not esters of fatty acids (Stepp 1911–1912).

One must ask how Stepp came to be overtaken by American and British investigators who ultimately accomplished the characterization of vitamin A. Perhaps the reason has to be sought in the choice of a medical career by Stepp, who went into clinical medicine, practicing as assistant in internal medicine already in 1916 in Giessen, where he rose to be professor of internal medicine and chief of the "Polyclinic" in 1922. He became professor of medicine in Munich in 1934. McCollum, and Osborne and Mendel, on the other hand, were without clinical responsibilities and able to concentrate on their nutritional and biochemical studies culminating in the discovery of vitamins A and D. Stepp clearly continued his interest in vitamins, and when he was on leave in 1924, he went to work in Baltimore with McCollum on such problems as the formation of vitamin A in germinating seeds and the distinction between the xerophthalmia-preventing vitamin A and the rickets-preventing vitamin D.

In the final analysis, because of certain contradictory and inexplicable results, Stepp cannot be regarded as belonging to the first rank of investigators in the discovery of the vitamins. Even though in the German literature he is sometimes considered to be "the actual founder of the science of vitamins" (Schröder 1964), he himself made no such claims. However, in a review (Stepp 1922) on recent discoveries in the fat-soluble vitamins, he states that he "first indicated the significance of certain fat-like substances as components of a complete diet. In numerous experiments I could provide evidence that though chemically pure neutral fats are dispensable, there is a need for accompanying substances not as yet identified occurring in all animal and plant cells. . . . I described the indispensability of these lipoids." And he refers to L. B. Mendel (1920) as having acknowledged as much.

If others can suggest a better explanation of Stepp's findings, we would be interested to hear from them.

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