The Nobel Prize and the Discovery of Vitamins

by Kenneth J. Carpenter
June 22, 2004

Introduction

In the course of the 19th century, chemists and physiologists studying the composition of foods and the nutritional requirements of humans and animals found that our diets needed to include the complex nitrogenous compounds called "proteins" (that, with water, form the bulk of our lean tissues), together with fats, starch and sugars that all provide usable energy during their oxidation in the body. It was also realized that bones contain high concentrations of lime (calcium oxide) and phosphate salts and the body, generally, has a variety of other necessary mineral salts, though it was felt that mixed diets normally supplied adequate quantities of all these without any need for special precautions.

With hindsight, we can see repeated early observations indicating that we also had a need for some other nutrients. Thus, sailors after 10-12 weeks on dry foods, during long sailing ship voyages before the days of refrigeration, typically developed scurvy, a disease characterized by weakness, pains in the joints, loose teeth and blood spots appearing all over the body, and finally sudden death "in the middle of a sentence" from the bursting of a main artery. However, desperately ill men would recover in 10 days or so after reaching land where they could be given fresh fruit or salad greens.

Another disease that seemed to be associated with a restricted diet was beriberi, marked first by weakness and loss of feeling in the feet and legs, then varied effects including edema of the trunk, and finally difficulty in breathing and death from heart failure. It seemed to be particularly associated with a diet of rice and little else. It had been described in some of the earliest medical treatises in China and Japan, but physicians from Europe only saw it in their countries' colonies in Asia. In 1803 Thomas Christie, a physician with the British army in Sri Lanka, wrote: "the chief cause of beriberi is certainly a want of stimulating and nourishing diet... However, giving "acid fruits" which I find of great value in cases of scurvy, has no effect in beriberi... I can suppose the difference to depend on some nice chemical combination." Christie was prophetic but, for the next 100 years, scientific methods were inadequate to pursue what those "nice combinations" might be. Their very existence was also almost forgotten in the time of the Pasteurian revolution, when microbial infection came to be thought of as the likely explanation for every disease.

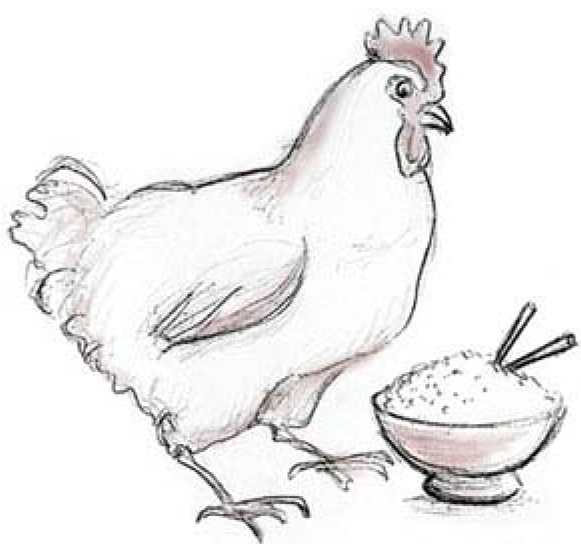
Christiaan Eijkman's Work in Java

An important breakthrough occurred in the 1890s in Java that was then a Dutch colony. Christiaan Eijkman, a Dutch military physician was assigned to try to grow the microbe supposedly responsible for beriberi by injecting blood from diseased native soldiers into animals. Some of the chicks that he was using developed a characteristic leg weakness (polyneuritis), but only, he discovered, when they were being fed on cooked white rice left over from the hospitalized soldiers' meals. Now was his chance to study what was lacking from this diet.

All harvested rice has to be de-husked before being cooked and eaten. If no more milling is carried out this is "brown rice;" but, if the grains are further "polished" so that the branny skin is rubbed off, it becomes "white rice" and has a longer shelf life since the fraction removed (i.e. the "polishings) rapidly becomes rancid under tropical conditions.

Eijkman was able to show that adding the polishings back to the diet of the sick chickens restored their health, and also that the minerals they contained were not responsible for their value. His suggested explanation for the disease appearing was that the very high level of starch in rice was toxic unless counteracted by an antidote present in the polishings. It was still unproven, of course, that the chicken disease was a model for human beriberi.

In 1895, just before Eijkman's health broke down and he had to return to Holland, he discussed his findings with Adolphe Vorderman, the medical inspector for the 100 small prisons scattered across the island of Java. Beriberi was known to be a problem in some, but not others, and Vorderman found that in the prisons using mostly brown rice, less than one prisoner in 10,000 had shown beriberi, while in those using mainly white rice the proportion was 1 in 39. This striking difference could not be related to any corresponding difference in hygienic conditions in the various prisons, and provided strong support for the relevance of Eijkman's work.[1] The story of Eikman's work is told in more detail in another Nobelprize.org production, "Vitamin B_1."



Gerrit Grijns – An Explanation Corrected

In 1896 the research was taken over by Gerrit Grijns, another well qualified M.D. from the University of Utrecht in the Netherlands with postgraduate research experience. He first confirmed Eijkman's main results and then found that chickens fed just on autoclaved meat would also develop polyneuritis that could be prevented by adding either rice polishings or beans to their diet. This and further work showed that the disease did not require the presence of excess starch, and he concluded: "there occur in various natural foods, substances which cannot be absent without serious injury to the peripheral nervous system... These substances are easily disintegrated...which shows that they are complex substances and cannot be replaced by simple chemical compounds." This was the first clear statement of what later would be called the "vitamin" concept, but it was published only in Dutch and did not become more widely known for another 25 years.

Many people now began to prepare active extracts from rice polishings that could be used to treat victims of beriberi, showing incidentally that the factor was soluble in water and alcohol. In Japan, Umetaro Suzuki was prominent in this work, and in the Philippines, American workers were able to save the lives of young babies being suckled by mothers living on little but rice.

The Invention of the Word "Vitamin"

Many scientists in Europe, as well as in Asia, began to interest themselves in the problem of actually isolating the factor in rice polishings, with a further dream perhaps of identifying and even synthesizing it. One of these was Casimir Funk, a biochemist born in Poland but trained in several European countries, who moved to London in 1910. In the following year, he reported that he had isolated the active factor. This was, in fact, incorrect but he then went on to suggest that this material belonged to the chemical class of "amines." Further, he supposed that, just as all the constituents of proteins (i.e. amino acids) belong to the same chemical class, so would the organic trace nutrients whose deficiencies were being envisioned as the causes of diseases such as pellagra and scurvy, in addition to beriberi. He therefore coined the term "vitamine" for these "vital amines." When it was realized a few years later that others in the class were not "amines," but a word was still needed, it was shortened to "vitamin."

Joseph Goldberger and Pellagra

In 1914 Joseph Goldberger, an officer in the U.S. Public Health Service, was put in charge of investigating the cause of cases of pellagra in the south of the country. Sufferers developed severe skin eruptions on parts of their body exposed to strong sunlight, and in many cases diarrhea and mental changes causing them to be placed in asylums, and there was a high death rate. Pellagra had the reputation of being associated with the consumption of maize (called corn in America) and it had been thought that batches of maize meal that had become mouldy and toxic could be responsible, but by 1914 in the South it was generally assumed to be an infection, perhaps one carried by insects as had been found to be the case for malaria.

Goldberger doubted the infection theory since there were no records of doctors or nurses catching the disease from their patients, and he actually ate skin scrapings and excreta from pellagrins to test this directly. On the other hand, he found that supplementing the diets at orphanages with eggs and milk resulted in fewer cases appearing. After further experiments with volunteers that confirmed the dietary explanation, he was able to produce an animal model of the disease with dogs and found that yeast supplements were potent in countering the condition, and this was confirmed to be true for patients also. His group was actively working to fractionate yeast and identify its active factor at the time of his death in 1929. Only in 1935 was it identified by others as nicotinic acid (also re-named "niacin"), an already familiar chemical.

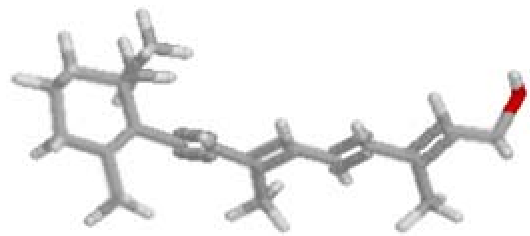
Academic Work with Rats and Mice

While other people had been studying clinical disorders, a number of academic workers had been interested in determining the nutritional requirements of mammalian species, using the convenient young rats and mice, starting with simple dietary mixtures and finding what more was needed to make them complete. Important early work was done in Germany but, unfortunately, the failures in growth were considered to be the result of ingredients in the diet that have been "denatured" by purification, rather than the lack of some hitherto unrecognized nutrient(s).

The clearest evidence for lack of an unknown "something" in a mammalian diet was presented by Gowland Hopkins in 1912. This Cambridge biochemist was already well known for having isolated the amino acid tryptophan from a protein and demonstrated its essential nature. He fed young rats on a diet of casein, lard, sucrose, starch and minerals; one half of them also received a small separate daily supplement of 2 ml milk. Only those receiving milk grew well, but after 2 weeks the treatments were switched. Those now receiving milk began to grow normally and, after 2 weeks at a stationary weight, those now without milk began to go downhill. Hopkins suggested that this could only be explained by the basic diet lacking traces of some unidentified organic nutrient and that the problem was analogous to human diseases related to diet, as he had suggested already in a lecture published in 1906.[2]

Fat-Soluble Vitamins

Strangely, Hopkins then went on to lead programs of work in intermediate metabolism rather than trying to discover what the "milk factor" might be, and others were actually unable to reproduce his finding with such a small quantity of milk.[3] However, important advances began to be made in the U.S.A. Elmer V. McCollum in Wisconsin found that, with his purified diet, rats began to lose weight after some 10 weeks, but would recover with small doses of butter fat, but not with olive oil. Then in 1914 he found that the activity remained in the ether-soluble fraction after the butter fat was saponified so that all the ordinary fat became water-soluble. He called this factor "A" and that in rice polishings "factor B." This was the origin of the system of naming what were later called vitamins. Vitamin A deficiency in humans, as well as rats, was later shown to produce serious eye damage (xerophthalmia) and it remains a major cause of blindness in the Third World.



Structure of Vitamin A, retinol.
Courtesy of Protein Data Bank, Brookhaven National Labs, S.W. Cowan, M.E. Newcomer, T.A. Jones, J. Mol. Biol. 1993, 230 1225

McCollum, after moving in 1917 to Johns Hopkins University in the U.S.A., where he had easier access to pathological help, realized that, with a diet containing unbalanced proportions of calcium and phosphorus, a lack of certain animal fats produced a condition analogous to human rickets. This disease was still a serious problem, particularly among infants growing up in large, industrial cities. Further work showed that the activity of these fats came from a second fat-soluble factor to be named "vitamin D." A whole succession of other workers were then able to show that it was at least related to the sterols and that it could be formed by ultraviolet irradiation of crude cholesterol *in vitro*, or through the skin of living animals or humans.

Sterols had previously seemed a rather uninteresting group of compounds with no exciting properties. However, when it was realized that a compound in their group could prevent the problem of infantile rickets, they began to attract more attention. Adolf Windaus, a German structural chemist had for many years been a leading investigator of sterol structure, and was called on by physiologists working on vitamin D to assist them with its chemistry. In 1928 he received the Nobel Prize in Chemistry for "his studies on the constitution of the sterols and their connection with the vitamins". But the vitamin connection was a relatively small last step in the long studies for which he was honored.

The Nobel Prize in Physiology or Medicine

The First Prizes

Now, at long last, we can start to consider the problem of the Committee responsible for this prize; they had not, so far, given any award relating to the discovery of the vitamins although they had been receiving nominations intermittently for the previous 14 years (for Eijkman, Funk, Goldberger, Grijns, Hopkins and Suzuki but, strangely, not for McCollum in this period). Their reluctance may have been influenced by the comments of skeptics that vitamins were only hypothetical entities postulated to explain various phenomena: "no one had ever seen one." After 1926, this was no longer true. B.C.P. Jansen and W.F. Donath, two more Dutch scientists working in Java, had finally obtained pure crystals from the fractional extraction of rice polishings; only one hundredth of a milligram was needed daily to cure a deficient pigeon, and the activity was confirmed in the following year for subsamples sent overseas.

So, the Committee for the 1929 awards apparently agreed that it was high time to honor the discoverer(s) of vitamins; but who were they? There was a clear case for Grijns, but he had not been re-nominated for that particular year, and it could be said that he was just taking the relatively obvious next steps along the new trail that had been laid down by Eijkman. On the other hand, Eijkman had been re-nominated for his work done 35 years earlier; he was also now an old man in poor health, so that it might well be the final year in which he would live to receive such an honor. Although it was known that he had held reservations as to whether or not beriberi represented a straightforward vitamin deficiency, there was no doubt that he had taken the first steps in the use of an animal model to investigate the nutritional basis of a clinical disorder affecting millions. Goldberger had been another important contributor, but his recent death put him out of consideration.

Structure of Vitamin B1.
Courtesy of Protein Data Bank,
Brookhaven National Labs

If Eijkman represented the approach to vitamins from a clinical perspective, there had also been the, at least, equally fruitful "academic" approach using rodents and purified diets. The only representative of this approach who had been re-nominated for 1929 was Hopkins, the leader of the "dynamic biochemistry" school in Britain and an influential advocate for the importance of vitamins, even though he had not persisted with his own relatively early work in the field, and his famous experiment could not be replicated. Nevertheless, he was awarded the prize jointly with Eijkman.

It was a strange outcome. Hopkins said that he had received the award for the wrong reason and Eijkman did not travel to Stockholm, at least nominally on the ground of ill health, though it has been suggested that he may have been equally deterred by skepticism about the cause of beriberi. He also apparently gave offense to fellow scientists in Holland by making no mention of Grijns in the speech that he sent to Stockholm, and they then organized a successful international appeal to finance Grijns' papers being republished in English translation in recognition of the importance of his contributions.

Among the important advances made in this field between the time of Hopkins' work and the 1929 awards was the work on the fat-soluble vitamins begun by McCollum and followed up by many others. For example, Harriette Chick had led a team, during the post World War I food crisis in Central Europe, who studied the treatment of rickets in Vienna and showed, using X-rays, that bone healing in infants was equally stimulated by ultraviolet irradiation or dosing with cod liver oil, and had nothing to do with hygiene. Nevertheless, the Committee in the following years decided, it seems, that this period of work on vitamins had now been adequately recognized.

American Work on Pernicious Anemia

The next award that we can, but only with hindsight, relate to vitamins was that given in 1934 to George Whipple, George Minot and William Murphy of the U.S.A. "for their discoveries concerning liver therapy in cases of anaemia," and the first to be divided between three people. Previously, pernicious anemia had been an incurable condition, but these workers had found that sufferers could survive if they would eat large quantities of raw liver each day, with the hope that this could soon be replaced by more potent liver extracts. There was no mention at the time of liver having a vitamin-like action since it was only essential apparently for counteracting a disease and not for meeting a requirement of normal people.

After the essential liver factor (cobalamin, or vitamin B_{12}) had finally been isolated in 1948, it became clear that even healthy people needed this factor but that they absorbed it efficiently so that a normal mixed diet was sufficient. Vitamin B_{12} was found to be absent from plant foods and present in liver in higher concentrations than in meat or milk. However, as originally demonstrated by William Castle in 1928, the stomachs of pernicious anemia patients were abnormal in failing to secrete an "intrinsic factor" that combined with cobalamin and greatly increased the subsequent efficiency of its absorption from the small intestine. He was able also to show that extracts from normal animal stomachs combined with pre-digested meat, could be given to pernicious anemia patients to produce normal synthesis of red blood cells. This work has since been described as a milestone in clinical investigation, but it received little attention at first and, although there were two later nominations on Castle's behalf, they were unsuccessful.

Szent-Györgyi and Vitamin C

In 1937 Albert Szent-Györgyi received the Prize for Physiology or Medicine "for his discoveries in connection with the biological combustion processes, with especial reference to vitamin C and the catalysis of fumaric acid." There is another strange story here. He was a Hungarian biochemist who had worked in a number of countries and had a special interest in oxidation-reduction mechanisms in the body. After detecting an antioxidant compound in the adrenal cortex, he was invited to Cambridge in England in 1927 and there, using a simple *in vitro* test to measure its relative concentration in fractions obtained from the tissue, he was able in a few months to isolate a compound that he named hexuronic acid, and that he showed to have the empirical formula $C_6H_8O_6$.[4]

Meanwhile, several groups had for years been attempting to isolate the anti-scurvy vitamin C from lemon juice, carrying out successive, time-consuming biological assays with guinea pigs at each fractionation stage. In 1932, Charles Glen King of the University of Pittsburgh in the U.S.A. reported success, and added that his crystals had all the properties reported by Szent-Györgyi for hexuronic acid. The latter had by now returned to Hungary and quickly confirmed the biological activity of his crystals. So, for four years, the vitamin had been isolated and to hand without Szent-Györgyi realizing what he had done. After multiple nominations, he received the Prize in 1937. It has been suggested that the citation was expanded to include more than just the isolation of vitamin C because of feeling in the U.S.A. that Charles Glen King deserved most of the credit for the isolation since "he knew what he was after."

In the same year, Norman Haworth from the University of Birmingham in England received a Nobel prize from the Chemistry Committee for having advanced carbohydrate chemistry and, specifically, for having worked out the structure of Szent-Györgyi's crystals, and then been able to synthesize the vitamin. This was a considerable achievement and led to vitamin C becoming widely available at low cost. The Nobel Prize in Chemistry was shared with the Swiss organic chemist Paul Karrer, cited for his work on the structures of riboflavin and vitamins A and E as well as other biologically interesting compounds. This was followed in 1938 by a further Chemistry award to the German biochemist Richard Kuhn, who had also worked on carotenoids and B-vitamins, including riboflavin and pyridoxine, and had been something of a rival to Karrer. Because of a Nazi veto Kuhn was not able to accept his prize until after World War II.

Henrik Dam and Vitamin K

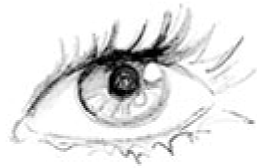
The next Physiology or Medicine awards in the vitamin field were given to Henrik Dam and Edward Doisy in 1943. Dam, a Danish biochemist working at the University of Copenhagen in Denmark was rewarded "for his discovery of vitamin K." Some years earlier, he had been investigating whether chicks needed to receive a source of sterols in their diet. In fact, they were found to be able to synthesize cholesterol, but some of his birds developed severe internal hemorrhaging caused by failure of their normal clotting mechanism. This problem was prevented by giving them a factor present in both green leaves and liver, but by none of the known vitamins. It was named "vitamin K," the first letter of the alphabet not to have been used by others (and also, by chance, the initial letter for "koagulation" the Danish equivalent of the English "coagulation"). A slightly different compound with the same biological activity was found to be present in fermented animal products such as fish meal.

The American biochemist Edward Doisy shared the award from the Nobel Committee for Physiology or Medicine, even though it was "for his discovery of the chemical nature of vitamin K." (Obviously, the whole subject of "vitamins" falls somewhere between the two originally demarcated areas of scientific work, i.e. Physiology or Medicine and Chemistry.) Doisy's synthesis of vitamin K had immediate practical importance. The condition of obstructive jaundice in patients was known to result in hemorrhages that endangered surgery designed to relieve the obstruction. It was now realized that the condition prevented the absorption of the vitamin, and that giving it by injection ended the problem. It has also reduced the danger of hemorrhaging in newborn infants.

George Wald and the Vitamin in the Eye

It was a further 24 years before the Nobel Committee for Physiology or Medicine gave another award for work involving a vitamin. This came to George Wald, one of three honored "for their discoveries concerning the primary physiological and chemical visual processes in the eye." He had grown up in Brooklyn as the son of poor Jewish immigrant parents, and after training in medicine at New York University in the U.S.A. and graduate work in zoology at Columbia University in the U.S.A. under Selig Hecht, obtained a grant in 1932 to work in Otto Warburg's laboratory in Berlin where he dissected animal retinas to obtain the light-sensitive, purple compound rhodopsin and found, by a chemical test, that retinas apparently contained vitamin A. He then moved to Karrer's laboratory in Zurich, Switzerland and extracted enough material for Karrer to confirm that it indeed was vitamin A.

From there Wald went to work in Heidelberg but conditions in Germany had changed: Hitler had come into power and Jews were unwelcome. The U.S. National Research Council, that had given him his travel grant, wanted him to leave after no more than a month. Nevertheless in that period, after dissecting retinas from 300 frogs, he found that rhodopsin on stimulation with light yielded both the protein opsin and a compound he called "retinene" (now "retinaldehyde") that in turn yielded vitamin A (now called retinol). It had been known for some time that vitamin A deficiency resulted in night blindness, but it was an unexpected discovery that a vitamin would participate directly in a physiological process.



Epilogue

To conclude, we must sympathize with the problems of the successive Nobel Committees in Physiology or Medicine and Chemistry through the 20th century, who had to try to make their selections among many deserving people in so many different fields, among which nutritional science was only one, and "vitamins" just a portion of that. They also had to limit their selections to those nominated in that particular year, and usually (though by no means always) it was only fairly recent research that was being considered, so that they did not always have the luxury of later commentators in a longer hindsight.

Those of us with a special interest in the subject can only be grateful, even though we may wonder at some decisions, that the importance of work involving vitamins was acknowledged in at least ten awards.

Table - Nobel Laureates and Their Work with Vitamins »

Bibliography

[1] Carpenter, K.J., *Beriberi, White Rice and Vitamin B*, University of California Press, Berkeley (2000).

[2] Weatherall, M.W. and Kamminga, H., *The making of a biochemist: the construction of Frederick Gowland Hopkins' reputation.* Medical History vol.40, pp. 415-436 (1996).

[3] Becker, S.L., *Will milk make them grow? An episode in the discovery of the vitamins.* In Chemistry and Modern Society (J. Parascandela, editor) pp. 61-83, American Chemical Society, Washington, D.C. (1983).

[4] Carpenter, K.J., *The History of Scurvy and Vitamin C, Cambridge University Press*, New York (1986).