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Invited Commentary

A celebration of 100 years of vitamin research but time to revitalise the science

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In 1912, the Polish biochemist Kazimierz Funk introduced the term 'vitamine' ('vital amine') for dietary factors that could prevent diseases such as beri-beri, pellagra or scurvy[1]. Although these diseases were known for centuries, their origins remained a mystery. It was Christiaan Eijkman, a Dutch physician and pathologist, who in 1897 started to investigate an outbreak of beri-beri in prisons in Java (now Indonesia). He observed that chickens fed on a diet of polished rice developed similar symptoms to the prisoners receiving a comparable diet. Eijkman demonstrated that unpolished rice and rice peelings prevented and even reversed beri-beri symptoms. It was Eijkman's collaborator Gerrit Grijns who identified thiamin or vitamin B_1 as the active anti-beri-beri compound. Its structure was finally elucidated and it was synthesised in 1936. In 1929, Eijkman shared the Nobel Prize in Physiology or Medicine with Frederick Gowland Hopkins. This was one of the first Nobel prizes awarded for research achievements on individual vitamins, their structure, biological function and relationship to disease, and many more followed (see Table 1). One may call this period of the first half of the twentieth century the 'golden age' of nutrition research. It should be mentioned that this year also celebrates the seventy-fifth anniversary of the Nobel Prize given to Albert Szent-Györgyi in 1937 for his research on 'hexuronic acid' that was later demonstrated by his fellow Joseph Svirbely to be the antiscorbutic factor that we now call ascorbic (for ascorbutus) acid or vitamin C.

In opposition to Funk's presumption that all vitamins would represent amines, McCollum and Kennedy introduced a classification based on solubility. They coined the terms 'fat-soluble A' and 'water-soluble B' to distinguish the vitamins present in milk and also noted that fractions A and B probably contained more than a single active compound[2]. Altogether, it took over 50 years until all vitamins relevant for human nutrition were isolated in chemically pure form. An important step along the way was the discovery that some micro-organisms also required organic growth factors, and it soon became clear that these factors were identical to those required by mammals. This finding opened the way to replace the time-consuming animal experiments by microbial assays, increasing the speed of analysis and work progress. Nevertheless, the isolation of vitamins quite often required brute-force methods and took years. In the case of biotin, the work started with 250 kg of dried egg yolk from which 1·1 mg of a highly active crystalline material was isolated[3]. Starting material for the isolation of folate was 4 tons of spinach leaves[4]. The final proof that the isolated compounds indeed caused biological effects was enabled by the chemical synthesis of the compounds. Chemical synthesis also opened the way for food fortification. This started with niacin in 1938 and soon led to the eradication of pellagra in the USA. However, identifying the biochemical processes that explained the essentiality of the compounds was still a huge challenge. Our knowledge that all B vitamins as well as vitamins C and K serve as cofactors in enzymatic reactions and determine the activities of hundreds of enzymes is the result of the hard work of thousands of dedicated scientists. This also holds true for those vitamins that have other functions by serving as antioxidants or as ligands for nuclear receptors or in light-transducing proteins.

Although much time has passed since the heyday of vitamin discovery and many more studies have addressed vitamin functions in human and animal nutrition, there are still uncertainties as to how much of the vitamins should be consumed by an individual to provide optimal health. These uncertainties are reflected, for example, in the dietary recommendations for vitamin intake as provided by various national bodies and scientific committees. Most interestingly, for some vitamins, the recommendations may vary up to 2·5-fold even between European countries with similar socio-economic status. This is one of the results of the analysis of Troesch *et al.* published in this issue of *British Journal of Nutrition*[5]. The authors compared mean dietary vitamin intakes based on food consumption data across a variety of countries and came to the conclusion that the majority of consumers did not achieve the intakes recommended. According to Troesch *et al.*, this gap is most pronounced for the fat-soluble vitamins and for folate. Of course, not reaching the reference intake of a vitamin does not mean that there is a vitamin deficiency, as the recommendations always have a statistically defined safety margin. The key question is of course whether this situation is something to worry about and so to start campaigns to increase vitamin intake or whether we have to reassess the recommendations.

Troesch *et al.*[5] based their analysis on food intake data from the USA, the UK, The Netherlands and Germany. Their

Table 1. Nobel prizes awarded for vitamin research

Year awarded	Researcher	Prize motivation
1928	Adolf Otto Reinhold Windaus	Research into the constitution of the sterols and their connection with the vitamins
1929	Christiaan Eijkman	Discovery of the antineuritic vitamin
1929	Frederick Gowland Hopkins	Discovery of the growth-stimulating vitamins
1931	Otto Heinrich Warburg	Discovery of the nature and mode of action of the respiratory enzyme
1934	William Parry Murphy, George Hoyt Whipple and George Richards Minot	Discoveries concerning liver therapy in cases of anaemia
1937	Paul Karrer	Investigations on carotenoids, flavins and vitamins A and B_2
1937	Walter Norman Haworth	Investigations on carbohydrates and vitamin C
1937	Albert Szent-Györgyi	Discoveries in connection with the biological combustion processes, with special reference to vitamin C
1938	Richard Kuhn	Work on carotenoids and vitamins
1943	Henrik Carl Peter Dam	Discovery of vitamin K
1943	Edward Adelbert Doisy	Discovery of the chemical nature of vitamin K
1953	Fritz Lipmann	Discovery of CoA and its importance for intermediary metabolism
1957	Alexander Robertus Todd	Work on nucleotides and nucleotide co-enzymes
1964	Dorothy Crowfoot Hodgkin	Determinations by X-ray techniques of the structures of important biochemical substances
1964	Feodor Lynen	Discoveries concerning the mechanism and regulation of cholesterol and fatty acid metabolism
1965	Robert Burns Woodward	Outstanding achievements in the art of organic synthesis

findings suggest that in all countries, the intake of folic acid is inadequate, which is not a new finding, but intakes below the recommendations were also found for fat-soluble vitamins and to a lesser extent for vitamin C. The assessment of food intake only provides a rough estimate of nutrient intake and this approach is becoming more imprecise with an increasing spectrum of food items including products that contain extra vitamins for technological reasons (vitamins E, C and carotenoids) or for providing health benefits. In addition, supplement use is a critical factor but the frequency of use is different in various population groups. For example, consumers who already enjoy a healthy diet tend to take supplements more frequently than those on a poor diet who would profit most from supplementation. It is also known that more women than men take supplements. So, diversification of lifestyles as well as the growing portfolio of food products makes dietary intake assessment more difficult than ever before.

The vitamin requirements of an individual are largely unknown and may depend on a plethora of factors such as diet, physical activity, time spent outdoors, age, smoking, medication and very likely numerous other parameters. What has become obvious in the last decade is that variation in genes involved in vitamin absorption, distribution, metabolism and function also affects vitamin status. For example, a substantial amount of vitamin A in an average diet derives from β-carotene, which yields two molecules of retinaldehyde when cleaved at the central 15-15′ carbon bond by carotene mono-oxygenase. It has been found that SNP in the *BCMO1* gene influence enzyme activity with subsequent effects on the conversion of dietary β-carotene to all-*trans* retinaldehyde[6]. Another example for a genetic contribution comes from vitamin D. Here, the circulating 25-hydroxyvitamin D levels are influenced by SNP that occur near genes that affect 7-dehydrocholesterol reductase, vitamin D 25-hydroxylase and the plasma vitamin D-binding protein[7]. Prominent SNP found in the methylenetetrahydrofolate reductase gene correlate with the individual folate status and disease risk[8]. SNP in the intestinal vitamin C transporters have been described as contributing to vitamin C status[9]. Some of the reported SNP are quite frequent in the population, and it is possible that their presence has compromised earlier studies on vitamin supplementation. These studies were performed with large cohorts and mostly could not demonstrate a benefit for, or even worse, reported increased incidences of disease in the treatment groups. Thus, beyond the dietary intake of vitamins, genetic variation contributes to vitamin absorption, distribution, metabolism, status and function. In addition, at least for some vitamins, the gut microbiota may also contribute to the host vitamin status[10]. Despite the fact that research in this area is booming, there are no recent efforts to validate and quantify the contribution of intestinal microbiota, for example, in vitamin synthesis or host metabolism.

Whereas in developing countries vitamin deficiencies are still a relevant cause for disease, developed societies face the problem that diversification of lifestyles may create some subgroups at risk for intakes exceeding safety levels while other subgroups may not meet the recommended values. The study of Troesch *et al.* hopefully fuels new discussions on how much of each vitamin is really needed and how we can provide it. As population-based assessment methods and fortification trials may not be very helpful in this respect, we need to assess vitamin status at the individual level, an approach that is essential to support developments in person-

alised medicine and nutrition. This is of course not trivial. For some vitamins, we still lack proper biomarkers that reflect the status. However, the life sciences offer a plethora of new technologies and smart devices that can be used to analyse blood cells, plasma, urine or other body fluids and samples for defining new relevant biomarkers. So, let us revitalise the research on vitamins towards a second 'golden age' of nutritional science.

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