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Functionally bioreactive

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Editorial

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An oft-repeated story from my time in Copenhagen recounts that a major local brewer (possibly the best in the world) removed the ascorbic acid preservative from their beer, whereupon a number of their workers subsequently developed scurvy. Apparently, beer contains most of the essential nutrients required for life and is sometimes consumed as a 'complete diet' and, more importantly, specific micronutrients such as vitamin C are essential if that life is to be a healthy one. The story is almost certainly apochryphal, as ascorbic acid itself has never been routinely used in commercial beer making, an isomer with no vitamin properties being preferred. But it is a nice story, rather in contrast to that of vitamin C. Hippocrates described the symptoms of scurvy and the role of diet was recognized for several centuries before, in 1747, James Lind, a Scottish naval surgeon, undertook one of the very first ever controlled research studies (with an *n* of 2!) to show that citrus fruits could reverse the condition. Even though this rather simple fact had been recognized, observationally, for some considerable time, Lind did not fully accept his own findings and sought more complicated answers to the cure for scurvy. Others did introduce citrus into sailor's diets, but the general vitamin concept did not emerge until early in the 20th century and took some years to become accepted (Semba, 2012). Vitamin C comes into a category of dietary components beloved of contributors to our Journal; it is an antioxidant. However, its physiological functionality relates more to its electron donor properties, and as a reducing agent it acts as a cofactor for many important mammalian and other enzymes (Padayatty and Levine, 2016). Reading this review I am struck by the humour; Goldilocks makes many appearances, to emphasize the importance of knowing plasma and tissue levels in investigative research, but is the last line of the abstract, '*and explore lines of investigation that are likely to be fruitful*' a deliberate pun? More than that I am impressed (if that is the right word) by the fact that we continually strive to know more and more about a dietary factor whose health impact has long been recognized. For humans, primates, guinea pigs and some other species, vitamin C is an essential dietary component that undoubtedly is more than bio*active*. The fact that it enables many enzymatic reactions means that is it bio*reactive*, ie, it creates a physiological response in the consumer. One might be forgiven for thinking that my use of the term bioreactive is nothing more than semantics, but I would disagree. Neither of my hardcopy dictionaries (dated 1983 and 1988) recognize the term bioactive, although it was in use by this Journal in 1989 to describe peptides derived from casein (Meisel and Frister, 1989). My online dictionary gives the definition '*Of or relating to a substance that has an effect on living tissue*' and herein lies the problem: what is a living tissue? In their review of bioactive peptides in milk, Vargas-Bello-Pérez *et al.* (2019) make the point that most of the evidence for bioactive effects comes from *in vitro* studies, listing 180 peptides from casein and lactoferrin for which bioactivities have been claimed (by contrast, there are generally recognized to be 13 vitamins required in the human diet). These putative activities are antihypertensive, antibacterial, antioxidative, immunomodulatory, opiod agonistic/antagonistic and antithrombotic. In addition, glycomacropeptide (released during renneting in cheese production) is claimed to have anorexic activity through stimulating release of cholecystokinin, and the list goes on; searching our Journal contents for 'bioactive peptide' yields 242 papers. The scientific interest is completely understandable. Bioactive components are the basis of functional foods, defined by the EU as '*food that is taken as part of the usual diet and has beneficial effects that go beyond traditional nutritional effects*' and estimated to have a potential annual value of between 25 and 60 billion euros globally. Dairy products constitute a major portion of this market, but very largely on account of pro- and pre-biotic properties of fermented dairy foods. As far as I am aware, there are no dairy products that are authorized by the European Food Safety Authority to make claims for improved health based on any direct bioactivity, by which I mean the creation of a physiological reaction in the consumer. In addition to *in vitro* efficacy, epidemiological demonstration of improved health is often cited as evidence of bioactive functionality. Epidemiology is an extremely important scientific discipline that has contributed and will contribute to many significant discoveries and advances, however, I become concerned when epidemiology is used as the sole or major evidence base for health claims. The problem is quite obvious. Unlike beer, milk does constitute a complete diet (for neonates) and an extremely nutritious food (for the rest of the population). In my view, it would take extremely powerful epidemiology to definitively

demonstrate functional food attributes (ie beyond nutrition) for bioactive peptides in dairy products. Animal models could arguably provide a more convincing evidence base, but have not been used to any great extent. An example is the study of Kobayashi *et al.* (2021) who extended *in vitro* analysis of denatured whey proteins on gut cell kinetics to include a safety and efficacy assessment done in suckling mice. Another problem can arise; what exactly should be fed, the putative bioactive factor alone or a dairy food containing it? These authors opted for the latter, adding their isolated whey fraction to milk for gavage. Given that numerous epidemiological studies have pointed to the importance of the food matrix (as opposed to individual isolated constitutents) this was probably a good choice, but it calls for rigorous control treatments (which, strictly, they did not use). From an Editorial standpoint, we shall continue to welcome submissions focused on bioactive components of dairy foods, although we shall also continue to add the word 'putative' wherever extravagant health claims are cited. More than that, we would get very excited by *in vivo* studies that rigorously demonstrate bioreactive functionalities of dairy components.

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