RDA for microbes – are you getting your daily dose?

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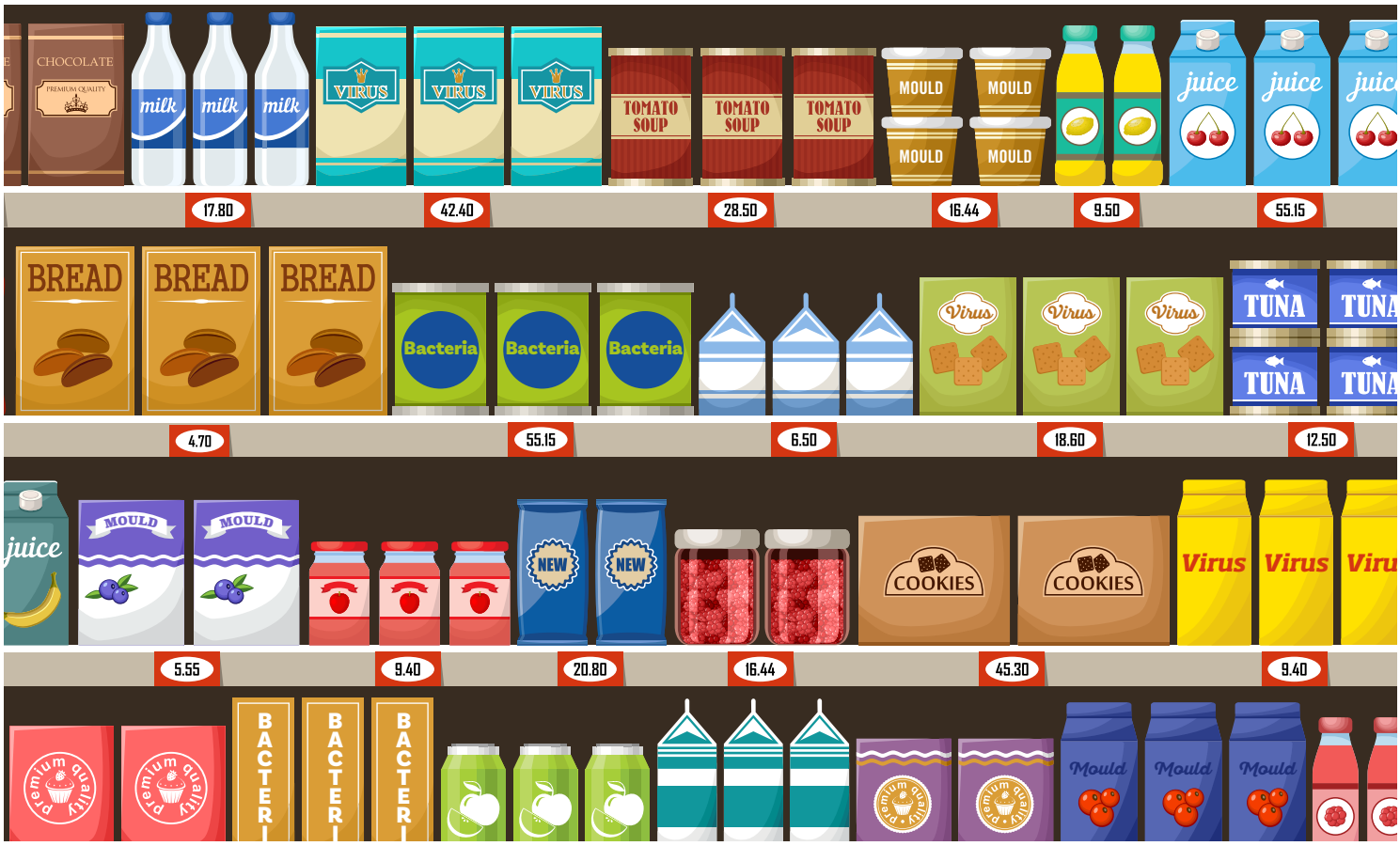
For almost all of human evolution our food and water has contained large numbers of microbes. Our immune systems evolved to cope with this daily intake, and our microbiomes (the collection of microbes on and in the human body) are increasingly recognized as playing an important role in human health. However, in recent times we have gone to great lengths to eliminate microbes from our diets, using food processing, water purification and hygiene to reduce our exposure. But has this come at a cost? Could our immune systems, primed to deal with trillions of microbes with every meal, be struggling to cope with their absence? Could this be a factor in the rise of modern inflammatory diseases in which the immune system misbehaves in response to dietary antigens or to our own epithelial cells? Perhaps we need to go back to consuming large numbers of (safe) microbes every day – a microbial RDA?

Throughout evolutionary history humans (and all other members of the Kingdom Animalia for that matter) would have encountered large numbers of microbes in the diet. Food and water collected from the environment by hunter-gatherers would inevitably have carried many bacteria, yeasts, moulds and viruses. The development of fermentation strategies for food preservation by our distant ancestors would also have ensured frequent ingestion of large numbers of safe microbes. It is also likely that our antecedents would not have been as particular in deciding when food was too spoiled to eat (early humans almost certainly did not observe 'best-before' instructions). It is difficult to guess at the numbers involved, but we could confidently expect our daily exposure to have been well in excess of 10^{10} microbes per day. Even the advent of cooking (approximately 2 million years ago) would not have significantly diminished the exposure to microbes in our diet. We can confidently expect that our immune systems, particularly the gut immune system, evolved to 'expect' daily exposure to large numbers of microbes. It is not surprising that a highly sophisticated immune system is located in the gastrointestinal tract with a vast array of receptors designed to recognize microbial molecules, and that our gastrointestinal immune system plays an important role in sifting out the beneficial or harmless food microbes from pathogens targeted for destruction. At some point in evolution we also discovered the benefits of drying, salting, sugaring and pickling our foods, while in more recent times the development of effective food processing tools such as pasteurization and canning, refrigeration, freezing, aseptic packaging, food preservatives, water treatment and washing of fruit and vegetables before consumption has inevitably reduced our exposure to microbes. Of course, these more recent advances have happened in much too short a time for our immune systems to evolve and adapt to this significant reduction in microbial intake.

It must be acknowledged and stressed that these food and water processing strategies have certainly reduced morbidity and mortality associated with food- and water-borne infections and thus form a vital role in protecting human health. I am not advocating a return to unhygienic food and water since this would be devastating to human health, particularly in a modern world where many people with compromised immune systems thankfully live long and productive lives. We do not want to return to an age where infectious disease claimed so many lives and only the 'fittest' or 'fortunate' survived into adulthood. But is it possible that these advances in food processing have come at a price in terms of losing our daily contact with dietary microbes?

It is only in recent years that we have begun to appreciate the importance of our microbiomes – the vast array of microbes that live on and in the human body. Leaving aside the usual tropes of how we are more microbial than human in terms of cell count, we have come to appreciate that these commensal bacteria play important



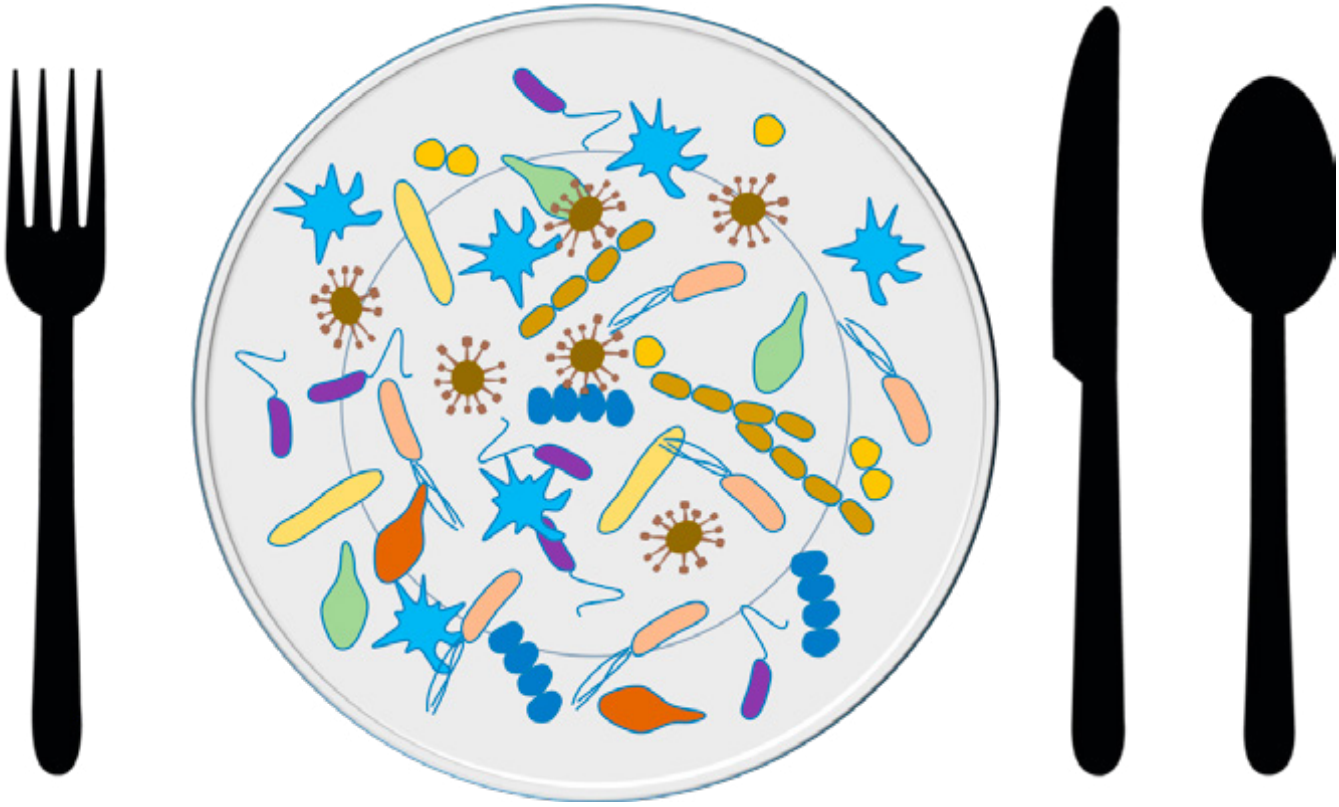
roles in our health. The evidence is compelling that these microbes influence health in many ways, including even a significant impact on mental health. In fact, over 10,000 papers were published in 2017 with 'microbiome' as a key word, emphasizing the current research effort devoted to this field. Our microbiomes are composed mainly of long-term resident or commensal bacteria we have accumulated over a lifetime, and the impact of dietary microbes is likely to be fleeting in comparison. But we should remember that most of our estimated 10^{14} resident gut microbes are located in the large intestine, whereas most of our immune cells (and those of our enteric nervous systems) are located in the small intestine. Thus, it is entirely feasible that dietary microbes arriving in the upper gastrointestinal tract could have a disproportionately larger impact on our immune system and enteric nervous systems than their relatively low numbers (in comparison with our microbiomes) would suggest. It is tempting to speculate that, in the absence of this daily influx of microbes, our underutilized immune systems could well be primed to react abnormally to other dietary antigens, or even to our commensal microbes. Could this play a role, however small, in the increased incidence of modern maladies such as food intolerances, low-grade inflammatory conditions and even atopic diseases (given our common mucosal immune system)?

Probiotics, prebiotics and synbiotics

Probiotics are safe living bacteria which have been shown to have a beneficial effect on human health. Several thousand human trials have been conducted with probiotics and the general consensus is that they can work well in certain health conditions, but the precise mechanism of action remain unknown for many probiotics.

Prebiotics are ingredients (often complex carbohydrates) which cannot be digested by the human body, but are consumed by the bacteria living in the human gut. They are selective for certain groups of bacteria, and those which favour the growth of beneficial bacteria are considered to be prebiotic.

Synbiotics are a combination of a prebiotic and a probiotic. In essence, the concept is that you provide both the beneficial bacteria (probiotic) and a selective food (prebiotic) which it can use in the gut, resulting in a synergistic effect (synbiotic).



Is there any evidence to support the hypothesis that dietary microbes can benefit health? Yes, there is. In 1907 the Nobel Prize winning immunologist Ilya Metchnikoff published his treatise on longevity entitled "*The Prolongation of Life: Optimistic Studies*". He proposed, on the basis of observation rather than experimentation, that Bulgarian peasants who ingested a large amount of fermented dairy products enjoyed long and healthy lives. He attributed this to the health benefits of the bacteria contained within yoghurt and other soured milks. This initial observation is usually credited as being responsible for the development of the probiotic concept which has grown into a multi-billion Euro industry and has also been the basis of thousands of scientific papers. It is not difficult to find papers in excellent journals describing trials conducted to the highest standards (double-blinded, placebo-controlled) which demonstrate a range of health benefits for probiotics across immune conditions such as IBS (irritable bowel syndrome), ectopic diseases and even in anxiety, stress and cognition. One recent paper in *Nature* described a large randomly controlled trial involving over 4,500 Indian children which resulted in a highly significant reduction in sepsis following the consumption of a combination of a probiotic and a prebiotic (an indigestible oligosaccharide which can only be metabolized by gut bacteria). The beneficial effect of probiotics is undeniable and scientists have worked hard to decipher the underlying mechanistic basis, but to date they have proven elusive. In fact, the broad range of health benefits associated with so many strains of probiotics has made many critical of the field, since if you assume a specific underlying mechanism for each health benefit, it seems unlikely that popular commercially available probiotics could have such wide ranging benefits. The broad range of benefits also seems improbable if you consider that most of the commercially available probiotics were selected decades ago on very simple criteria such as good growth rates in microbiological media, resistance to bile and an ability to survive gastric transit.

However, if we consider that it may simply be the consumption of large numbers of safe bacteria that could confer a broad range of benefits then this may not be such a conundrum. This concept was featured in a recent consensus paper on the definition and scope of probiotics which referred to 'core benefits' of probiotic species – capturing the idea that the consumption of large number of almost any safe bacteria may have

broad ranging benefits, particularly in preserving health and in alleviating mild health problems. The same paper stressed that there are almost certainly individual probiotics that have more specific benefits, and so anyone choosing to take a probiotic because they suffer from a particular health issue would be well advised to look for strains or products with proven clinical evidence to support efficacy in those conditions. Nonetheless, the idea that consuming large numbers of safe bacteria is beneficial to preserving and even restoring health has some compelling supporting evidence. Consider a meta-analysis (one of many) conducted in 2012 which looked at 84 trials spanning 10,351 patients, 11 probiotic species or mixtures, and across eight gastrointestinal diseases. The authors concluded that "*Across all diseases and probiotic species, positive significant effects of probiotics were observed for all age groups, single vs. multiple species, and treatment lengths*". Surely studies like this argue convincingly for the benefits of safe bacteria consumed in high levels in the diet.

As an aside, it has always seemed odd to me that we accept without question the fact that the ingestion of a relatively tiny number of food-borne pathogens can have a massively disruptive effect on human health, even leading to death, but we are sceptical of the idea that the ingestion of much higher numbers of safe microbes could have any positive impact on human physiology. Perhaps even as scientists we instinctively subscribe to the idea that it is easy for a microbe to be bad, but much less likely for one to do good?

So, how do we persuade a public brought up on the importance of hygiene, cleanliness and the prevailing message that the only good bug is a dead bug, to increase the numbers of microbes in their diets? Perhaps we could adapt the concept of an RDA (recommended dietary allowance) for microbes, taking advantage of the fact that this terminology is already familiar to consumers in the form of nutritional advice. The idea is simple; in addition to the existing RDAs for macronutrients, vitamins and trace elements, dietary guidelines should also advise consumers to deliberately include safe microbes in their daily diets. This should prove an easy message to convey and could be accomplished in a number of ways, but recommending increased consumption of fermented foods and the use of probiotics in food or in food supplements are two obvious solutions. What levels, and what microbes, I will leave to another day and/or to experts better able to consider this aspect, but I believe the microbial RDA concept is worthy of debate in a time of such high levels of chronic disease and gastrointestinal discomfort among so many individuals within society. ■

Further reading

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