NUCLEOTIDES: SPECULATION ON LIFESTYLE-INDUCED ESSENTIALITY

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During the course of our lives, few of us have knowingly encountered scientific revelations that suggest deficiency of an entire category of micronutrients may be contributing unnecessarily to dysfunctional health or disease. We tend to assume that the science of micronutrients is well understood and relatively complete - a branch of science that's matured considerably since Albert Szent-Györgyi and a fellow researcher's discovery in 1931 of vitamin C, the molecule responsible for the long-known anti-scurvy activity of lemons and limes.

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Today, we find ourselves in an era, not where a new category of micronutrients has been discovered, but one when the importance of an already recognised micronutrient category - that until now has been considered by researchers in the field only as 'conditionally essential' (1,2) - might actually be seminally important for good health. In fact, based on its plethora of properties and activities, ranging from its role in DNA repair, gut mucosal repair and immune function, to name but a few, it may be just a matter of time before this category is generally regarded as 'essential' to human health. The micronutrient category we're referring to is of course nucleotides. In this article, we'd like to take you through some of the main landmarks in the story of discovery that leads us to this powerful speculation.

NUCLEOTIDES

Nucleotides are ubiquitous, low molecular weight, intracellular compounds that are best known as the key structural components of the 'molecule of life', deoxyribonucleic acid, or DNA. They are comprised of a nitrogenous base (= nucleobase), a pentose sugar (ribose or deoxyribose) and one to three phosphate groups. In DNA's most familiar double helix structure, two nucleobases are loosely bonded by hydrogen to form the steps in DNA's ladder, while the pentose-phosphate molecules form the backbone of the spiral.

The term ribonucleotide refers to molecules where the pentose sugar is ribose, not deoxyribose. Ribonucleotides are, in turn, categorised according to their nucleobase types; purine ribonucleotides are those where the ribose is bound to any of the purine bases adenine (A), guanine (G) or inosine (I), while pyrimidine nucleotides are those where the ribose is linked to any of the pyrimidine bases cytosine (C), uracil (U) or thymine (T).

It is clear that the requirement for nucleotides will depend on the rate of requirement of new cells. Cellular proliferation will be greatest at times of rapid growth and development, but even in adults, there are particular times where proliferation rates exceed those associated with normal metabolism. The immune system, for example, especially when reacting to infection, can ramp up output of specialist defence cells such as neutrophils dramatically (3). But it's the intestinal tract that has the highest rate of cellular turnover in the body, this rate being greater during periods of infection or when damage to the gut mucosa is in need of repair (4).

The question is: can the body produce or salvage the necessary nucleotide building blocks to produce all these new cells, even when demand is at its highest? Extensive research has revealed that the body can both synthesise new nucleotides, as well as being able to salvage 'spare parts' to allow the production of vital DNA and RNA for each cell. These two pathways are referred to, respectively, as the de novo synthesis and salvage pathways (5).

However, it has also become apparent that there is a third and important way in which nucleotides are supplied to the cells of our bodies. This is from exogenous sources - through the diet. During periods of greatest cellular proliferation, it seems endogenous sources may not be sufficient for the body's needs. This has led to a view that dietary nucleotides are 'conditionally essential' (1,2). It is also important to note that the two endogenous pathways are costly in metabolic energy terms, making dietary intake of nucleotides particularly important when the body's resources are already under pressure (6).

WHEN DOES THE BODY DEMAND NUCLEOTIDES MOST?

Research to date reveals clear evidence for a particularly high nucleotide requirement at times of rapid growth, malnutrition, infection and injury (2,7,8). This understanding has, in turn, spawned research that has demonstrated the benefit of supplemental dietary nucleotides in particular situations:

1. in infant formulae with the aim of mimicking the nucleotide content of breast milk (2, 9);
2. to help enhance immunity and gastrointestinal health in malnourished young children (8,10,11);
3. to support adult immunity following surgery and transplant (12);
4. to help offset the effects of oxidative stress in athletes (13, 14);
5. for patients with irritable bowel syndrome (15).

What's more, recent mechanistic findings that reveal nucleotides' fundamental role in DNA repair and the maintenance of chromosomal stability (16) - two of the most important cancer protective factors - is likely to stimulate further research on the potential role of supplemental nucleotides in cancer prevention strategies.

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Table 1. Purine, RNA, and protein content of selected foods (from Clifford and Storey, 1976)

	Adenine	Guanine	Hypox-anthine	Xanthine	Total purines	RNA	Protein
Organ meats	mg/100g						%
Beef liver	62	74	61	0	197	268	20
Beef kidney	42	47	63	31	213	134	18
Beef heart	15	16	38	102	171	49	19
Beef brain	12	12	26	112	162	61	11
Pork liver	59	77	71	82	289	259	22
Chicken liver	72	78	71	22	243	402	20
Chicken heart	32	41	12	138	223	187	18
Lamb liver	32	43	54	18	147	88	22
Lamb heart	30	23	20	98	171	50	19
Fresh seafoods	mg/100g						%
Anchovies	8	185	6	212	411	341	20
Clams	14	24	12	86	136	85	17
Mackerel	11	26	5	152	194	203	23
Salmon	26	80	11	133	250	289	23
Sardines	6	118	6	215	345	343	23
Squid	18	15	24	78	135	100	15
Canned seafoods	mg/100g						%
Anchovies	0	39	14	268	321	6	30
Clams	30	5	7	20	62	44	20
Herring	15	180	6	177	378	82	17
Mackerel	23	109	16	98	246	122	26
Oysters	39	22	30	16	107	239	9
Salmon	23	39	13	13	88	26	26
Sardines	19	95	30	255	399	590	24
Shrimp	16	12	15	191	234	10	22
Tuna	27	13	11	91	142	5	29
Dried legumes	mg/100g						%
Garbanzo bean	17	14	18	7	56	256	21
Cranberry bean	21	19	23	12	75	248	17
Split peas	88	74	11	22	195	173	21
Red bean	54	51	15	42	162	140	20
Lentils	104	82	20	16	222	484	28
Blackeye peas	77	80	32	41	230	306	22
Large lima bean	42	41	14	52	149	293	21
Baby lima bean	46	39	25	34	144	190	19
Pinto bean	57	54	16	44	171	485	20
Small white bean	59	74	25	44	202	305	18
Great northern bean	56	68	25	64	213	284	18

LESSONS FROM OUR EVOLUTION

Purine and pyrimidine nucleotides are likely to have been the first complex chemical structures to emerge from the 'primordial soup', the broth that is thought to have provided the essential ingredients required for the development of life on this planet. It has been proposed that these early nucleotides may have been formed through the reaction of mixtures of cyanide and methane, or urea, in the presence of ultraviolet light from the sun (17). As the structural components of nucleic acids, nucleotides can thus be considered the proverbial building blocks of life.

There is now consensus that early hominids were not exclusively vegetarian (18). They were likely reliant on animal foods, not only to provide protein (19), which is more efficiently converted to energy from animal than from vegetarian sources (20), but also to provide amino acids and other micronutrients (21).

Evolutionary anthropologist Katherine Milton stated: "We need to bear in mind that carnivores and omnivores do not eat only muscle tissue or only muscle and fat, but instead eat brains, viscera, bone marrow, the liver and other organs. These different animal tissues provide different types and proportions of particular nutrients." (22)

From an evolutionary perspective then, it becomes relevant to compare the likely nucleotide content of our modern, western diet with those of ancestral diets, especially those that were common place over 10,000 years ago before the domestication of animals and plants and the industrialisation of agriculture and food production methods. One of the simplest ways of getting a feel for this is simply to analyse the nucleotide content of different food groups and compare the total amounts that may be consumed, according to the combination of different food groups. A useful analysis was conducted over 30 years ago by Clifford and Storey (1976) (23), although analysis was limited to various nucleobases, total purine, RNA and protein content (Table 1). The RNA content approximates to total nucleotide content.

Given that organ meats and offal provide among the highest sources of nucleotides, and these sources are now largely excluded from the modern, western diet, it has become something of a quest for nucleotide producers to further evaluate contemporary dietary sources for their total nucleotide content.

A summary of some recent analyses are shown in Figure 1, these being based on analysis of freeze-dried samples by High Performance Liquid Chromatography (HPLC). The results are represented on the basis of the nucleotide content per typical portion size to allow estimation or comparison of dietary intake. The results reveal some dramatic differences in likely nucleotide intake in meat versus vegetarian diets, again pointing to the highest contents in offal meats that are less consumed today.

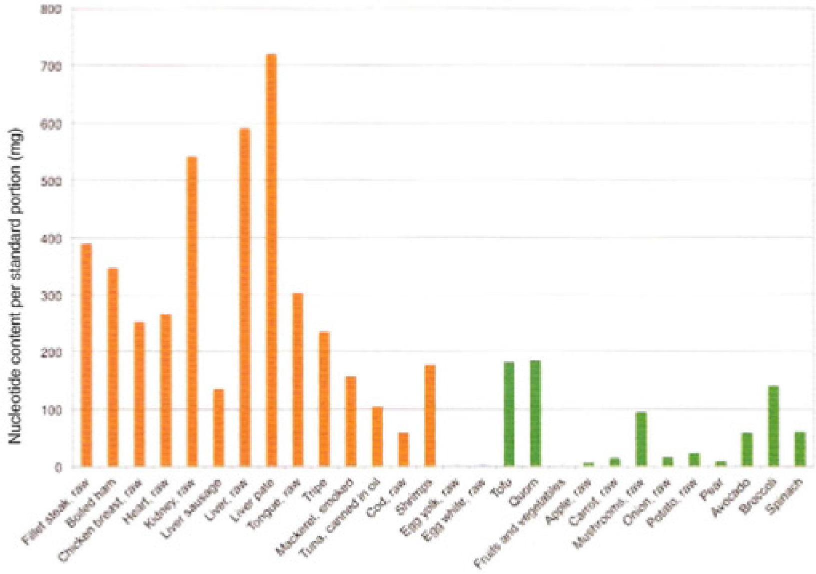
Considerable differences in nucleotide profile have also been found between different protein sources, and experience with farm animal studies has demonstrated over the last 20 years that a full spectrum of both pyrimidine and purine nucleotides are required for optimum results. For humans, it is advised that supplementary sources should not be purine dominant, as benefits are reduced, and, at very high intakes

(>1,000mg/day per adult, or >17mg/kg body weight), purine nucleotides may elevate serum uric acid concentrations above the normal range (24). Levels four times higher than this could, with long-term ingestion, contribute to hyperuricemia and gout. Owing to different metabolic end-points, high intakes of pyrimidine nucleotides have not been associated with any adverse effects (24).

WHAT CAN WE LEARN FROM OUR VETERINARIAN COLLEAGUES?

In short, a lot! Nucleotides are not the only area of nutrition where veterinarians have outshone their anthropocentric counterparts in terms of putting theory into practice. Veterinarians, historically, have been responsible for some of the most influential evidence demonstrating the essentiality of minerals and trace-elements. And because - as far as most of us are concerned - animals don't speak, nutritional regimes that are shown to deliver results tend to be those that are incorporated into animal production methods. It's highly relevant, therefore, that progressive pig and fish farmers have for over 20 years understood the value of adding carefully balanced nucleotide additives to their animal's feed. Why do they spend money on these additives? Quite simply because they are able to maintain the quality and immune health of their stock while decreasing, or even eliminating, use of antibiotics.

Figure 1. Evaluation of total nucleotide content of a range of meat (orange) and vegetarian (green) protein sources according to typical single portions (analysis by Chemoforma/ProBio, produce purchased from supermarkets in Zürich, Switzerland).



The role of supplementary nucleotides on enhanced immunity is very well demonstrated. However, there has been considerable discussion over possible mechanisms. One of the most illuminating findings is that nucleotides appear to facilitate DNA repair resulting from damage caused by radical oxygen species (ROS). For example, in 2005, a carefully controlled study in pigs showed that genotoxicity of a high polyunsaturated fatty acid diet, expressed by

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the degree of DNA damage to lymphocytes, could be completely eliminated by supplementary nucleotides (25). In support of the importance of nucleotides' DNA repair capability, a very recent study has shown that DNA repair may be even more important to good health and reduced cancer risk than radical scavenging by antioxidants (16).

This might well explain the particular and unequivocal success experienced by fish (26) and pig (27) farmers using supplementary nucleotides. As the metaphor goes, the proof of the pudding is in the eating…

LOOKING CLOSER AT THE NUCLEOTIDE CONTENT OF OUR DIET

So, what about our own diets? How much have they changed with regard to nucleotide content and profile? A number of patterns emerge here. First, there are very large variations in the nucleotide contents of different foods and as a species we have seen considerable dietary shifts, especially since the domestication of plants and animals associated with agriculture (28). There is also no doubt that decreased meat and especially offal consumption have dramatically reduced both the amount as well as the nucleotide content of meat products consumed (Table 1, Figure 1). This is likely associated not only with changing consumer preferences but also with modern, mechanised butchery practices and meat preparation methods.

SPECULATION ON NUCLEOTIDE ESSENTIALITY IN CONTEMPORARY HUMANS

There is now widespread recognition among scientists that dietary simplification associated with the industrialisation of the human food supply is contributing to increased incidence of preventable chronic, inflammatory diseases (29), which now place the greatest burden on healthcare systems the world over (30). Poor food choices and inappropriate lifestyle, including physical inactivity, exacerbate the problem.

It is becoming evident that, like animals subjected to intensive production systems, many humans are now subjected to consistently high levels of chemical, physiological and immunological stress. Such stresses, it seems, may generate demands on the body's nucleotide pool that simply cannot be served by endogenous production. Available food choices and declining dietary intake of balanced nucleotides in contemporary diets are, again, unlikely to meet the necessary shortfall, especially given available sources, dietary choices and the fact that the optimum daily requirement for nucleotides appears to be in the hundreds of mg/day range for adults.

Reverting to levels of dietary nucleotide intake associated with our pre-agricultural past, when offal was an important element of our meat intake, now appears a major challenge for most of us. This is especially the case if this intake is to be achieved consistently, on a daily basis, week in, week out. Supplementary intake, for many, remains one of the few reliable methods of ensuring consistent nucleotide intake, especially of the appropriate, balanced profile.

We can therefore speculate: could it be that fundamental nutritional benefits associated with nucleotides, such as DNA repair, cancer risk reduction and gastrointestinal and immune health, would be well served by consistently elevated intake of those invaluable DNA spare parts that appear to be otherwise in short supply? We propose that this requirement for supplementary nucleotides could be contemplated as a form of lifestyle-induced essentiality, as distinct from the more usually considered physiological essentiality. ■

References available on request Email: info@networkhealthgroup.co.uk