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Nicotinamide's Ups and Downs: Consequences for Fertility, Development, Longevity and Diseases of Poverty and Affluence

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AIMS AND SCOPE:

To further explore the role of dietary nicotinamide in both brain development and diseases, particularly those of ageing. Articles cover neurodegenerative disease and cancer. Also discussed are the effects of nicotinamide, contained in meat and supplements and derived from symbionts, on the major transitions of disease and fertility from ancient times up to the present day. A key role for the tryptophan – NAD 'de novo' and immune tolerance pathway are discussed at length in the context of fertility and longevity and the transitions from immune paresis to Treg-mediated immune tolerance and then finally to intolerance and their associated diseases.

ABSTRACT: Nicotinamide in human evolution increased cognitive power in a positive feedback loop originally involving hunting. As the precursor to metabolic master molecule NAD it is, as vitamin B3, vital for health. Paradoxically, a lower dose on a diverse plant then cereal-based diet fuelled population booms from the Mesolithic onwards, by upping immune tolerance of the foetus. Increased tolerance of risky symbionts, whether in the gut or TB, that excrete nicotinamide co-evolved as buffers for when diet was inadequate. High biological fertility, despite disease trade-offs, avoided the extinction of *Homo sapiens* and heralded the dawn of a conscious, creative, and pro-fertility culture. Nicotinamide equity now would stabilise populations and prevent NAD-based diseases of poverty and affluence.

KEYWORDS: Demographic, neanderthal, neolithic, evolution, meat

'What makes a plenteous harvest, when to turn, The fruitful soil,
and when to sow the corn; The care of sheep, of oxen . . .'

Virgils Georgics

Introduction

Tryptophan and nicotinamide metabolism is intricately linked as both are precursors for the metabolic, immunologic and behavioural master molecule NAD. The lesson of pellagra is that deficiency of NAD causes neurodegenerative and psychiatric diseases. Pellagra also profoundly affects the immune system leading to susceptibility to acute pathogens as well as welcoming symbionts that excrete nicotinic acid in a metagenomic homeostatic system. Such symbionts include TB and members of the gut microbiome, even worms, which become dysbiotic and cause disease when the diet is exceedingly poor. Dietary deficiency is not the only route to NAD deficiency as via NAD consumers such as SIRT6 and PARPs many forms of stress or mutations lead to higher requirements as does growth and reproduction.^{1,2} Excess of nicotinamide from diet and supplements could induce NNMT, a common marker of modern diseases: adjustments in nicotinamide dosage or enzyme inhibitors may therefore have a role in preventing or treating current illness.^{3–7}

Dietary-Driven Evolution – Omnivore Advantage

The importance of nicotinamide dosage is best seen from the perspective of evolution. Our distant ancestors upgraded from grasses to fruits and insects then meat as increasingly well-equipped hunters, butchers, and cooks. We are an omnivore (not a carnivore although Neanderthals got closer) with high

meat consumption during our formative period as hunter-fisher-gatherers. An omnivore has survival value in a variable world (as long as xenobiotic metabolism or cooking deals with plant toxins) and enables a species to manipulate brain power and behaviour, including reproductive, of its own citizens. Man uses convergent evolutionary tricks, like isogenic eusocial insects, by using vitamins to divide the labour force.

Meat is Good for Brains – But Led to Small Populations

Moving up the food chain 2 to 3 million years ago when prey was plentiful, thanks to climate change providing plentiful grasslands (rather than forest), and eating more meat gained more nicotinamide and allowed larger brains – pellagra exemplifying the degenerative and atavistic opposite.⁸ This move culminated a story that began with animals eating animals first in the pre-Cambrian increasing the NAD supply for big-brained species.

Social norms were centred on meat sharing and taboos. Our enlarging cognitive, social, and technological brains, despite our puny size, captured the meat supply, alongside the equally difficult task, particularly in non-temperate zones, of sourcing sufficient fruit and nuts, tubers, and vegetables.^{9–23} Notably, hunter-fisher-gatherer population sizes were low and suffered local extinctions as did related species, namely, the Neanderthals.

Diet Pushed and Pulled

Whether due to climate change or hunter-induced megafaunal extinctions, whose parties reached all corners of the world, there was a decline in meat availability around 50 000 years ago,



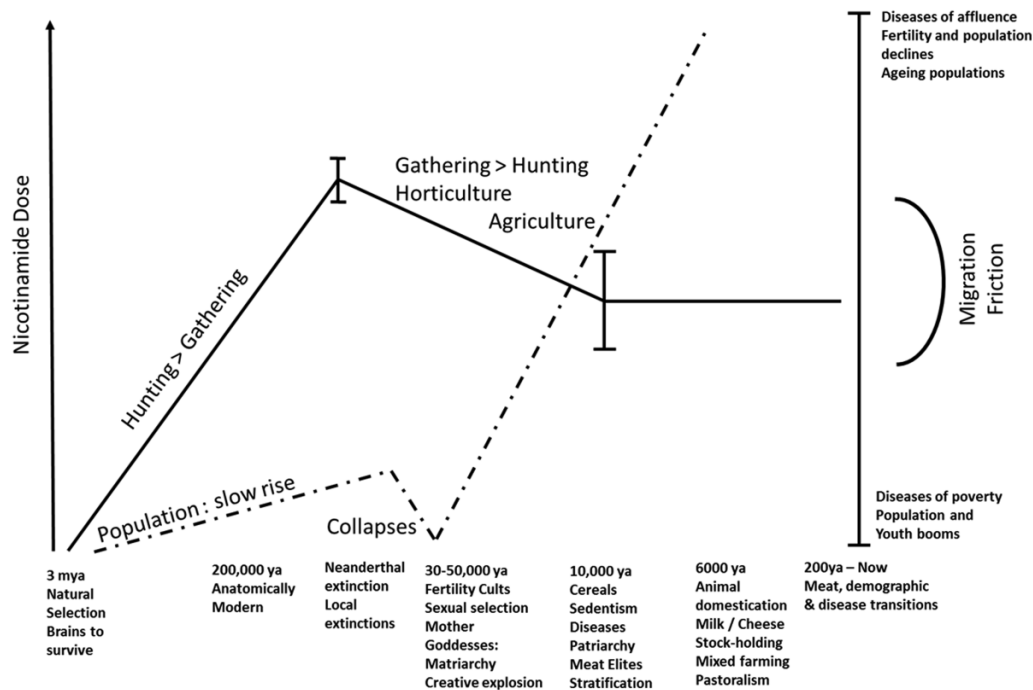


Figure 1. Nicotinamide dose – the ups, downs, and increasing variances correlate with population booms and busts and the emergence of common diseases. Not shown are European examples of meat consumption rising after the Black Death with centuries of good health and population stability. Later in the 18th century, meat consumption fell with the emergence of diseases, such as TB and pellagra, that we now link with the tropics and poverty in the less developed world and with localised population booms. From 1850 onwards, in the United Kingdom and United States, meat consumption rose, until recently, and modern demographic and disease transitions later completed in the rest of the developed world (some now reversing) and are in progress elsewhere or have stalled (such as in sub-Saharan Africa).³⁶⁻⁴³

but a corresponding increase in plant diversity after the Ice Age and usage of berries, nuts, barks, vegetables (eg, sprouts, leaves, and seaweeds), and underground tubers, rhizomes, and bulbs as a ‘broad-spectrum’ revolution.²⁴⁻³² We argue this pushed our diet towards plants and then a ratchet kicked in pulled by the higher fertility possible on a lower meat diet – even at the expense of the emergence of many dietary and secondary infectious diseases, not simply explained by crowd infections³³⁻³⁵ (Figure 1).

Fertile Crescents and Fertile Peasants

Nicotinamide is important for the maintenance of high intelligence and health as discussed in this supplement. However, severe gradients between rich and poor appeared after the Neolithic agricultural and cereal revolution that began in the Middle East ‘fertile crescent’ but evolved independently at several other sites. Meat shortages led to meat elites holding the power, although the poorer classes have been the engine of population increases and Malthusian crashes whether from famine, war or plagues.⁴⁴⁻⁴⁸

Social Stratification – Meat Elites and Meat Strife

A second revolution of animal domestication with more meat and now milk and cheese and ploughs increased cereal production. This happened a few thousand years after crops (later in the New World due to lack of domesticable species). Progress came with stock holding and (cattle)capitalism and

frictions within and between states – but also the birth of democracy and mixed farming.⁴⁹⁻⁶¹ Differential access to resources, rather than political or religious power for its own sake, has been invoked with evidence of more meat for the rulers (unlike egalitarian hunter-gatherer societies). This explains ruler’s interest in irrigation and hydraulics and other agricultural and storage granary schemes. But the real reason was to create a sliding scale between meat elites that rule through cognitive prowess and a more fertile labour force useful for agriculture, building manufacturer, or as foot soldiers to gain more resource by trade or by force.⁶²⁻⁶⁸ Both extremes are needed and could explain why democracies representing all have been so successful compared to oligarchies.^{69,70}

Culture, Language, Counting and Writing – Smart Elites

Language would have helped the hunt and later writing and maths kept tally of sheep and goats and cereal yields (to tax) in large part to allow for redistribution of rations not originally to the poor but to the non-agricultural classes that included artisans and political or religious oligarchies – who often held convenient belief systems on animal and human sacrifice that enhanced their own diet. Science and astronomy had their appeal for agricultural and family planning by the time of the year or month and later for navigation in search of supplies. All would have been driven by the clever members of much bigger consumer societies.

Quantity vs Quality: 'r' and 'K' Strategies

Later innovations included pastoralism and use of desert space to increase animal production and use of animal products especially milk and with the necessary fermenting skills, cooking with cultural learning, pottery for storage, and genetic change to digest more carbohydrates and lactose. So the scene was set for good nicotinamide sourcing.^{71–73}

High nicotinamide comes with relative infertility and immune intolerance both to the foetus and other otherwise innocuous antigens through suppressing the tryptophan-NAD immune tolerance pathway as discussed in 3 articles in this supplement.^{74–76} This gives a mechanism that explains how the quantity ('r' selection) and quality ('K' selection) trade-off of human fertility variation works and integrates with disease and ageing.^{10,21,23,77–84} An additional biochemical point is that induction of the tryptophan-NAD 'de novo' and immune tolerance pathway requires a dietary supply of tryptophan and other B vitamins, such as B2 and B6 as well as iron and zinc, much of which is also sourced from meat; so, when the diet becomes too poor, the immune system completely fails.^{85–87} These mechanisms solve the paradox of how severe dietary deficiency causes immune paresis and infertility but moderate deficiency of nicotinamide causes immune tolerance and high fertility with high nicotinamide levels causing immune intolerance and infertility.

Cognitive Variances – Environment Not Genes

The beneficial effects of meat on cognition as exemplified by pellagra is undoubted but so is an effect on the normal ranges of political, collectivist versus individualist, and even religious biases that have been recognised at least since the 17th century.^{88,89} The rise of IQ as the diet and environment improves (known as the Flynn effect), along with some evidence of reduced age-specific dementia incidence, is for certain but it decelerates and then peaks just like some recent reversals in fertility declines. One could relate this to the final fall in meat and therefore nicotinamide intake in 'flexitarian'-rich countries.^{90–93} Fertility and IQ are negatively correlated with a long history of dysgenic theories being proposed, and acted upon by eugenicists, but actually is mediated by the environment with nicotinamide improving intelligence but decreasing fertility by different lead mechanisms and perhaps different doses.^{94–96}

Death (and Fertility) in Venice

Intriguingly, a natural experiment towards the end of the late 18th century pellagra epidemic in northern Italy (particularly the Veneto region) among polenta and maize-dependant peasants analysed by a very distinguished epidemiologist 30 years ago gives strong support for this otherwise surprising suggestion.⁹⁷ Counties with a high incidence of pellagra deaths had low fertility and a high incidence of birth defects and stillbirths, whereas those counties where better economics improved diet moved to a much higher fertility rate that bucked the trend of those counties that had never had any significant pellagra where fertility was declining as part of

their secular demographic transition. In effect, low nicotinamide delayed the demographic transition by some 50 years. Women of reproductive age are prone to pellagra from increased needs and meat preferentially channelled to men and children and hormonal effects on tryptophan metabolism.^{98–100} Fertility differences are driven by dysmenorrhoea and male impotence or behavioural effects of nicotinamide deficiency. Compounded over many generations, the increase in fertility from low (or high) to modest dose that is at least 20% higher would be enough to affect population growth dramatically - and is clearer than the literature on macronutrients and fertility where there are contradictory effects.^{101–103}

Count the Babies – Discount Pre-conceived Ideas

Teleologically speaking, when supplies fluctuate between famines with plagues, and feasts, one can see that an early baby boom helps but needs to be contained. Sometimes feasts would include more meat as happened in the Palaeolithic (and after the Black Death or in the European and American transitions 1850–1950) but was not the case in many historical cereal-driven booms and busts or in sub-Saharan Africa now. Then, the natural nicotinamide switch to lower fertility fails allowing Malthusian corrections, whether plagues or wars.

One might have argued a priori that the better fed would have, or want, or be able to afford more children even when allowing for better infant mortality and the demise of child labour with long expensive educational years. Many conscious decisions may be post hoc rationalisations or blamed on late marriage and careers. An underlying biological explanation for the relative infertility of the rich would better explain their infertility clinics and the high natural fertility of the poor with their lack of success with contraceptive programmes.

A dietary and biological basis could also explain defects of current theories on demographic transitions.^{104–111} Low fertility appears to inevitably follow declining death rates but this is correlation not cause given we argue high nicotinamide leads to low fertility and longer lives but by different albeit overlapping routes – good ageing relating more to repair mechanisms dependant on the NAD supply and less on immune tolerance that affects fertility. A different dose response for the 2 mechanisms may define the delay and the length of that delay that can stall (or even reverse) drives the size of the population boom.

Different Diets not Hygiene.

Different sections of society have different diets going for quality or quantity of offspring on a spectrum. This defined the quest of the original societies for new lands and more meat or plants and whether by fair means or foul.^{112,113} Locally, as agriculture developed from a feudal system towards capitalism, overall productivity rose but at the risk of nicotinamide deficiency from excess cereals and less common pastures 'enclosures' available to peasants, let alone price (people will always increase meat in diet as incomes rise). Capitalism supports cooperative classes except when going too far from mixed farming and an omnivorous diet and market failure can be linked with both the

Italian and the American outbreaks of pellagra when the commercial drive for cereals or cotton for export was extreme.^{114,115}

This hunger for meat chimes with disease causation and the 'hygiene hypothesis'. However, it positions dietary change as primary and microbiome absence as secondary, with less need for symbionts, setting the scene for auto-immune disease.¹¹⁶ The best example with data is the decline in TB as meat and nicotinamide rise in diet as happened in the United Kingdom 1850-1950 (before antibiotics) as auto-immune disease and cancer took off.

Recap: Mothers of Necessity and Invention

The move back down the food chain came after becoming anatomically human at a time of very low populations (with lineage extinctions and 'bottlenecks') just before becoming behaviourally modern, around 30000 years ago – an era known as the Gravettian. Changes in fertility ranging naturally from local averages of just over 1 to around 8 (replacement value is about 2) children per woman multiplied over millennia were driven by diet and culture.

Psychedelic plant-derived serotonin or tryptamine derivatives may have been important then (rediscovered now) in evolving consciousness, imagination, and relationships with nature through adding perspective and by disrupting circadian and natural oscillations in default NAD-driven networks.¹¹⁷⁻¹²² This hitherto unexplained creative explosion, and we argue reproductive explosion was exemplified by cave art. Cave art emphasised the importance of hunted animals in grasslands (not forests) with many fertility symbols also seen in early portable art, such as 'Venus' figurines.¹²³ Many aspects of bonding such as marriage, (allo)parenting, grandparenting (evolution of long lives), kin and non-kin alliances, and developing ancestor worship, transition, and birth and death rituals coincided with the increased gathering, gardening, and later cereal food production and all increased viable children.^{117-122,124-133}

This steady drive down from gardening to often monocereal agriculture was because natural plant food included anti-fertility compounds (some used as abortifacients), whereas cereals do not (excepting ergotism), and cereals have exceptionally low levels of tryptophan and available nicotinamide. This gardening phase may have been necessary then and remains necessary now as many compounds were incorporated into our diet for drug usage both for medicine and as psychedelics. Many cultural issues over their preparation and cooking and de-toxification were important to learn and teach. Failures to pass on such teaching were critical to some outbreaks of pellagra where careful preparation of maize or use of a mixed diet can be important as it was with avoiding cyanogens in tubers.

A Fertility Crisis in the Mesolithic 'Gravettian' Triggered (Agri)Culture

Ornamentation, urbanism, cultural relics, rituals, and religions could all relate to solving this early fertility crisis. This crisis was

primarily solved by less meat and more plant-based food with more plant-based 'sickle and scythe' technology shifting the tryptophan 'de novo' pathway. Extravagant sexual selection overtaking natural selection for survival was also key to a mating brain. This was the era of mother and cereal goddesses and matriarchy.¹³⁴⁻¹⁴⁴ Hunter gatherers and pastoralists to this day have low fertility except when their diet moves towards more plant foods.¹⁴⁵

Biochemistry and Diet Explain History Better than the History Books

Historical events can be seen as agriculturalists fighting for pastoral lands or water (or now oil), or modifying their own land and crops for greater productivity, or as traders of meat for cereal. Farmers often lost out to mounted pastoralists such as Amorites, Huns, Goths, Mongols, or Scythians who overcome and then merged in a new equilibrium aided by inter-ethnic marriages and cooking. Most dramatic was the Colombian exchange where the meat-rich Old World easily overcame the meat-poor New World due to superior skills and disease. The poor constitution of those in the New World is true to this day in poor countries where diet is the commonest causes of immune incompetence – measles, for example, is 200 times as likely to kill where there is malnutrition.

The poor mysteriously win in the end – now explained by their better demographics with higher fertility even if there is a price to pay over cognitive quality and longevity.¹⁴⁶

Demographic and Disease Transitions – Not As Yet Understood

Now we can make sense of what has happened globally since the creation of the Third World by the richer nations chasing after new lands and water for agriculture, not just the gold – though now often the oil is the goal as the mechanisation and fertilisation of farming fails without a cheap supply. As a result, many in poor countries are meat and nicotinamide deficient leading to pellagra mimics such as environmental enteropathy or compensatory symbionts sent rogue by diet or drugs, such as TB or worms, being common but rarely diagnosed or treated. Increasing the nicotinamide dose switches populations towards higher longevity but many immune-mediated diseases as it switches off the immune tolerance pathway and Treg production. We already have the demographic link with booms on moderate NAD deficiency but busts on both severe deficiency and too high a dose in a 'U'-shaped curve.

However, successful societies needed a fertile and menial workforce that might resolve the curious case of progress correlating with moderate inequality and poverty.¹⁴⁷ This like poverty in the undeveloped world is no longer sensible and in effect an own goal reducing overall human capital.

Nicotinamide Dose may need Adjusting for Individuals and Circumstances

Even for the dietarily well-endowed at times of toxic or anoxic stress the nicotinamide dose may have to be increased temporarily, or adjusted permanently with some genetic mutations in

mitochondrial and NAD circuitry. These mutations survive from past dietary conditions evolved to cope with nicotinamide thrifty or luxurious times - or are pleiotropic, pro-fertility, pro-growth genes that are now risk factors for late onset cancerous and degenerative disease.

Nicotinamide Toxic and a Common Cause of Modern Disease?

Too much nicotinamide could lead to a phenotype that includes auto-immune diseases and the metabolic syndrome. Depression, sickness behaviour, and other neuropsychiatric diseases could be symptoms of both too low and too high a dose. Such an explanation could transcend Cartesian brain-body divided thinking with an 'inflamed brain' encompassing serotonin, dysbiosis, kynurenine, cytokine squalls, the vagus nerve, antibodies, and stress.¹⁴⁸⁻¹⁶⁸ Cancers that induce NNMT, as discussed by Ramsden et al,¹⁶⁹ are common. There is no shortage of mechanisms as induction of NNMT has good and bad effects on the methyl- and epigenome. Nicotinamide has a double-edged effect on NAD-consumer SIRT6 and PARP1 being a supplier of NAD and an inhibitor. NNMT induction early in life from diet or stress may stick and NAD deficiency could occur despite a diet within the normal range.

Trans-Generational Toxicity: Epigenome Health

Dynamic variation in lifetime exposure could have other untoward effects. A low dose and pellagra-like syndromes early in life even if corrected may pre-dispose to the metabolic syndrome later and deficient parents may pass on problems to children and even grandchildren by epigenetic means perhaps including intelligence and obesity.^{5,170}

The Answer: Judicious Meat and Nicotinamide Supplementation

Better nicotinamide homeostasis through diet and not relying on symbionts may reduce both diseases of poverty and affluence and cognitive health as well as the risk of dysbiotic and new pathogen pandemics hatched in poverty that are at risk for the rich and the poor.¹⁷¹⁻¹⁷³ Dietetic advisors failed to check that pellagra went away or that nicotinamide supplements were safe where the dietary dose from meat and milk was already high.

Meat: Stinting and Stunting

The emphasis of international aid has been on cereals and calories not meat. The meat case can get confused with the politics of pastoralism, or reducing illegal trade in bush meat, or concerns linked to the environmental cost of meat production. Pastures, however, are often not suitable for crops and we cannot eat grass and extract maximal energy from the sun without help from ruminant microbiomes. The situation in Asia and particularly sub-Saharan Africa is the unsustainable issue as there is little sign of the completion of their demographic transition. Can it really be a coincidence that meat intake is so low and pellagra still exists?

Nicotinamide Equity is Urgent: Measuring NAD(H) Would Help Make the Case

The urgent need for tryptophan and nicotinamide equity goes literally against the grain of received wisdom. Meat equity is central to our healthy metabolism, cognition, and immune status and to future generations futures. Virgil was right, a balanced diet derived from mixed farming is the sustainable model - the cereal-based Roman Empire should have listened (so resisting the pastoralist Goths) as should the world now. Nothing makes sense except in the light of evolution so we should learn the lessons of the archetypal disease, pellagra. We live in an NAD world of unequal NAD empires and NAD haves and have-nots. This iatrogenic situation is artificial and nobody really benefits long-term - it is only not obvious because NAD metabolism is not monitored.

Author Contributions

AW and LJH contributed equally to the manuscript and both approved the final version for publication.

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Lead Guest Editor **ADRIAN C WILLIAMS**

Adrian C Williams is a professor of Neurology at the University of Birmingham, UK. In 2012, he took a sabbatical to study human evolution at Oxford. As part of a master's thesis, he developed ideas on Nicotinamide and its importance for brain development and the need to source it from meat and symbionts. Surprising symbionts could include a co-evolution with tuberculosis, which excretes nicotinic acid – odd for a pathogen. He has been heavily influenced from studying the history of pellagra. He believes that new versions have not been eliminated, for instance, 'environmental enteropathy' and poor cognition in poor countries. Worrying (though avoidable) varied nicotinamide doses over lifetimes may risk epigenetic side effects such as the metabolic syndrome, and, transgenerational influences on intelligence could create vicious cycles and poverty traps. Latter, he has developed hypotheses, including those in this supplement, on the role of nicotinamide and the tryptophan immune pathway in explaining demographic and disease transitions. Even the first population boom at the time of the Neolithic agricultural evolution has never been explained: the move down the food chain to more plants and less nicotinamide was, he thinks, the cause of the rise of fertility, not a response to population pressure.



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Guest Editor

LISA J HILL

Lisa J Hill is a Lecturer at the University of Birmingham, UK. Lisa has a keen interest in neurological diseases and is working on the roles of nicotinamide in brain development and evolution.



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