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The 4 D's of Pellagra and Progress

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ABSTRACT: Nicotinamide homeostasis is a candidate common denominator to explain smooth transitions, whether demographic, epidemiological or economic. This 'NAD world', dependent on hydrogen-based energy, is not widely recognised as it is neither measured nor viewed from a sufficiently multi-genomic or historical perspective. Reviewing the importance of meat and nicotinamide balances during our co-evolution, recent history suggests that populations only modernise and age well with low fertility on a suitably balanced diet. Imbalances on the low meat side lead to an excess of infectious disease, short lives and boom-bust demographics. On the high side, meat has led to an excess of degenerative, allergic and metabolic disease and low fertility. A 'Goldilocks' diet derived from mixed and sustainable farming (preserving the topsoil) allows for high intellectual capital, height and good health with controlled population growth resulting in economic growth and prosperity. Implementing meat equity worldwide could lead to progress for future generations on 'spaceship' earth by establishing control over population quality, thermostat and biodiversity, if it is not already too late.

KEYWORDS: Climate change, CO₂ emissions, NAD worlds, protonopathy, Parkinson disease, demographic transition, disease transitions, deaths of despair, new levellers, metabolic rift, meat, nicotinamide, anthropocene, coronavirus, COVID-19, disease X

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'Exploration is not so much a question of covering the ground as of digging beneath the surface'.

–Claude Levi-Strauss

'And at the end of all our exploring will be to arrive where we started and know the place for the first time'.

–TS Eliot

Introduction

Our evolution has been characterised by articulated interactions between diet and agriculture and pro-family social and sexual cultures to raise healthy innovative children (Figure 1). Ultimately, the energy needed for such progress is derived from the sun and the soil in an 'NAD World' (Figures 2 and 3).

By the 4 'D's' of progress, we mean the major inter-related transitions of Demography, Domestication, Development and Disease. If these transitions were actual diseases, the lack of consensus on causation, prognosis or the value of interventions would lead to serious questions as to whether the 'diagnosis' was correct. Even when talking about diseases, 'beneath the surface' reasons behind the switch between chronic infectious and auto-immune disease and longevity as societies become wealthier are not understood – important as they represent a major preventive opportunity for otherwise 'lost generations'. We will suggest, as a few others have done in the context of health and economic losses from malnutrition, that the aspect of modernity responsible for all these transitions is diet.^{1–3} Our contribution relates to emphasising the importance of a good diet (rather than simply subsistence) and generous meat, with

the main active component being nicotinamide (Vitamin B₃). When deficient, this vitamin causes pellagra and the 4D's of Dementia (and low intelligence quotient), Diarrhoea (and chronic infections such as tuberculosis [TB]), and a characteristic Dermatitis (not always present) along with premature Death and a breakdown of symbiotic and social relationships. Nineteenth-century slave-owners recognised the consequent loss of productivity from poor diet and pellagra, yet we still do not fully recognise or act upon their insight when the food chain is longer extending to workers in other poorer countries.

Pellagra is, along with TB (that excretes nicotinic acid), a protean and archetypal disease of the poor: neither conditions are natural but are, by evolutionary standards, recent man-made inventions, as is poverty itself. We continue to make the case that not only is the diagnosis of pellagra missed in the poor but that nicotinamide status is the missing 'diagnosis' and first rung on the ladder that drives demographic, developmental and disease transitions. The upper classes and a series of empires got ahead on the meat curve driving capitalism and invention with the proletarian fertile classes, and countries, providing the labour in a fragile and misunderstood social contract. First of all, it is worth seeing this all in the context of an early 'D' – our Domestication.

Domesticator and Domesticated

Man was considered domesticated by Aristotle and Theophrastus and later by Blumenbach (1805), a professor of Medicine, who linked it to the emergence of culture and agriculture. Other species are domesticated by others, famous examples include leaf-cutter ants that farm fungi and, in co-evolutions, become dependent on



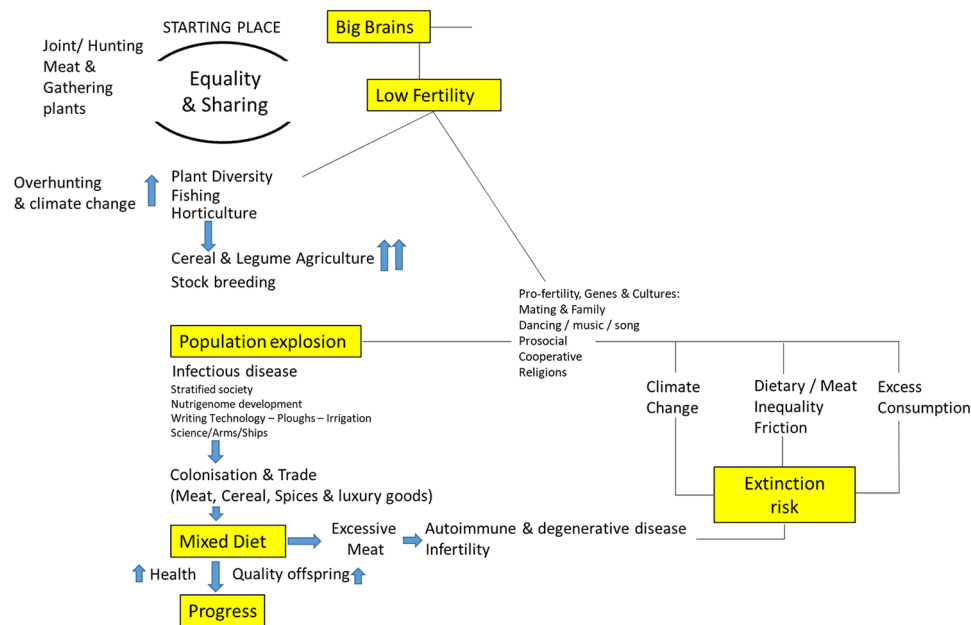


Figure 1. One thing led to another: Factors behind high populations and cultural dominance, or extinction.

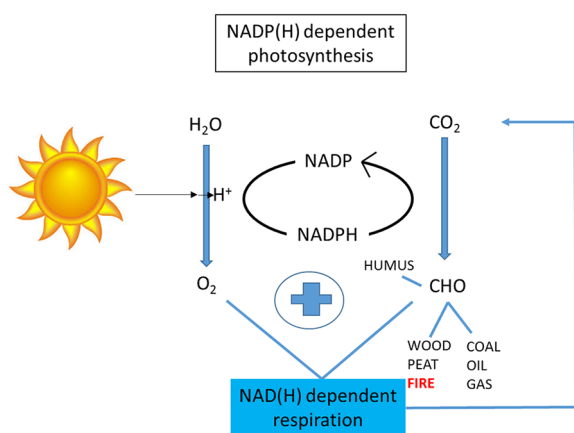


Figure 2. Basic formulae of photosynthesis, respiration and derived sources of topsoil and external energy. Essentially this is an 'NAD world'. NAD indicates nicotinamide adenine dinucleotide; NADP: nicotinamide adenine dinucleotide phosphate.

each other's reproduction, altering genomes and building niche-constructed environments.⁴⁻¹⁴ However, no plausible agent (some imagine supernatural forces) domesticated us (a fact that stymied Darwin) – so how did we auto-domesticate and why? We argue that a push down the food chain, forced by climate change and over-hunting of megafauna, began an unconscious selection of domesticates that merged into conscious selection, experimentation and domestication of plant, animal and even microbial domesticates pulled by higher reproductive rates of ourselves on a higher plant-based diet as well as themselves.¹⁵ So they domesticated us as we domesticated them – and all in the cause of bipartisan higher fertility, for us more babies. Illuminating wolf-dog and plant breeder experiments show how easily domestication can take place and that the pre-condition of potential tameness was necessary but the real selective and sufficient pressure was higher reproductive rates, as domesticated dogs or crops.¹⁶⁻¹⁹

Our cultural evolution was towards cereals and co-operation as part of a domesticated package that enabled higher fertility and the teaching and social learning of receptive and innovative children.²⁰⁻³⁴ The successful raising of children is intrinsic to our unusual metamorphoses and long life history with prolonged childhoods and adolescence through to mating, child-care and grand-parenting. This increase in fertility required a runaway sexual selection process enabling mating in an overarching social process incorporating commitment to the cause of reproduction, including art and science or state inducements and religious initiatives.³⁵⁻⁴⁷ Some apparent paradoxes such as violence, particularly to those outside family groupings, can be explained by protecting one's own progeny. In other words, depending on circumstance and context being good or evil, whether as an individual or as a state, when either benefit reproductive rates or the resources needed to bring up well-fed children.⁴⁸⁻⁵³

Demography

'Fecundity is totally checked by the plethoric state'.

–Thomas Doubleday in *The True Law of Population*: 1842

Population undoubtedly shaped the modern world, and trade-offs between quality and quantity of offspring or between fertility and longevity are evident at times of dietary hardship.⁵⁴⁻⁷³ Whether as hunter-gatherers or when on 'Western' diets, when meat intake is high, fertility falls often to below-replacement levels; whereas, whenever diet has been more cereal based, whether during the Neolithic or in sub-Saharan Africa now, populations boom.⁷⁴⁻⁸³ Human population growth rates and the link with agricultural revolutions and the rise in 'green-house' gases are shown in Figure 4. We have argued that this increased fecundity

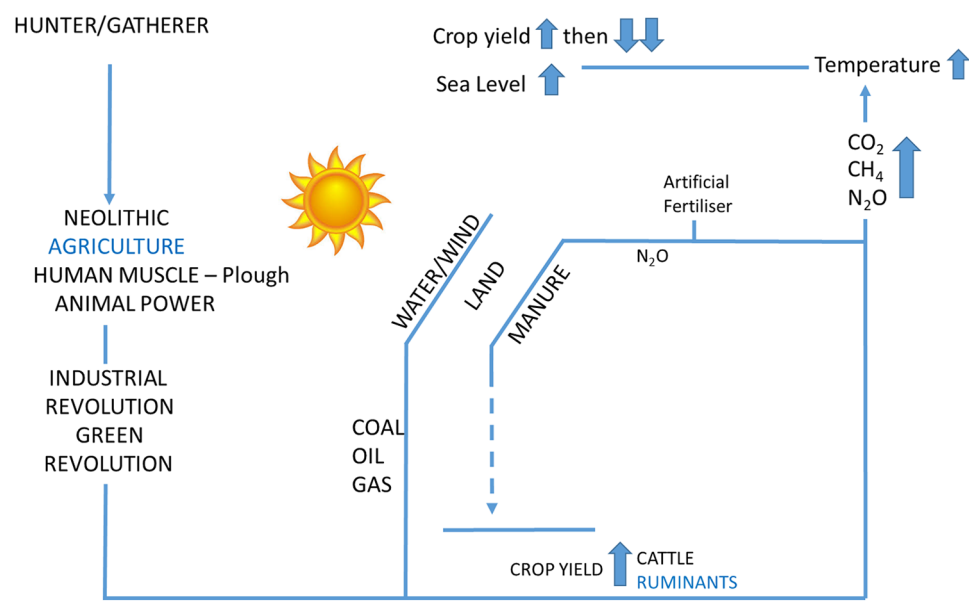


Figure 3. Some interactions between agriculture, increasing crop yields, meat and greenhouse gases.

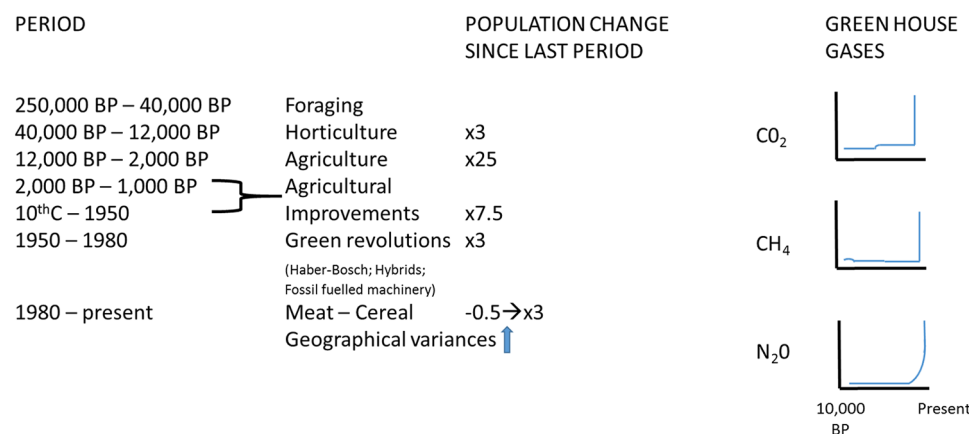


Figure 4. Human population growth rates and agricultural revolutions aligned with atmospheric concentrations of greenhouse gases over the last 10000 years in the anthropocene.

is due to relative immune tolerance of the foetus when on a high cereal diet with low nicotinamide levels, leading to induction of the tryptophan to nicotinamide adenine dinucleotide (NAD) pathway.⁸⁴⁻⁸⁹ This is the core hypothesis from which much else follows. Indeed, this move down the food chain during the Mesolithic first to horticulture and then agriculture may have saved us, but not the Neanderthals, from extinction (at the price of much disease) given that hominid populations were so low at that juncture.⁹⁰⁻¹⁰⁶ A pro-fertility culture with strong sexual selection and nutri-genomic adaptations contributed. Population pressure did not initiate this process but once started became part of an unchecked ratchet requiring more and more food and making it hard to reverse, leading to exponential increases on cereal diets, with contributions from cultural and religious beliefs around birth control (religions may rely more on high reproductive rates to spread than they do on converts). Now brakes may need to be applied, as although high populations were undoubtedly beneficial in the past, currently, the opposite is generally

true, if we are to avoid the agricultural and subsequent Green revolutions becoming ‘the worst mistakes in the history of the human race’.^{83,107-113} Our suggestion for how populations expanded in the first place and how demographic transitions are hastened by increasing the meat supply is shown in Figure 5.

Development

‘For when husbandry flourishes all other arts are in good fettle’ . . .

–Socrates

There has been a great deal of discussion over development and the pros and cons of various forms of intervention in aid to encourage prosperity with no consensus over the benefits of aid or how to improve prospects for the future.¹¹⁴⁻¹²⁷ We argue that, with rare exceptions, where valuable natural resources are present and that they are actually used to buy in a good diet, no society has ever succeeded without attention to sustainable

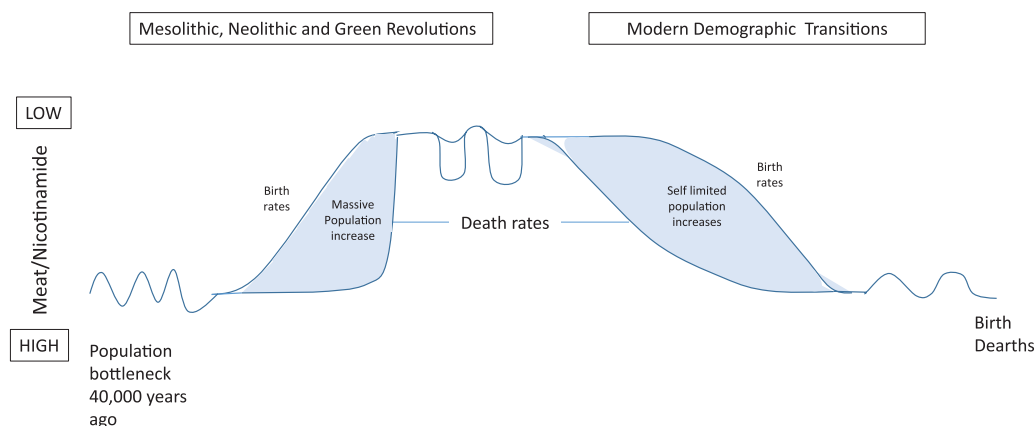


Figure 5. Neolithic and green revolutions were similar in that more cereals can drive exponential population increases. Modern demographic transitions are different as an increase in meat drives self-limited population increases as fertility later falls.

agriculture and maintaining soil quality with mixed farming with stock breeding and husbandry so that a sufficient proportion of its citizens have a broad-based omnivorous diet. Studies from the economics of destitution and failed states support a major role for a good diet and a hunger for meat.¹²⁸⁻¹³⁵ Europe led, first in Italy, then the Netherlands and Spain and then England, France and Germany before America picked up the baton: as all by luck had a good supply of both plant and animal domesticates and a temperate climate largely on an east-west axis allowing for easier spread of farming and on a beneficial soil. With a decent investment in human capital with high intelligence and industriousness with reasonable lifespan without population explosions path-finders in these countries, well known to have higher meat diets ('rosbifs'), one thing led to another, from technology to the arts, in a progressive and interactive manner – whereas the laggards further South or East were until recently very cereal-dependent.¹³⁶

Diseases of Protons, Proles and Patricians

The 'Big' history of diseases, other than trauma, really starts in the Neolithic and culminates in the extraordinary shifts, within a generation at times, from chronic and acute infectious disease to allergies and later-onset diseases of modernity.¹³⁷⁻¹⁴⁵

We have made the case that pellagra is a man-made 'proto-nopathy' due to loss of NAD and hydrogen-carrying capacity that is of evolutionary importance: in a sense evolution in reverse, and as pointed out over 200 years ago by pellagra-ologists, such as Lombroso and Strambio, atavistic and truly degenerative with its loss of cognitive and social skills.^{146,147} The characteristic rash is an exaggerated sunburn so those with a darker skin will be protected, though making it harder to diagnose or self-diagnose or treat (by altering diet). Dark skin was thought to be our original state with pale skin evolving to allow more Vitamin D production in northern climes and loss of hair helping with heat control in the tropics. However, this now seems unlikely and dark skin evolving to avoid sunburn in the tropics where meat is harder to obtain, and therefore, sunburn could have been exacerbated by nicotinamide deficiency

and impaired DNA repair is a possible scenario. The greater toleration of sun damage may be a mixed blessing if it makes cognitive impairment harder to recognise and/or correct that could affect progress of affected populations.^{148,149}

There are clear links between diseases that appeared in the Neolithic, such as TB and gut dysbioses (that excrete nicotinic acid), and conditions that appeared more recently such as cancer, autoimmune and degenerative disease with nicotinamide metabolism and, in the latter cases, high meat consumption.¹⁵⁰ Much depends on the activity of major NAD-dependent processes such as poly (ADP-ribose) polymerases (PARPs), Sirtuins and CD38 that ultimately depend on nicotinamide in the diet to produce their agonist NAD but is also an endogenous inhibitor suggesting, as does the induction of Nicotinamide N-Methyltransferase (NNMT), strong feedback mechanisms to buffer moderate extremes of dietary dosage but perhaps risking longer term pathology.¹⁵¹⁻¹⁶⁰ Analogous to pellagra, there is an apparent mirror image effect when nicotinamide levels are high with many diseases of affluence affecting gut microbiomes, mitochondria, free radical chemistry and disturbed proteonomics, including prion-like behaviour – all downstream points where interventions would have been futile or deleterious in pellagra. We have used Parkinson disease as one example, some cancers and the metabolic syndrome may be others, that involve gut dysbioses (in a taxonomic direction suggestive of a high meat diet), T-cell and metabolic disturbance with prion-like alpha-synuclein aggregates with spreading behaviour via the vagus nerve.¹⁶¹⁻¹⁷³ Dementia may also have misleading downstream metabolic, dysbiotic and amyloid and tau and other protein aggregation but may be related to low nicotinamide levels early or late in life or excessive consumption or catabolism from other stresses.^{174,175} Similarly, with cancer, autoimmune and metabolic syndromes, there is biochemical evidence of loss of nicotinamide homeostasis, whether dietary from increased consumption or excessive catabolism, or implied from benefits of measurement and intervention.^{153,176-203}

Serotonin Syndromes

Moving down the food chain to a more plant-based diet would have reduced tryptophan intake and affected not only the immune tolerance system but the availability of serotonin and tryptamines – although psychedelics may have compensated and explain our addictive attraction to such secondary plant compounds.^{204–209} Changes in serotonin could have been important in moving from a hunter-gatherer society to a more sedentary and collectivist behaviour – gregariousness even in locusts is driven by a poorer diet and serotonin, and has been implicated in domestication syndromes.^{210–213} Higher meat societies tend to be more individualistic and narcissistic. The price may be effects on mood that explain an ‘anti-depressant era’ using pro-serotonergic agents and may explain ‘deaths of despair’ arising from self-harm, chronic pain syndromes and drug addictions that are reversing previously, steadily increasing longevity trends.^{214–219}

Genetic Advances and Late Disadvantages

Even if much progress is driven by diet, one would expect a genetic contribution shown by the known signatures in the genetic record if extracting and conserving optimal amounts of nicotinamide, while avoiding toxicity, were all so important to a ‘run-away’ process involving mitochondrial energetics aided by NAD and consumption pathways.^{220–223} This nutri-genomic point is well established from lactose tolerance (milk containing much nicotinamide riboside) to the use of NAD-consumers and in-house production of nicotinamide with salvage pathways and the development (in meat eaters) of the NNMT pathway.^{224–227} Nicotinamide riboside is of considerable interest as a potent bioavailable form of nicotinamide (including homeorhetically from both human maternal and domesticates milk) that is likely to have been important during evolution and particularly in neurogenesis and brain development, let alone is curative of overt pellagra and perhaps some other pathologies.^{228–231} Increasing fertility and sexual selection for not only physical but behavioural, cognitive and language prowess as secondary ‘ornaments’ is marked with many X-linked genes involved with both fertility and cognition.^{1–20,16–64,66–84,232} Pro-growth and pro-fertility genes, some useful when diet was poor and infection rates were high, evolved late and now are showing up as ‘antagonistic pleiotropic’ at-risk genes for late-onset cancerous and neurodegenerative disease often with a link to NAD metabolism, for instance, through impaired DNA repair mechanisms.^{21–34,36–49,178,199,200,202,227,233–244} DNA methylation also played a part in recent human evolution compatible with changes in diet and effects on the methylome.^{245,246}

Diagnosis and Prescription – NAD World View

‘I thynke breakfastes necessary in this realme’.

–Thomas Elyot in *Castel of Helth*: 1532

The diagnosis, we feel, points to mid-range nicotinamide dosage being the recipe for success at an individual and population

level. When sourced from animal products, NADH proton and electron-based mitochondrial energetics and NAD-consumer metabolism and repair mechanisms and the methylome allow a healthy metabolism, let alone resilience against many environmental stresses. We have made the case for nicotinamide being a key factor enabling bigger and better brains. Brain size may not have enlarged at the time of the creative explosion but restructured and changed its cortico-striatal neurochemistry towards a more prosocial dopaminergic and serotonergic state.^{247–250} The balance with acetylcholine and cognition and oxytocin and vasopressin and reproduction and caring for each other in monogamous pairs and for infants would have been key.^{251–256}

Climate Change and Meat

‘I see Freedom with Law and Peace, a stupendous trio all issuing forth against the idea of caste; what historic denouements are these we so rapidly approach?’

–Walt Whitman

There is no disputing that meat is expensive in monetary terms, shutting out the poor from a balanced diet, and previously was difficult and dangerous to obtain (as it still is from “bush meat”), but it is also expensive in environmental costs.^{254,257} Agriculture in general and meat production (such as methane emissions) specifically are a highly significant driver of the ‘Anthropocene’ as are the dramatic increases in population.^{258–267} Climate has had major influences on our diet and evolution and, in turn, has homeostatic mechanisms to control the amount of CO₂ in the atmosphere, though how robust they are veers between the optimistic ‘Gaia’ and the pessimistic ‘Medea’ hypotheses.^{268–272} Agriculture and deforestation (remarkably warming of the atmosphere after deforestation was mentioned by 2 physicians in the 17th century) and many other knock-on effects such as on loss of biodiversity have crucial roles in the carbon cycle as did earlier geological disruptions from volcanic activity and rock weathering. Agriculture from the beginning intersected with greenhouse gases by affecting carbon and nitrogen cycles, and this progressively intensified to very high levels with loss of topsoil, artificial fertilisers, fossil fuel usage for mechanisation and transport, and direct excretion of methane by ruminants among several other effects compounded by the sheer number of domesticated animals. By contrast, the Great Dying in the Americas after 1492 may have arguably led to cooling of the earth from the reduced agricultural activity, and such plagues may have even been triggered by meat poverty and subclinical pellagra – these are the only possible documented example of atmospheric CO₂ levels dropping in the Anthropocene from human activity.^{35,36,50,51,65,66,82,83,107,108,130,131,273–276}

This has culminated in many calls for more plant-based diets and even taxes on meat or ‘meat retreats’ and ‘meatless Mondays’. A ‘flexitarian’ approach may well be the answer for those on a Western diet but ignores the needs of poorer

individuals and countries that are stuck in a Faustian pact with often subsidised cereals stimulating population growth. We argue that meat redistribution and meat rations, enabled by reduction in wastage and the use of unconventional sources such as insects or synthetic products, is needed to control populations (with no coercion), improve health and well-being and the 'ultimate resource' of human capital.

New True Levellers

'Money must not any longer be the great god that hedges in some and hedges out others'.

—Gerrard Winstanley in *A Declaration from the Poor Oppressed People*: 1649

We have explored under the dietary and biochemical bonnet unearthing the way that meat and nicotinamide made us clever and healthy in the first place but led to social stratification. This is still true but is why meat, cattle and pastureland should now become a common good.

Earlier attempts include the 'Diggers and Levellers' who were political, labour and land reform movements in the early 17th-century United Kingdom at the time of the 'Little Ice Age' and re-emergence of famines and the plague that influenced the course of the English civil war and later Marxian thoughts.²⁷⁷⁻²⁸¹ Marx had been influenced by the chemist Liebig on metabolic rifts in society and the breakdown of some natural cycles, such as the nitrogen cycle, as animals (and their manure) were moved off the land to factory farms to feed cities. In retrospect, if such theories had stuck with the mode of sustenance, rather than expanding to the mode of industrial production, they would have had more traction by majoring on the need for a balanced diet and sustainable mixed farming and care of the soil (that then acts as a carbon sink).^{282,283} Similarly, as the physiocrats such as Francois Quesnay, a physician, diagnosed, the basis of economies has to be metabolic, related to land and water use, capturing the energy of the sun in a concentrated form that we then use to magnify its effect through a series of positive feedback loops or 'zig-zags' as illustrated in his 1750's 'Tableau Economique'.²⁸⁴ All their ideas were modernised as 'food sovereignty' and now should happen to the benefit of all.^{285,286}

Action should stop an exponential population overshoot before the consequent low biodiversity '6th mass extinction' event applies to ourselves – whether the coup de grace is climate change and heat or hurricanes or sea-level rises, high food prices and starvation, plague, migration, riots or war. The answer may include geo-engineering and genetic engineering of domesticates, but the larger part will need social engineering to improve equality and a reasonable diet and education and consequent fertility rate for all.²⁸⁷⁻²⁹⁵ A difference of just 0.25 children per couple makes all the difference to population growth over moderate timescales. Climate change forecasted to hit the poor southern 'Tropic of chaos' the hardest with risk of wars, plagues and mass migration could have a counter-intuitive cure in global meat justice.²⁹⁶⁻³⁰²

Engels View and Engel's Law

Friedrich Engels pointed out the poor dietary conditions of industrialised London's poor along with others who compared 'darkest London' with 'darkest Africa'.³⁰³ These variances in meat intake narrowed in the United Kingdom due to meat imports but have widened globally maintaining disease patterns (such as TB), wrongly called 'tropical diseases'. Action is needed to enable square meals for all, which avoids diet-induced poverty traps and automatically reconstructs societies – not fire-fighting with charity and aid often with land grabs disrupting the local peasantry, or, cheap calories without adequate wages or provision for meat – repeating damage done in colonial times.

Engel's law states that higher wages means a lower proportion is spent on food but a higher proportion of that is spent on meat (and vegetables).^{37-39,58-60,73-75,92-94,117-119,141-143,152-154,161-163,191-193,197-199,203-205,237-239,291-293,304-310} This law is distorted by competing 'luxuries' such as flavourful but non-nutritious 'empty calorie' sugars and other processed foods. An active pro-meat programme is necessary.

Despite our emphasis on nicotinamide, we would be cautious about short-cuts, except in emergencies, using vitamin supplements alone. Nicotinamide is not the only important factor in meat and on its own drains metabolism of methyl-groups also supplied by meat, as is a large proportion of the essential amino acid tryptophan. Also, carbohydrate intake affects tryptophan metabolism as does the intake of other amino acids that compete for transport across the gut and blood brain barrier. Protein in the diet and caloric restriction also affect NAD metabolism (and related mTOR, insulin-like growth factor 1 [IGF1] pathways and oxidant stress) as does aging and exercise, so this is a complex area with much potential that needs considerably more research and clinical trials, but until then, meat supplements may be safer.^{159,178,307-321}

Conclusion

'My interpretation is that the most sensible things to do are to hasten the arrival of a cleaner energy regime and to hasten the demographic transition'.

—JR McNeill in *Something New under the Sun*: 2001

NAD-dependent solar energy and other cleaner renewables replacing fossil fuels are sensible but are unlikely to be enough. It may seem extraordinary that nicotinamide and tryptophan-serotonin homeostasis could solve demographic, disease and development transitions and even climate change and migration friction in one swoop but that is the advantage of an accurate upstream preventive 'diagnosis'.³²²⁻³²⁹ A properly constructed carrying capacity of the earth that considers the need to hasten demographic and related other transitions, rather than simply assessing the production of grain needed to provide enough calories to subsist, brings the issue of population size and human capital into sharp focus. This fits with an

original suggestion 50 years ago that we need to move from ‘cowboy’ economics relying on unlimited resources and no consideration for future generations to ‘spaceman’ economics – it has been well said that the ‘invisible hand’ of traditional economics does not write the cheques (for the true environmental costs).³³⁰ Given the undoubted upfront environmental costs of meat production, it is ironic that if meat justice had been encouraged earlier, current populations would all have completed their demographic transition long ago and simultaneously removed the infectious diseases of poverty and, by redistribution and moderation, mitigated allergic, degenerative and metabolic diseases of affluence.

A real NAD world cost-benefit economic theory would read-just the true long-term cost of meat downwards and the true cost of cereals upwards given the latter’s effect on quantity rather than quality benefits to the population. By healing a divided world, meat equity would reduce tension whether from war or from emergent diseases “X” with zoonoses such as HIV, SARS, Ebola and Coronavirus being eyes of future storms hatched in meat poverty and wild bush and exotic wet meat markets – and avoids seeing recent history as a clash of civilisations, religions or populations or as an ethical tragedy (even though it is).^{331–337} If we do not figure this out and act upon it, basic human needs that start with diet could deteriorate fast with agriculture both being the cause and the casualty of climate change. Recent suggestions for a refreshed enlightenment as “Green New Deals” and a global co-operation to control the ‘thermostat’ with climate change mitigation and adaptations now crucially combined with ‘carbon’ taxes that pay for a reduction in inequality (égalité) and a better diet – we say with optimal meat – are promising.^{338–347} Increased solidarity (fraternité) ending ‘Hunger Games’ could mend dangerous metabolic, ecological and global rifts, and as TS Eliot said, we then can arrive at where we started as meat sharers enshrined by common custom and laws.

Author Contributions

ACW and LJH contributed equally to the writing and proof-reading of the article.

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