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Chapter

Pellagra: Down Not out If down and out (Part 1)

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Abstract

Pellagra is caused by a dietary deficiency of milk and meat leading to insufficient nicotinamide (vitamin B3), the precursor to nicotinamide adenine dinucleotide (NAD). “Pellagra sine pellagra” was well recognised and may be common as supplementation was never globally implemented and a screening test never developed. Meat and milk intake varies 30-fold globally so there are perhaps 2 billion at risk of deficiency. Such patients will have physical and cognitive stunting, poor conduct and be prone to acute and chronic infections, including TB, and premature ageing, including dementia. Resilience may be poor to NAD-consuming insults whether chemical, microbial or traumatic that conspires to cause brain injury but comes with the opportunity for pre-conception dietary corrections breaking cycles of deprivation and poor educational outcomes. Such individuals may otherwise be subject to discrimination as was the pellagra ridden “Butterfly” caste causing racial and ethnic tensions. Poor countries with many having to spend 50-80% of income on food and very little on animal produce cannot develop properly unlike wealthier meat rich empires, past and present. The many benefits of experiments with food programmes and basic income support are because, as Engels curves predict, more is spent on milk and meat enabling demographic, epidemiological, and economic transitions and modernity.

Keywords: NAD, pre-conception nutrition, addiction, opiates, cycles of deprivation, empires, meat transitions, demographic transitions, epidemiological transitions, TB, poverty traps, metabolic syndrome, class ceilings

1. Introduction

Cycles of life, right from life's origin to humankind, depend upon nuclear fusion reactions and low entropy photon- energy from the sun. Photosynthesis splits water into the oxygen that we breathe and hydrogen that combined with CO₂ forms the carbohydrates that we eat and is carried by NAD to mitochondria forming proton-motive forces during oxidative phosphorylation producing usable energy as ATP and reduced nicotinamide adenine dinucleotide phosphate (NADPH) for growth [1-3]. Increasing use of oxygen and NAD supplies allowed animal evolution from the Cambrian (when animals started eating animals) to mammals (increasing milk supplies) and man [4].

	NATURAL VARIANCE	UNNATURAL VARIANCE	COST / COMMONS	POLLUTION / DANGERS	
RESPIRATION	SUNLIGHT	POLAR	← LAND OWNERSHIP →	FEW	
	O ₂	Altitude	NONE	Free commons	Air pollution in poor areas
COMBUSTION	H ₂ O	High in rivers or deserts helped by irrigation	High dam use / desertification	Variable from common good to meters	Pollution in poor areas Water borne infections
	CHO	LOW	Medium Monocultures	CHEAP	RARE
	NAD	Medium for hunting / High by natural animal domesticates	High enclosures / appropriations	EXPENSIVE	Bush meat Wet Markets ↓ Food poisoning Pandemics
	EXTERNAL ENERGY	Significant in availability of animals, wood, water, coal, gas, oil	Exacerbated by commodification from slave manpower to electricity	OFTEN EXPENSIVE	CO ₂ pollution high without sustainable solar / tidal nuclear / wind usage

Figure 1.

Basic elements of the energy cycle had a natural variance based on geography. Human history often exaggerated these variances first by making hunting meat easier in some geographies and quite dangerous for the hunters even as they shared in an equitable way as social insurance - and then with the advent of agriculture natural domesticates varied by continent and meat became expensive everywhere often shutting out the poor. Meat was more available in the middle-east and Europe and less available in the Americas and Africa - that also had to contend with many carnivorous competitors and more parasitic disease in the tsetse belt.

High meat intake and sharing by hunters was a major feature of our evolution, early economics and relationships with animals and each other in our “social leap [5–11]. Combined with selected plants, some psychedelic, and use of fire (cooking releases nicotinamide from meat and from (maize) plants if cooked carefully and learnt culturally) - meat was an important factor in how our brains expanded and our minds changed [12–14]. Oxygen is freely available, water less so and NAD supplies needed for energy and as metabolic master molecules are much harder to obtain. This difficulty has worsened while we “niche constructed” agriculture as sources became expensive creating self-reinforcing transgenerational “poverty traps” that are hard to escape from and contrast with rich others as “meat elites” that “hit the jackpot”: more recently we moved away from mixed farming and agroecology to industrial farming with damaging effects on carbon, nitrogen and phosphorus cycles and made inequalities of meat consumption worse in places (Figures 1–3) [15–22].

2. Engel’s curves and social metabolisms

As Cicero said (43 CE) in his essay De Natura Deorum “we create, as it were, a second world within the world of nature” but our conscious keystone species currently has this world divided geographically effecting a NAD and proton-related lottery of our life chances and (brain) health – as well as contributing to climate change endangering biodiversity from many mammalian and other extinctions [23–25]. Life is energetically expensive and constantly needs to overcome the second law of

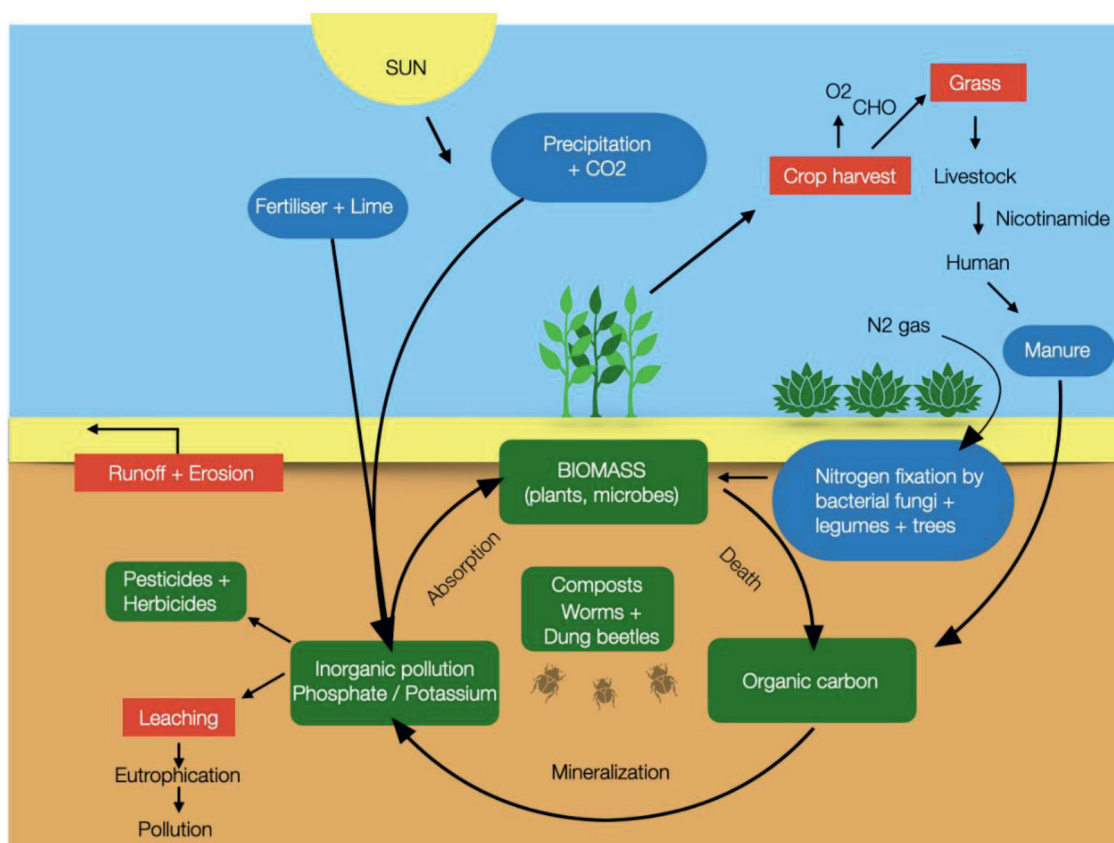


Figure 2. Many natural cycles such as the nitrogen and carbon cycle were enhanced by good farming techniques but later these got disrupted in the short-term quest for high yields. For instance animal (and often human) manure is usually no longer returned directly to the soil – The classic metabolic rift. Use of natural gas to make ammonia-based fertiliser damages the carbon and nitrogen cycle with methane leaks and CO₂ and N₂O emissions compounded by eutrophic effects on biodiversity compared with natural nitrogen fixation by clover and legumes. This creates a second metabolic rift as artificial fertilisers mean that animals and plants need not be grown together. Ruminants contribute to CH₄ emissions and new pastureland usually requires deforestation. On the other hand perennial grasses are often on land that cannot be used for crops and if well-managed, often with silviculture, can act as a carbon sink, as can the oceans at the same time as supplying sources of nicotinamide.

thermodynamics (as Schrodinger pointed out in “*What is Life*” in 1943) and combat increasing entropy but preferably not, as is happening, at other people’s expense [26–31]. This ties in with concepts of a social metabolism and free energy that interacts with internal homeostatic mechanisms (Claude Bernard’s 1850 “*milieu interieur*” that can easily be overwhelmed both for the individual, as our discussion of pellagra will demonstrate, and for the anthroposphere [26, 32–34].

Much has been said on the damage done to health and happiness from relative inequality and the spectre of “status anxiety” but absolute disposable income in relation to the cost of a balanced diet may be the more important foundation: Engel’s curves predict that once calorie intake is satisfied from starches and sugars families spend more on fresh vegetables and meat (**Figure 4**) [35]. This rise up the food chain that improves both health - and wealth is not a zero-sum game as it is the basis for expansion of markets for actual luxuries and modernisation [36–42]. Low incomes makes this impossible and is exacerbated by relative prices of healthy versus unhealthy foods often being worse with added “poverty premiums” in poor countries and neighbourhoods and the distraction of technological luxuries in a post-industrial world - let alone increasing costs for energy or rent leading to “slow micronutrient starvation” and metabolic risk [43–47]. The true cost (hours of work needed) to pay

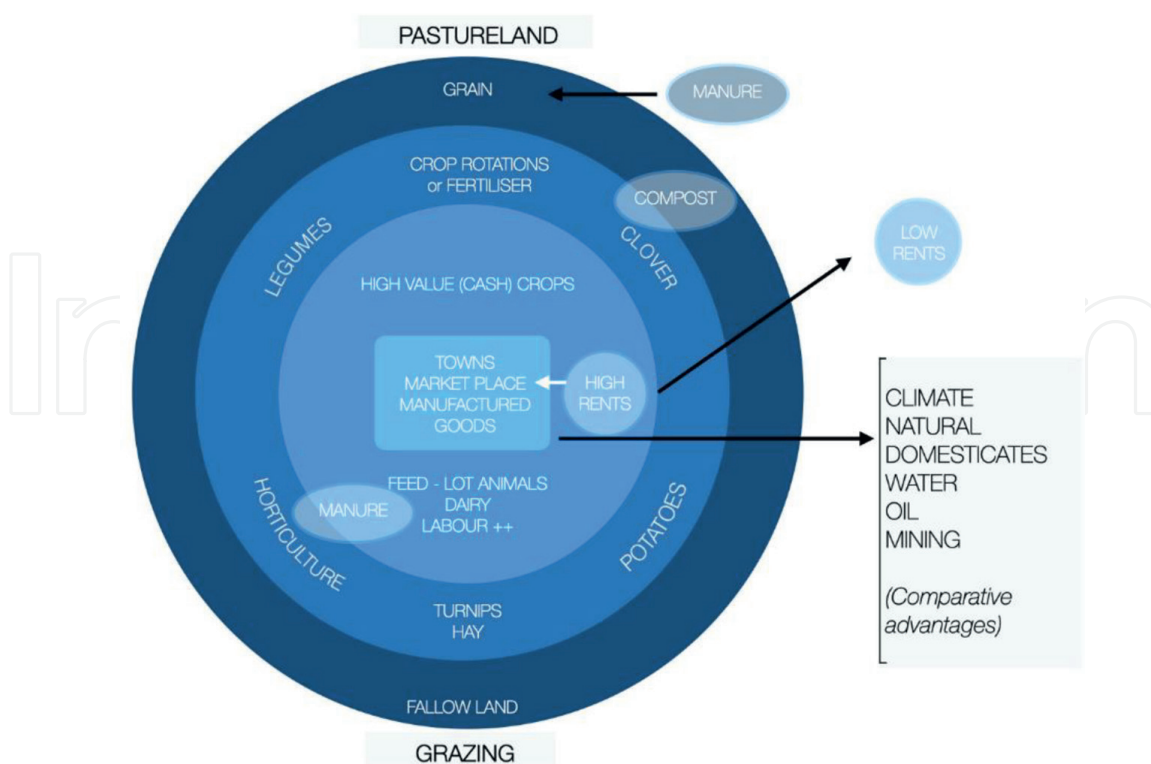


Figure 3.

Many cultures closely integrated a balance between cereals vegetables and animal products. Mixed farming is shown but trading relationships between pastoralists and agriculturalists were common. Where a balance was difficult behaviours included warfare to obtain land or cattle or slaves for farm labour or captives to cannibalise. Hunting was maintained for longer if domesticates were inadequate or sometimes if climate change meant that it had to be re-introduced. Class fights over pastureland with attempts to enclose it and severe punishment for poaching was common. Mixed farming leading to reasonable diets for all through frequent feast days was easier when transport constraints contained food products locally. Industrialisation and urban rural splits developed and even if there were some benefits to the development of water and railway networks to supplies this usually favoured the rich core, with more meat/milk or out of season or tropical foods, not the periphery or third world where the export of cash crops farmed on plantations often destroyed local mixed farming. Distance created space for complexity in supply chains with monopolies and corporate and financial middle-men and though lowering prices non-accountable costs to health and well-being and the climate with environmental degradation and labour exploitation rose. Many pellagra outbreaks were linked to market failures such as that of cash crops such as cotton.

for a breakfast of bacon and eggs has fallen by over 90% over a hundred years for workers but this advantage has not been shared with all within or across countries [48, 49].

In part 1 we talk about pellagra largely in the context of economic class; in part 2 we talk about the development of high meat, and therefore nicotinamide, divergences and convergences between countries and continents. As Charles Dickens said (1859) in another crucial and informative era “it was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness...” – we argue it is time to correct a basic and foolish inequality from which many other inequalities derive but we need to review nutritional science and the importance of NAD and the history of pellagra first [50–58].

3. Nutritional science: 19th and 20thC history and public health

Following on from Hippocrates and dietary and exercise regimens and the importance of diet for human progress and “perfectibility” Condorcet, Godwin and

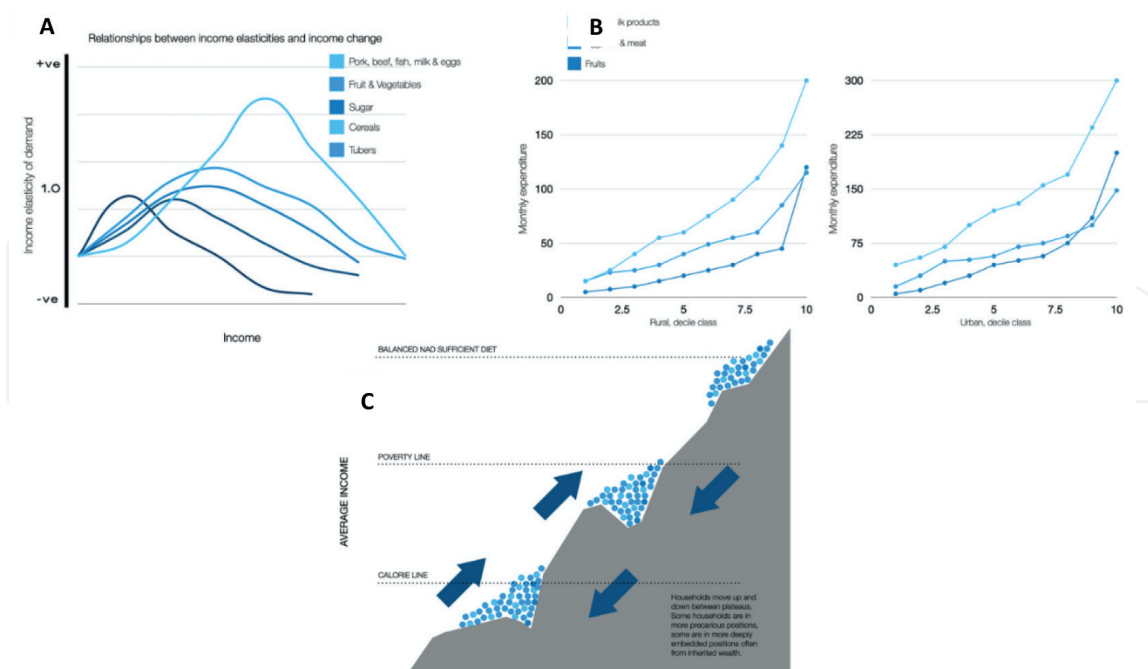


Figure 4.
 A) Engel's curves illustrate how the poor will favour cheap starches and cereals for their calories and only when their income rises and a lower proportion of income is spent on food will they eat much meat or vegetables that are more expensive and involve more waste. Income has to pay for other necessities such as rent and (from wood or charcoal to electricity) heat for warmth and cooking as defined first by Maslow's hierarchy of needs. Increasing (technological) "Veblen" luxuries may compete with a healthy diet as do excessively cheap calories from sugars and oils in ultra-processed foods. B) Engel's curves also often differ between rural and urban populations and as we will see later between rich and poor countries. Rich countries are more likely to have subsidised meat and fortified with vitamins, including vitamin B₃, cereals. C) an optimal nicotinamide rich, but not too rich, (around 10–15 mg/day) will be well above the poverty line but by no means unachievable if it was made a priority.

Frank (who in 1970 commented "starvation and sickness are pictured on the face of the entire working class. You recognise it at first sight") took a more optimistic stance than Malthus. Magendie ("pas d'azote"), Mulder, von Liebig (who developed meat extracts), von Voit, Chittenden ("Nutrition of Man" 1907) and Atwater began to understand the difference between nitrogenous protein and non-nitrogenous calorific fuels and made specific arguments for greater rationality over food choices, including meat. Physicians, such as See (1887) made dietary and sanitary recommendations that included milk to strengthen resistance and reduce exposure to (infectious) disease and infant diarrhoea as did early public health officers such as Newman (who wrote on the importance of nutrition in his book "the building of a Nations health" (1939) and Newsholme. All was who helped by the rise of statistics from Petty (1655) to Graunt and Farr's Life tables who championed the proverb "prevention is better than a cure" [59]. Villerme (1818) and de Chateauneuf showed large differences in mortality and diet between rich and poor in Paris as did a contemporaneous survey in Naples and called for protection against the high price of food: as did Paton (1901) in England and a BMJ leader in 1913 ".or is it that the wages they command are so low that they cannot purchase the necessities of life" [60]. Even at the height of "Germ" theory (Robert Koch (1890) and the success of earlier sanitation projects (Edwin Chadwick 1840s) and the first antibiotics some such as William Allison (1830s) and Rene Dubos (1940s) ("think globally, act locally") and Thomas McKeown (1970s) championed a role for diet and the ever- changing ecology to which man has to adapt with microbes being necessary but not sufficient

to cause disease [61, 62]. Nutritional interactions with physical degeneration and infection are complex and bidirectional as was pointed out early by Price (1930s) and Scrimshaw (1960s) and others before and since and here [63–65].

Hopkins (1906) led the charge following others, such as Eijkman, on “unsuspected dietetic factors” then named “vitamins” by Funk presenting the idea that beriberi, rickets, xerophthalmia, scurvy and pellagra were nutritional deficiency diseases. Later Kwashiorkor (described in 1933 on maize diets) was initially felt to be more related to protein malnutrition by many but is cured by milk and theory has reverted to it being a form of juvenile pellagra and a general concentration on the importance of micronutrients. Inadequate income rather than lack of education was a controversy partly eliminated by Boyd-Orr (1936) who with others at the FAO (Food and Agricultural Organisation) founded in 1945 and the World Bank (influenced by Berg’s “the nutrition factor: its role in national development”) tried hard to recognise this as a global not just a national issue such as the self-interested response to the poor height and health of army recruits at the time of South African Wars. Cod liver oil usage (vitamins A & D) became common and fortification of some foods including niacin became mandatory in some countries in 1946 and manufacturers soon included large doses in many foods and drinks following on from a period of “Vitmania”. Interactions of nutrition and infection were noted as “mutually aggravating” in a comprehensive monograph in 1968 (as remains true for more recent infections such as HIV). Thomas McKeown (1976) proposed the decline in infectious disease particularly TB was largely down to better diet; this was criticised but is now almost orthodox – the data was available then to link it with meat and nicotinamide (an anti-TB antibiotic) but that had to wait till 2013 [66]. Amongst other anecdotal observations a study with a control group from 1946 had shown that a meat and milk richer diet supplied by the Red Cross reduced the incidence of TB in prisoners of war by 15 fold. From the 1930’s to recently repeated studies in many populations showed that milk increased linear growth as did meat and animal products and cognition along with increasing foetal weight relative to gestational age (SGA) and reduced mortality [45, 67–69]. Recommended daily intakes adjusted for physiological stresses, including for nicotinamide, have been in place for many years but are rarely monitored and screening programmes for NAD/Tryptophan deficiency have rarely been used even though eminently possible [70].

4. Poverty and subsistence: Austerity never works

Poverty has long been measured in terms of its relationship to basic nutritional subsistence and the role of rulers responsibilities in providing calories at least for the proletariat long recognised in early empires. Landmark studies included Eden’s “The state of the poor” (1797) that was explicit on the effects of rising food prices and was an empirical foundation for Poor Laws as were Booth and Rowntree’s surveys and descriptions of “frugal lines” in the late 19th century. Poverty was often then thought inevitable or necessary to encourage work or was the fault of the poor and their habits and addictions. Poverty Enlightenment in the 1800’s saw the emergence of a new respect for the poor as people and no longer “shadows in a painting” with the economy seen as a tool for promoting human welfare – an important insight of Adam Smith. By 1890 Marshall in his “Principles of Economics” was writing of the “cumulative evil” of poorly fed children on economic potential and the need for progressive income taxes to help children rise out of poverty. Further enlightenments

saw poverty as a severe constraint both on personal self-fulfilment and on aggregate economic growth and spawned many anti-poverty and better nutritional policies – even as opposition re-surfaced in the 1970's. More recently the dangers of poverty to the well-being of the rich have become better realised whether from war, migration or pandemics. Engel's law as modified by Bennett has been used as a measure of the escape from poverty line and traps and has been substantiated on many occasions whether at a house-hold, country (enabling a move from farming to industrialisation) or at an international level correlating with economic growth. Growth on its own rarely led to reductions in poverty unless it started in the agricultural and service sector enabling lower real food prices and better diets and higher meat intake before there is disposable income to support other aspects of an industrial and consumer society. Once economies are more established (or have used natural resources wisely) this becomes hard to appreciate as agriculture then plays a fairly insignificant role in gross GDP and financialization and "rentier capitalism" that conveniently forgets its roots and responsibilities. Progress is being made given that around 1820 80% of the world population was extremely poor but nutritional status as measured by amount of "wasting" or "stunting" (that includes cognition) is still high and the poor or poor national governance are still being blamed. The example of pellagra demonstrates that most lingering criticisms are however the effect not the cause of poverty in a vicious transgenerational cycle as we will demonstrate.

5. Preconception nutrition: precondition for equality of opportunity for unborn billions

The evidence for the importance of good diet not only early and throughout life but pre-conception and in previous generations continues to mount, building on the epidemiology of the Dutch winter and studies on low birth weight, and affects on both initial (brain) health but also the risk of later onset metabolic disease. This can account for much of the "missing heritability" of many diseases and demonstrates that very early investments (Heckman Curve) can be by far the most cost effective compared with end – of- life health costs- and emphasises the dangers of hunger and austerity measures [71–76] (**Figure 5**). Epigenetic mechanisms include DNA methylation and interactions with NAD/Nicotinamide metabolism with interventions favouring animal based foods and fairly low quantities of milk and eggs having major beneficial effects on cognitive performance and behaviour [77–84]. This also explains the high investment parents will place to allow long successful childhoods so important to our evolution but when impossible comes at the price of reducing social mobility for many but does allow for significant neurodiversity [85–90]. Other periods when brain development is sensitive to environmental and dietary influences are adolescence and "mother brain" with changes in white and grey matter and a pruning of synaptic connections that may be important for brain reserves and ageing well [91, 92]. Improvements of diet throughout life would have short-term and long-term future gains that compound so there is a high discount rate for the current cost for descendant generations fulfilling an obligation to unborn billions for their health and a more cosmopolitan attitude rather than more superficial concerns for local social justice [93, 94]. Better nutrition such as school "breakfast clubs" and free lunches (with dignity) works at all ages and even once in college (or prison, hospital or care homes) it can be shown that hunger on campus affects learning and results, let alone later in life [95, 96].

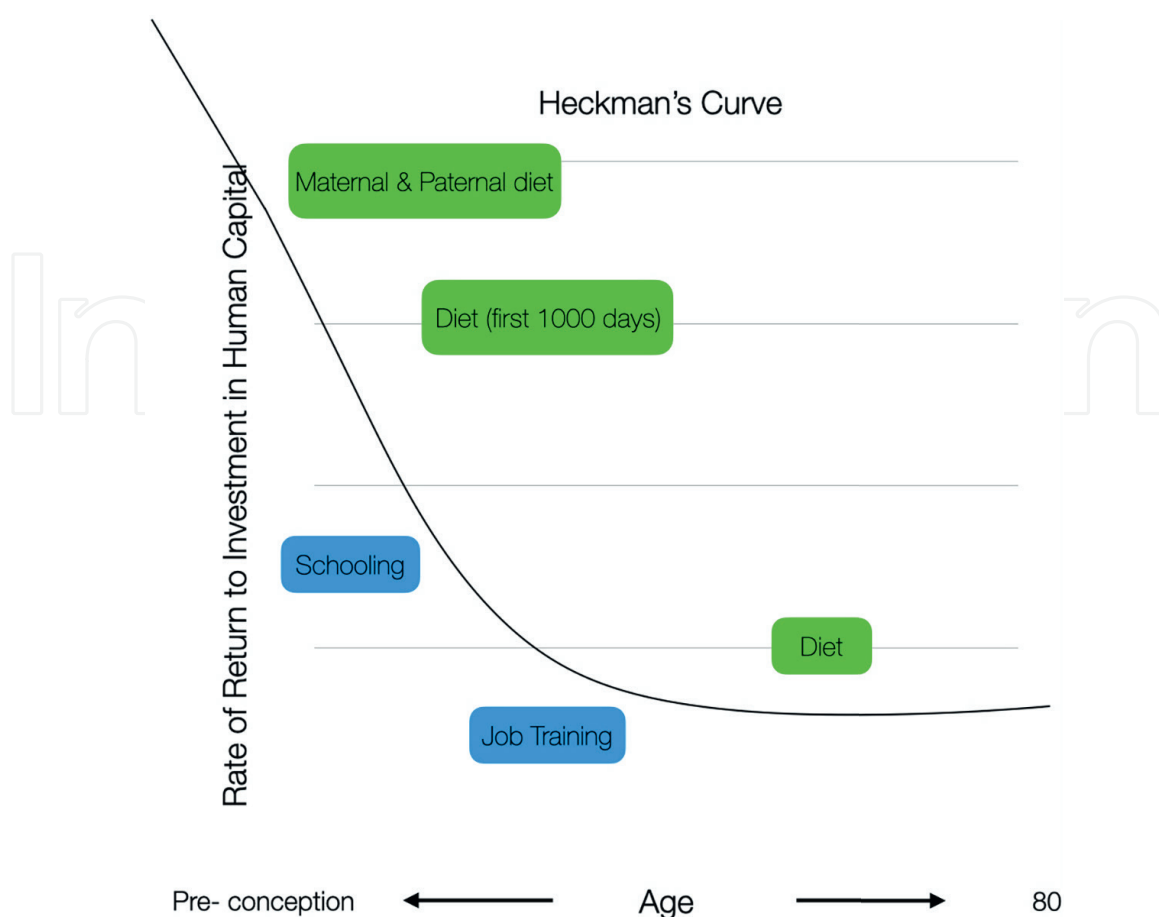


Figure 5.

Heckman's curves illustrate how the rate on return to investment for diet and education rises steeply if begun early - with reductions in many forms of brain and cardiovascular disease. In the case of diet this includes pre-conception parental and even grand-parental diet working through epigenetic and DNA-methylation paths that interact with nicotinamide metabolism. The graph would be steeper for poor countries with short-term benefits merging with long-term compound benefits for future generations. There are limited time windows where catch-up growth can occur with some developmental plasticity but this can create mismatches later in life where ample diets can precipitate metabolic disease and the full gamut encompassed in the developmental origins of adult disease (barker) hypothesis. Low nicotinamide early may cause a phenotype with less neurones more prone to the ravages of ageing but also leads to low induction of nicotinamide methylation that does not forecast a luxury diet and risks nicotinamide toxicity even if diet improves later.

6. NAD history of a key molecule

Harden (1906) discovered NAD as a cofactor whilst investigating fermentation and this was followed by demonstrations of NAD(P)(H) role in anabolism and calcium signalling and NAD(H) in hydride transfers and mitochondrial energetics. Mitochondrial failure is a major feature of many neurological degenerative conditions and often involves other organs. More recently NAD-synthases "feeders" (NMNATs) have been shown to have an important role in (Wallerian) degeneration [97, 98]. NAD-consumers as ADP-Ribose polymerases are known to be important in DNA repair (PARPs) and Sirtuins in ageing (NAD declines with age) with agonists or supplementation extending lifespans and rejuvenating stem cells and promoting tissue regeneration at times of stress, including food scarcity [99–101]. Sirtuin deacetylation (including histones) and NAD affect epigenetic mechanisms regulating genomic and epigenomic stability. NAD turnover is high and supply pool is competed over and is compartmentalised and fluctuates such as with circadian rhythms and is dependent on dietary nicotinamide. There is an endogenous pathway from the degradation of (dietary derived) tryptophan on

the kynurenine pathway that also profoundly affects immune tolerance and is affected by many disease processes and pregnancy [102–104]. Hormetic anti-ageing influences from plant derived compounds, as part of their own defences, such as resveratrol also predominantly act through agonist actions in NAD-Consumer pathways, as does exercise and caloric restriction [105]. NAD connects with the social and sexual dyad relationships through oxytocin regulation [106, 107]. NAD fluxes through energetics and its consumers and signalling is a central master-controller of metabolism and we, in a very real sense, live in a NAD metabolome and microbiome with symbiotic and social breakdowns when the supply fails [108]. Satiety and avoidance of food, sex and gambling addiction and substance abuse from alcohol to cocaine has been linked with circadian NAD replete pathways affecting opioid, nicotine and cannabinoid receptor and dopamine, serotonin, oxytocin and adenosine reward circuits [109]. We may be addicted to these surrogates for NAD as we may be to NAD and its metabolites just like some extreme mutant cancer cells [110]. NAD replacement may work for a wide variety of diseases of ageing as may Nicotinamide N-Methyltransferase (NNMT) inhibition as this enzyme is induced, perhaps by high nicotinamide in diet, in a wide variety of “diseases of modernity” whether metabolic, cancerous or degenerative [109, 111, 112]. We are be in a “NAD World” with many of our senses, metabolism, physiology and actions attuned to obtaining and the optimal use of this supply in our “umwelt” [113, 114].

7. Pellagra’s epidemics

Pellagra was first described in the medical literature by Gaspar Casal (1735) in a European epidemic amongst poor polenta eating peasants. He recognised its basis in a poor maize based and low meat diet as had the people affected (one offering to sell her house for a round of butter) [115]. Another famous epidemic was a century ago in the south-eastern “cotton” states of America triggered by economic hardship amongst sharecroppers and slaves. South Africa also had outbreaks triggered by rinderpest in cattle, poverty and apartheid. More recently outbreaks have occurred usually in war-torn African countries. Death rates are high and undiagnosed let alone untreated cases are common [116, 117].

8. Clinical features: 4 D dysfunction & degeneration across generations

Dermatitis was common and sometimes pathognomonic as a seasonal form of sunburn. Darker skins were somewhat protected limiting diagnosis and self-diagnosis that could otherwise lead to self-treatment and eating more meat before specific treatment was even available risking cognitive decline. (During our early history this may have favoured white skinned peoples in more northern climes that also had more meat in diet but less sun). Dementia and poor intellectual development were important features that included a raft of other neuropsychiatric syndromes, including a myoclonic encephalopathy, and poor and antisocial behaviour. Mimics of Parkinson’s and Motor Neurone disease were noted. Diarrhoea was common due to inflammation and dysbiotic infections – other dysbiosis included TB – and there was susceptibility to acute infections. Death and premature ageing were common although rarely mentioned by the current ageing literature. Women were affected twice as often as men (and often have less access to meat in the home). Pigmented skin protects against the characteristic sunburn rash but may be a mixed blessing if then poor cognition is overlooked and not (self-) treated particularly as in Africa, Asia and the Americas meat was less available.

Pellagra was thought at the time as being a systems failure and degenerative in the atavistic reverse evolutionary sense of the term (even before the importance of meat in our evolution was realised) let alone being neurodegenerative in the modern sense. Pellagra is also an excellent example to remember in the nature via nurture and in Mind-Gut axis debates [118]. Pathology crossed many current classifications as there was evidence of degeneration, mitochondrial dysfunction, oxidative stress, dysbiosis, amyloidosis and manifestations with no discernible histopathology [41, 119].

9. Addiction: early opioid and other drug epidemics and wars

Alcohol addiction and ritual drinking bouts “potationes” was well recognised but by interfering further with NAD status makes things worse and can be a cause of pellagra alongside thiamine deficiency and Wernicke’s and Korsakoff syndrome both treated with multivitamin preparations. Addiction to food and feast days is more understandable but other addictions whether sex of gambling played in to developing pellagrins a poor reputation. Self or institutionalised and medicalised treatment with drugs even infants is more surprising. In the 17th century the poor cultivated on an industrial scale and ate poppy seed bread “pavrato” or “pane papaverino” and may well have caused the first “opioid” and “cannabinoid” epidemic. Other pain killing and hallucinatory herbs, including hemp, or spoiled rye with ergotism and St Vitus’s dance were as a response to this “disease of wretchedness” benumbing an already stunned undernourished population who could only dream of a land of Cockaigne and a world to be turned upside down “mundus inversus” as often too weak to rebel. Opium has been used since the ancient world but not on this scale that subsequently got magnified with major effects in China, note 19th C “opium wars”, and recently as is well documented causing incarcerations (though not of the Sackler’s or other manufacturers of fentanyl and analogues) and life expectancy falls particularly in the USA [120–124]. This ultimate in unconscionable abuse of bio-power perhaps started with pellagra-related “deaths of despair” three centuries ago but is only recently recognised as having a link with NAD deficiency helped by NAD infusion [125].

10. Treatment

Joseph Goldberger in the USA during their epidemic beginning in 1902 is rightly credited for renewing the dietary link (proposed for the Nobel Prize three times) as then it was widely thought to be due to a poison in maize or infectious or genetic. He recommended high meat and fresh diets or the use of brewer’s yeast to good effect for both prevention and cure and recognised the similarity with “black tongue” in dogs and the link to tryptophan. Conrad Elvehjem discovered nicotinic acid and the link to pellagra (1937) and Tom Spies and colleagues rapidly (Time magazine Team of the Year 1938) treated patients who even in advanced cases could respond.

11. Butterfly castes to butterfly effects: racial, class and other divides are not so black and white

Pellagrins whether white or black were derided as inferior human beings or even as a different race, with many epithets still used against “deplorables”, and were known

as the “Butterfly caste” (referring to the characteristic dermatitis) and “problem pellagrins”. At various times those from Ireland and Italy have been treated much the same so colour may be a distraction from the real underlying cause of many “them and us” as really “have and have-not” divides and extreme reactions such as the Klu Klux Klan, segregation, apartheid and genocides and the occasional successful revolt such as on Haiti.

Racial and colour awareness can be dated back to at least biblical times as in the Christian and Jewish myth of the “curse of black skinned Ham but the origin of whole populations having inferiority complexes has been dated to the 17th century German speaking countries (extraordinary given the later history of racial purity and Aryan supremacy) relative to the French who were dominant in all spheres of life whether material or cultural and was exacerbated by the thirty year war – when German livestock were rounded up and driven away - and these countries were in an early financial crisis with hyperinflation and a credit crunch [126].

Anthropologists travelling the world, such as the neurologist W.H.R. Rivers, dispelled some myths that “primitive” races had sharper perception as their minds used little energy for higher mental functions (the “Spencer hypothesis”) although not many were convinced during strong eugenic movements [127–129]. Other anthropologists from the 1930’s on have documented behaviour changes and dehumanisation during the “hungry season” (when meat is scarce and pellagra outbreaks start) or when peoples are removed from their hunting grounds noting societal and familial breakdown (with cannibalism and infanticide at the extremes) and include Turnbull’s 1960’s studies of the Ik tribe “Mountain People” and Scheper-Hughes 1990’s Brazilian study “Death without weeping” of slow starvation often medicalised and treated with drugs [130–134]. Similar observations were made in the Ukraine 1930’s famine, the Siege of Leningrad in 1941, and many Chinese famines as described for the 1960’s Mao responsible famine in “Hungry Ghosts” [135]. Acquired constitutionally poor phenotypes secondary to financial hardship and a slide down Engel’s curves precede societal stigma and institutional bias to “wastrels” and discrimination and medicalisation can hide the basic nutritional cause and responsibility even in the face of rebellion [63].

Bacon’s 1676 rebellion is remembered as, for once, poor whites and poor blacks united to fight for their rights, yet still failed as did similar attempts later in America, well analysed (by Du Bois around 1900) and South Africa. The calculated response by well fed and nutri-genomically well-endowed northern European groups, who felt superior (and were taller), was that poor whites, often indentured servants or imported criminals, needed preferential material or status enhancing treatment so as not to spoil their own case for supremacy (upset by many shocks such as the Japanese attack on Pearl Harbour) [136, 137]. Hence Jim Crow laws, with apartheid menial jobs with and low incomes then prohibition “wars” first on alcohol and then drugs with incarceration all denying “inferior” groups any realistic chance of levelling up.

As Martin Luther King said in 1968 when about to launch the Poor People’s Campaign just before he was assassinated “*in one America people have quality food and education, in the other the best minds can never come out*” [138]. Based on personal reversible experiences, the current mayor of New York has recognised that a diet derived from slavery to unhealthy soul food is a key front line in the fight for civil rights [139]: and, we say, was the original bottom line with a low meat intake affecting physiology and behaviour with a the willful drive to degeneration by further dietary restrictions and then blaming the victims [140–142]. Recent calls support this view that poor diet is the common denominator as in Louis Gates comments in “*America*

beyond the colour line” .“if King came back, he’d say we need another civil rights movement based on class not race” reflecting class divides in people of all colours and the long-term effects of “segregation sequiturs” such as low wealth and income and poor diet - democratic socialism with strong economic rights underpinning diet and (electrical) energy rights is the way forward [143–146]. Pellagra’s butterfly effects from origins in the southern states and south Africa bastions to this day of some of these frictions are still the most acute could worsen despite the importance of diet and pellagra prevention being well known for over a century [147].

12. Euthenics not eugenics

Ellen Swallow (1900) is credited with emphasising diet and ecology in human health and combating eugenics with euthenics and social welfare responses to inequality and the vagaries of birth and racial improvement; life not being self-authored [148]. Others despite their interest in eugenics emphasised diets with both proponents for vegetarianism improving the race, such as Graham and Kellogg (1914) and for meat, such as Woods Harrison (1911) - later taken seriously by countries such as Japan and China. McCarrison working in India and Boyd-Orr in Kenya understood that there was an interaction between tribes, races and diet with the Masai and Sikhs benefitting from blood and meat- based diets with taller heights and better health (including less TB) [149]. Even monarchies were at times pioneers of welfarism and sceptical of genealogy or meritocracy as were some social reformers - common prosperity as a mantra is now even championed in China is realised to have a dietary and euthenic habitat related basis – much based on the need for more meat [150].

13. Pellagra prevention

For most of our evolution and history as hunter-gatherers this was pre-solved as our diet was so meat based both as a source of micronutrients and for calories particularly in temperate zones so catastrophes would have caused localised or seasonal famines rather than chronic or widespread or lifelong malnutrition [151–155]. High intake of nicotinamide from hunting may have been important to the evolution of large cooperative brains with pellagra being an atavistic example of evolution in reverse gear. Furthermore there was a very strong sharing culture particularly for meat with anyone attempting to obtain the “lion’s” share actively shunned [156]. Storing and preserving meat developed to overcome “seasonal” hungers or other interruptions to the usually ample supply helped by hunting parties leading the global diaspora. However, that led, along with climate change, to megafaunal extinctions on land and sea and a move to smaller prey and the beginnings of herding. After the agricultural neolithic revolution pastoralism developed to help boost the meat supply. The neolithic revolution was overall a net negative meat transition with adverse effects on health, height and brain size whilst populations exploded on a more pellagra-genic diet with malnutrition as hinted at by descriptions on “steles of famine” [157, 158].

Pastoralists and agriculturalists had trading arrangements allowing for a balanced diet (despite some taboos), even if these were at times fraught – much early raiding and warfare can be seen in this light as will be later empires acquiring pastureland. Pastoralists were not only providers of meat but also developed “secondary products”, at multiple independent sites, butter/ghee and soured dairy products from milk curds

MACRO & MICRO-NUTRIGENIC ADAPTATIONS - NAD RELATED		
Amylase copy number	-	Starches
Alcohol dehydrogenase	-	Beer / Wine
Lactase persistence (Northern European)	-	Milk
Nicotinamide methylation (Carnivores)	-	Meat / Milk
NAD ENVIRONMENTAL - HOMEOSTATIC INTERFACES		
NAD / NADH (Redox state)	-	Mitochondrial ATP (Brain) power
NAD (P) H	-	Anabolism Xenobiotic detox
NAD - Consumers + sensors (Sirtuins)	-	Circadian rhythms Foraging - meals Master metabolic controls
Signalling / Chromatin making	-	Genetic memory Fetal programming / thrifty phenotype (DoHaD & transgenerational effects)
Nicotinamide / SAM metabolism	-	Ageing (Calorie restriction) Exercise

Figure 6.

There were several nutrigenomic adaptations during our recent evolution that enhanced our NAD diet most notably the development of lactose tolerance. Nicotinamide n-methyl transferase (NNMT) induction protected us from nicotinamide excesses and close control of NAD metabolism evolved through upgrades of NAD -consumers. Close links with environmental stimuli were forged affecting most metabolic and (neuro) physiological pathways.

(and whey) as fermented cheeses and yoghurts with low lactose levels but just as rich in nicotinamide riboside and more easily stored and transported.

In the best example of parallel cultural and genomic convergent evolution, suggesting extremely strong selection pressures lactase persistent genes emerged independently in several pastoralist populations, particularly in northern Europe, to overcome the natural decline in enzymic activity after infancy and avoiding the unpleasant symptoms of lactose intolerance such as flatulence and diarrhoea whilst cultural evolution developed cheeses [159] Other nutrigenomic developments allowed for greater ability to digest starches and alcohol that connect to NAD pathways and NNMT that, as with other carnivores may guard against nicotinamide overload as would many rearrangements in NAD-consumer pathways all of which are active in general and brain metabolism (**Figure 6**) [160].

Some population, such as those in Mesoamerica, had to adapt to low meat diets due to a lack of easy animal domesticates compared to the “big four” of current animal domesticates that were all herding pre-domesticates in the middle east’s fertile crescent. A major staple maize co-evolved and achieved God-like status (as did cattle elsewhere as the “food of the Gods”) as it is easy to grow and a good source of calories but not of tryptophan or nicotinamide [161–163]. In a cultural evolutionary approach, suggesting strong selection pressures, in the fields it led to the “3 Sisters” joined by beans and squash enabling growth through nitrogen fixation and both protection

of the soil and as sunshade - and a broader diet with extra nicotinamide and amino-acids. As striking was the (subconscious) development of cooking with lime as “nixtamalization” releasing bound nicotinamide - a practice not always exported to other continents leading to pellagra outbreaks in Europe and elsewhere. There are other examples of cooking practice that evolved to reduce toxicity from cyanogens and other toxins as did enhanced xenobiotic enzymes but this is the most striking example of releasing a micronutrient and reducing toxicity from its potential deficiency [162].

After the discovery of nicotinamide and its relationship to pellagra in the 1940's supplementation programmes were introduced in places starting with bread. Brown bread contains some nicotinamide in the germ but when processed to white bread is largely removed: although white bread was initially the preserve of the rich it became more popular, in a curious and unfortunate inversion, amongst the poor on low meat diets. (Later the pasteurisation of beer had the same effect by removing brewer's yeast an important source of vitamin B3 used as treatment in some epidemics). Manufacturers soon followed first of cereals, as “Vitmania” took hold and later widespread currently in “high energy” drinks and even teas. However, this usually targets the wrong global populations at risk of deficiency and has the disadvantage of being a potential drain on the methylome, unlike adequate meat. Along with effects on NAD-Consumer enzymic activity this could give mechanisms for a hypervitaminosis B3 as is suggested by excessive induction of NNMT in many diseases of “modernity”. In other words, creating the worst of all possible “NAD Worlds” with missing treating cases of subclinical endemic pellagra at the same time as increasing the potential for nicotinamide overload and toxicity [17].

14. Endemic pellagra

During the pellagra epidemics, particularly the American outbreak in the southern cotton states a century ago, not only was it recognised that many cases went undiagnosed but that the rash was often not present and a condition of “pellagra sine pellagra” was endemic and probably had been since well before the Civil War – and may indeed have contributed to the confederate defeat. Low IQ in recruits and poor physical health, such as diarrhoea (now called “environmental enteropathy” or TB, were well recognised as a problem at the time: the finding of better IQ scores from black northerners compared with white southerners was an important if inconvenient truth for many. TB disappears once income and diets improve, presumably as nicotinamide is a TB antibiotic, and this has had a profound effect on population health although may lead to the emergence of allergic and auto-immune disease [164, 165] (**Figure 7**). At risk groups on low to very low meat diets may always have harboured sub-clinical cases and may still do whether seen through the lens of class or continent/country. It is worth a short historical detour to investigate this possibility accepting a lack of data due to no biochemical screening tool for NAD/Tryptophan deficiency in use, inexplicable and unacceptable for an easily treatable condition.

15. Class and NAD scales and ceilings: meat pecking orders

Since the Mesolithic and neolithic move down the food chain to a less meat based and more horticultural then cereal and calorific diet hierarchical class-based systems evolved in all sedentary civilisations [19, 152, 166]. If meat is less available it might make some sort of teleological sense to develop an upper ruling and

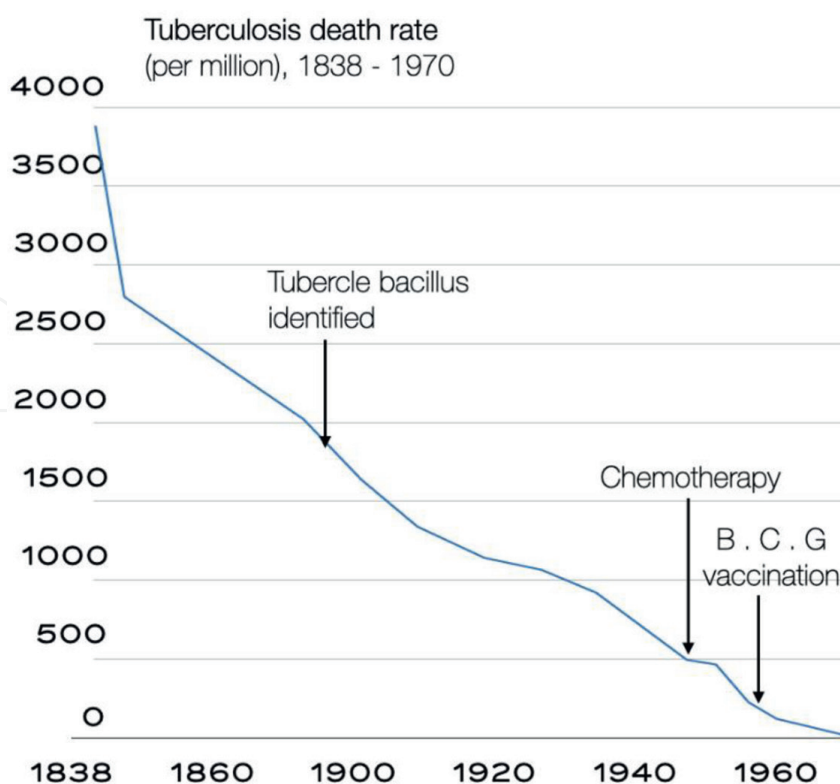


Figure 7.

TB rates fell dramatically before medicines became available and is a hallmark of modernity with a shift that increases life-span but comes with more allergic and auto-immune disease. Sanitation has little effect on this non-water or food-borne microbe and better housing increased rents reducing money for food and has, on documented occasions, led to more TB. Nicotinamide and its analogues are TB antibiotics so there is a biological explanation and given TB's role in "educating" the immune system absence of this "old friend" may explain its replacement with the emergence of allergic and auto-immune disease.

officer class on the better diet with high level cognition and a proletariat working and infantry class with, almost by definition, higher fertility. Higher populations allowed for greater divisions of labour and inventiveness. Much of human history can be explained in this light with trading (and wars) with pastoralist (mounted) "barbarians" to obtaining more pastureland by conquest ("Lebenstraum") – given class wars when the ruling classes did not honour their promises to feed the "common" people whose lands and hunting or farming rights they had taken as part of "enclosure" movements (**Figures 8** and **9**). Extreme versions such as wars to obtain captives for human sacrifice rather than land as state sponsored cannibalism for the upper classes in Mesoamerica [167]. Recent versions are evident the history of the working classes and their "snakes and ladders" of failures, whether white or black, if only education and not income or diet is addressed [168–171]. When the political will is there it is possible as examples include successful victualling often cited as being important for victory in all wars and well documented for the Napoleonic wars with significant meat intakes for the sailors compared with their enemies (and non-combatants at home) [172, 173].

High meat, milk, butter and cheese intake amongst the wealthy often amounting to gluttony and "orthorexia" is well documented everywhere that it has been studied for the last 10,000 years with documented effects on height, health, IQ and power as is the opposite effects of forced often monophagic vegetarianism on the working classes or low-income unemployed, especially women and including children [174–176]. Meat as the centrepiece (sometimes along with cheeses) has



Figure 8.

Gillray's 18thC cartoon may have been the first to illustrate the connection between class differences and cuts of the national "plum pudding" with meats to the king and his courtiers down to the "scrapings" for the labouring poor (the value of roast beef and the evils of alcohol were also well depicted by Hogarth). The carving up of empires between great powers and "state epicures" and "greedy-guts" divided the world to the great detriment of the poor in poor southern nations. Now rather than Palmerston and Napoleon leaders from Eurasian and Western blocs and food monopolies carve up the world – The dangers of this are profound and a common purpose needs to be established fast to correct this basic human right and create a world safer from pandemics.

long been important for the rich and for distribution in feast days - that used to be a lot commoner – or by monasteries (who had a beneficial effect on agriculture even after their dissolution). Peasant dishes can get gentrified, an old example being the addition of meat in medieval times to "frumenty" porridge, with many more examples when dishes were imported to richer climes as in the "hunger for America" diasporas from Europe [177, 178].

The rise of the middle class bourgeoisie on middling and more meaty diets honed in restaurants in countries who by happenstance got ahead on the meat curve is a likely basis for prosperity in a feed-forward cycle given effects on cognition and behaviour and a culture of truth and "matters of fact" that recognises talent from all classes as the history of the Royal Society and other legal and scientific institutions demonstrate [179–183].

Nevertheless a dangerous class divide persists that is known as the "Lockian proviso" and can be summarised as "*if the process of civilization has deprived the members of society of certain liberties (to gather, pasture, engage in the chase) compensation would be due to those persons for whom civilization was a net loss*" allowing a moral argument to steal under those circumstance offers taken up from "Robin Hoods" if there is inadequate pre-or re- distribution to the poor [184–186]. Rulers cannot rule by force alone so a cultural consensus and social contract is normally achieved even if periodic realignments have to be made after periods of austerity and "gilded" ages – we may be in one now exacerbated by Covid with monetary policy in the rich world risking a two-track divergent economic recovery between both classes and countries with their

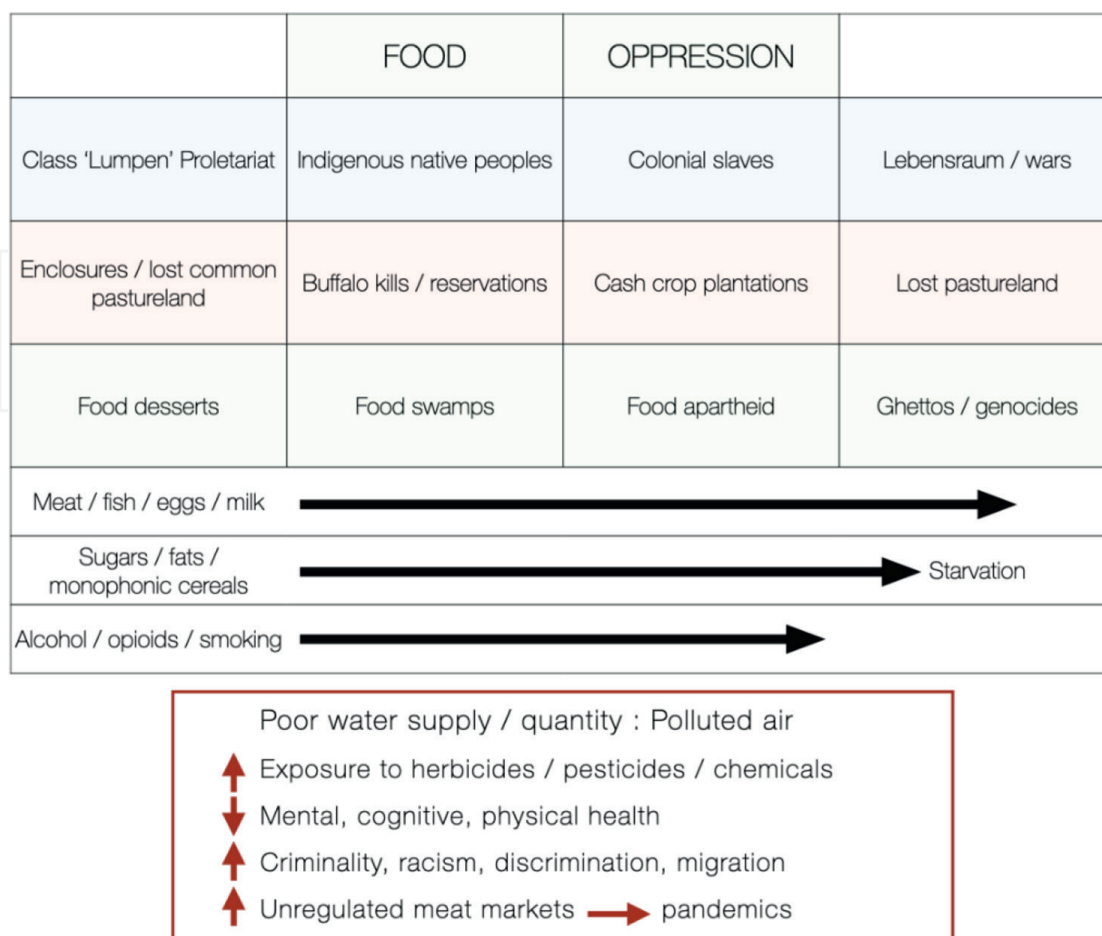


Figure 9. Most forms of oppression have been crimes of commission (despite being resisted and criticised at the time) mediated by interrupting “swords v ploughshares” food and animal product chains often in (civil or class) and “guns or butter” conflicts, raids and wars. Sometimes these constraints targeted those who started from a poorer dietary base such that infectious disease collaborated in population destruction, such as the Americas, but not always as the bourgeoisie were attacked in the midst of collectivism as with the Russian kulaks and in Cambodia, China - and many Jewish pogroms. Crimes of omission have contributed to at least as much malnutrition and premature deaths or weaponised food supplies.

debt burdens and poor access to increasingly expensive food and agricultural investment funds [187–189]. Cries that we cannot afford more solidarity should remember what Keynes (1942) said “anything we should actually do, we can afford.”

16. Discussion

Discussions about causation and the origins of class and racial inequalities typically consider only the last 3–400 years and when dysfunctional blame proximate factors such as the need for cheap or surplus labour or, various forms of (neo) slavery and related lack of (hereditary) capital or, “laissez-faire” neoliberalism or, weak democratic institutions and corruption or, property laws and loss of the “commons”. However if one takes a longer view it is clear that our pre-history ancestors were far more egalitarian in general and particularly so over the sharing of meat. Later class gradients of meat eating emerged and perhaps allowed some increased diversity in a largely isogenic species with high human capital when meat intake was high but higher fertility amongst the proletariat that may have

been of overall benefit. However, when taken to extremes with very low intakes “precarious” and “underclasses” let alone frank pellagra developed that became racialised and has caused much friction over the last few millennia. This underlying dietary motor has become obscured although poor diet as a transgenerational and within lives mechanism for exacerbating or causing (racial) sexual and transgenerational inequalities is gaining traction and is, we believe, a constructive and practical way of dealing with reparations by eliminating food deserts and swamps with their “empty” calories and “amputation capitals” and other metabolic ghettos – we should re-invent being “together at the table” and adequate sustenance with sustainability for all [190].

Reducing resource stress and food insecurity improves cognition and reduces loss of cognitive bandwidth by having to spend less time on earning to provide a basic diet over and above calories and giving more time to spend on education and family - with no need for breaking laws.

17. Conclusions

Engel’s Law (1857), is one of the most robust regularities in economics, showing an uncanny fit both within and across countries with increasing incomes (or falls in prices) leading to a decline in the share of family income spent on food. Indeed, given other necessities such as heating, clothes, shelter and entertainment, it can be used as a measure of poverty. Bennetts (1941) modification demonstrated that as income rises less is spent on starches or cereals and more on milk and meat and fruit and vegetables up to a point where it then can fall off for meat. Indeed, we have previously proposed a hypervitaminosis B3 and there are other signals that too much meat may be toxic. Engel’s curves are subject to major distortions if calories become very cheap but meat fruit and vegetables remain expensive as then this normal progression will become attenuated – especially if there is also competition from other “luxuries” with remarkable penetration such as mobile phones. These destroy the market for meat as demand seems to fall as there is not enough disposable income to support a safe market encouraging dangerous black markets in “bushmeat”. No wonder there is no longer the same clear divide between the move from infectious to auto-immune disease and obesity now becoming common and now a feature of poverty due to the emphasis on cereals and oils and sugars and empty calories in food swamps creating a “double whammy” and sick societies [191].

We have given some background on NAD metabolism with pellagra being the “tip of a metabolic iceberg” and the importance of animal products as the source of nicotinamide and how its deficiency can cause many disease, dysbiotic and social phenotypes that include poor cognition and anti-social behaviour with addictions creating classes that become dysfunctional. In *“Silencing the past: power and the production of history”* Trouillot (1995) insisted that *“the ultimate mark of power maybe it’s invisibility; the ultimate challenge, the exposition of it’s roots”* and this meat-power relationship needs to be made visible so that it can be corrected and allow multiple “Phoenixes” to rise.

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Conflict of interest

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