Chapter

Poverty and Pellagra's Penumbras

Adrian C. Williams and Lisa J. Hill

Abstract

Pellagra has largely been forgotten. This is unfortunate as important lessons are to be learnt about the diseases and social and economic consequences of poverty – and for the root cause of poverty (and of affluence) – that involve dietary nicotinamide and nicotinamide adenine dinucleotide (NAD) homeostasis. NAD disruption can occur not only from poor diet but from increased consumption from genotoxic, infectious and metabolic stresses. NAD deficiency is closely linked to poor physical and intellectual development, premature ageing and diseases of ageing. Acute infections, many with NAD-consuming toxins, that may differentially affect the NAD-depleted, now include COVID-19. Some Covid manifestations, such as myoclonic encephalopathy and "Long Covid," resemble pellagra clinically and biochemically as both have disturbed nicotinic and tryptophan metabolism. Symbionts that supply nicotinic acid, such as TB and some gut micro-organisms, can become dysbiotic if the diet is very deficient in milk and meat, as it is for 1–2 billion or more. High doses of nicotinamide lead to inhibition of NAD-consuming enzymes and excessive induction of nicotinamide-n-methyl transferase (NNMT) with consequent effects on the methylome: this gives a mechanism for an unrecognised hypervitaminosis-B3 with adverse effects of nicotinamide overload for consumers on a high meat diet with "fortified" foods and "high energy" drinks. Methods of measuring NAD metabolism routinely for screening the populations at risk of deficiency and in metabolically ill or infectious disease patients should be developed urgently. Successful intervention should improve human capital and prevent many aspects of poverty, reduce discrimination and even the drive to emigrate.

Keywords: nicotinamide, tuberculosis, meat transitions, ageing, neurodegeneration, dementia, obesity, cancer, ACE2, Covid-19, NAD, Long Covid

1. Introduction

The 4 "D's" of Dementia, Dermatitis, Diarrhoea and Death are taught to medical students but the interesting history of pellagra and its wider phenotype is largely forgotten [1–4]. A characteristic blank facies and a festinating gait, fasciculation of the tongue or myoclonic encephalopathy are classic features of well-known neurological diseases that were actually first described in the pellagra epidemics. Many other close mimics of neurodegenerative and neuropsychiatric disease, including frank psychoses were seen. Pellagrins harboured dysbiotic infections and succumbed to acute infections explaining the high mortality, the gut manifestations and the high incidence of tuberculosis (TB). Pellagra was widely believed to be hereditary and certainly ran in families. Transgenerational effects created vicious cycles of ill health and poor brain development and further poverty in a man-made economic and market failure that caused a nutritional and metabolic trap.

Sufferers were exposed to considerable discrimination and "Othering", whether as poor whites or blacks, that attracted the attention of eugenicists and sterilisation programmes as their fertility was high (when short of outright starvation), yet this situation is cured by a simple dietary intervention.

2. History and background

The 18thC European epidemics, as described by Gaspar Casal (1735), affected poor Mediterranean peasants on monophagic maize based polenta diets and little meat. The peasants themselves were all too aware of the condition and the relationship to lack of animal products, such as milk, meat and butter. Earlier cases must have existed, perhaps called leprosy in biblical and in earlier times (true leprosy "disappears", like TB, on a high meat diet or nicotinamide administered as an antibiotic). Central American peasants in the New World largely avoided pellagra by a cultural evolutionary approach that involved eating and growing maize with beans and cooking with alkali releasing nicotinamide – but these cultural adaptations were not transported with the plant (that compared with other cereals is low in both nicotinamide and tryptophan) in the Columbian exchange.

Casal agreed about the important role for diet and only later were genetic or infectious, from rotten maize, aetiologies favoured. The early 20th C American epidemic, that killed hundreds of thousands, predominantly affected poor blacks (and whites) working as semi-slave sharecroppers thrown in to poverty with the collapse of the cotton market and the loss of their own farms and hunting rights to plantations, eating maize, molasses (rum) and small quantities of low-quality pork. Joseph Goldberger working in the 1920's after ground-breaking epidemiological and experimental work showed once again that diet was the crucial factor [5–7]. The discovery of nicotinic acid by Elvehjem and a role for tryptophan led to the cure of patients by Spies and the prevention of others through supplementation programmes in milled bread in the 1930s-40's.

Pellagra was long believed to be degenerative in the dehumanising sense of the term. Recent research is clear that Homo sapiens evolved on a high meat diet: pellagra can therefore be seen as an atavistic example of human evolution in reverse gear. This does not downplay the role of dietary balance with plant foods and their contribution to our cooking and (agri-)culture and consciousness given their psychoactive, poisonous and medicinal properties [8–11]. Still, typical early modern and modern societies, unlike hunter-gatherers that share meat, have ruling "meat elites" that will go to almost any lengths to obtain it from wars or if necessary (in the past), human sacrifice creating their own dietary habitat and stratified classes of cognitive, creative and social capital in fragile social contracts [12–14].

Pellagrins, living in a very low meat habitat, were seen a different race having a different physiognomy that crossed colour lines even though it was an archetypal disease of poverty, rather like TB with which it is associated. Inferior cognition, antisocial and addictive behaviours led to discrimination as the "Butterfly caste." This iconic example of cultural and retaliatory "honour" wars may be a denominator common to other disadvantaged groups and their identity politics (or the drive to migrate), that can distract from the underlying economic and dietary issues that need to be faced – and resolved by (meat) redistribution [15–17]. Pellagra casts a long shadow. Some historians date many of the tensions, racial discrimination and stereotyping with insulting epithets between poor whites and blacks from these times as in "The Mind of the South" with distant echoes in segregation, incarceration and apartheid around the world, such as in South Africa (another pellagra zone), to this day [15, 18].

3. Pellagra summary

Pellagra was a systems failure causing premature ageing and widespread neurodegeneration or dysfunction with evidence of mitochondrial failure, oxidative stress and proteinopathy. Poor intellectual development and dementia were key features as were many neuropsychiatric effects and poor social behaviour. Severe forms resembled Jacob-Creutzfeld disease (still misdiagnosed at times), with myoclonic encephalopathy and common biochemical features with NAD disturbances [19]. Gut infections and a high incidence of TB were major features. There were many undiagnosed and untreated cases as the exaggerated sunburn rash (Casal's necklace) was often not present or as noticeable ("pellagra sine pellagra") particularly in those with pigmented skin.

4. Modern copy-cats

Pellagra demonstrates that a disorder that mimicked many neurodegenerative conditions, as now classified, can have a single and simple dietary cause even when there is evidence for (epi-) genetic involvement, dysbiotic microbiomes, mitochondrial and oxidative stress, and proteinopathy (**Figure 1**). This is not surprising as NAD is so central to metabolism in a "NAD" world (**Figure 2**) [20–23]. Dietary nicotinamide backed-up by the degradation of tryptophan on the kynurenine and "immune tolerance" pathway are the precursors to NAD. NAD(H) is critical to mitochondrial energetics as NADH, other dehydrogenase reactions, anabolism (as NADP), and NAD consumer pathways [24]. Stress from chemical or microbial toxins, requiring DNA or tissue repair by poly ADP ribose polymerases (PARPs) and Sirtuins could have the same pathological result by consuming NAD.

Some cancer and age-related antagonistic pleiotropy-type or somatic mutations clearly interact with NAD metabolism and may respond to nicotinamide supplementation or restriction later in life [25–27]. Others such as high energy neurones in the frontal cortex or in dopaminergic neurones may suffer if there

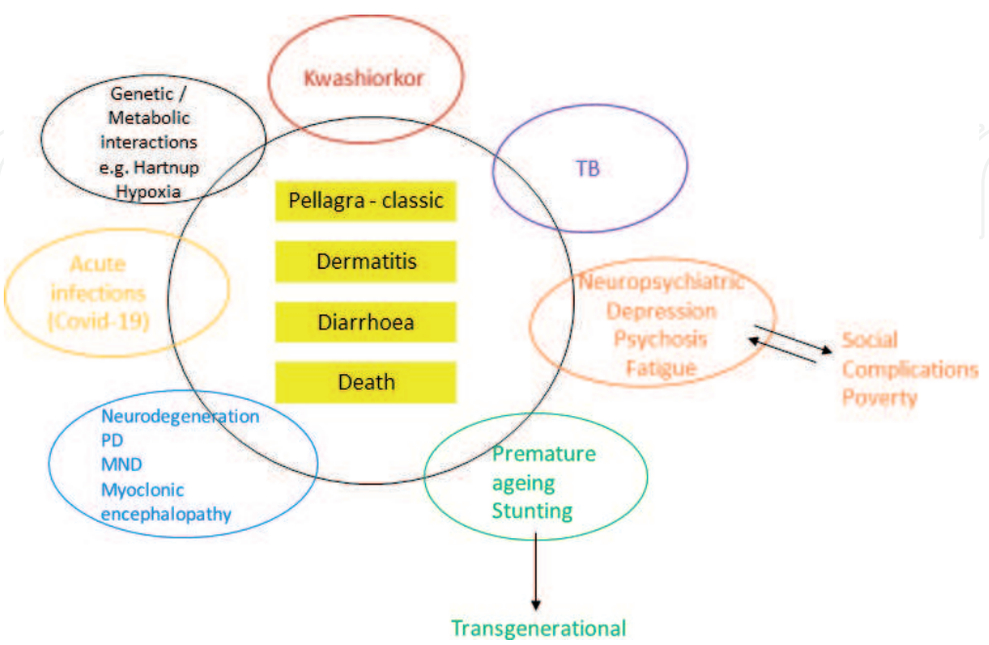

Figure 1.
Pellagra's penumbras. Classical pellagra encompassed multi-organ involvement and disturbed symbiotic and social relationships in the context of poverty. NAD deficiency may involve an even wider multifactorial phenotype and involve excess consumption and nicotinamide overload.

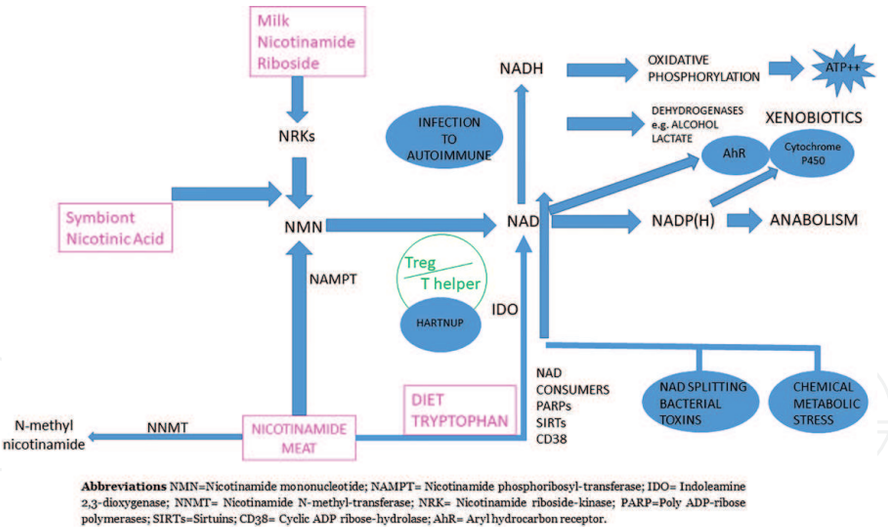

Figure 2.
NAD is so central to our metabolism and our relationships with the outside milieu that it is appropriate to call this perspective an "NAD world" with many opportunities for lost homeostasis that could lead to the prevention of at the least many diseases of poverty.

are "too many mouths to feed" and need supplements [28–30]. Epigenetic developmental origins of health and disease (DOHaD) or somatic mutations may also be helped by a steady satisfactory dose of nicotinamide throughout lives and across generations avoiding various trade-offs such as poor repair or "disposable soma's" to allow high fertility and unite downstream mechanisms: such as reactive oxygen species, mitochondrial failure, DNA methylation and protein misfolding or physiological and immune collapse with the beneficial effects of calorie restriction, ketogenic diets and exercise [31–37]. Pellagra probably used all these mechanisms although this is best documented for mitochondrial, oxidative stress, and amyloidosis.

5. Test and trace

Pellagra may be being missed even with classical presentations let alone "pellagra sine pellagra" and when hidden in the pellagra penumbra where NAD deficiency may exacerbate other conditions. Alcoholism is a known risk factor and some cases treated rightly for thiamine deficiency with multivitamins may be obscuring cases with a pellagrous element contributing to lack of awareness of the condition. Pellagra may be endemic in the millions in poverty who are meat and milk deprived masquerading as Kwashiorkor ("juvenile pellagra") or "environmental enteropathy" or as poor cognition or general ill-health and susceptibility to adverse effects of infection or trauma. A community screening test that would not be difficult to develop should be a priority and where found family and other contacts should be traced as they will be at risk [38–40].

6. TB known cons but some surprising pros

Tuberculosis, common diarrhoeal illnesses and very high death rates from acute infections, such as smallpox and measles, decrease markedly as societies modernise and increase their meat and nicotinamide intake. Nicotinamide and its analogues, such as Isoniazid, are TB antibiotics and many bacterial toxins (including TB's), interact with NAD-consumer pathways so being NAD replete would improve host

resistance making this less of a mystery [41–47]. Intriguingly this is more complex as TB excretes nicotinic acid (used as a test for pathogenic forms for many years), suggesting that when diet is poor, but not too poor, a low population of TB can act as a helpful symbiont, as may some gut organisms in stark contrast to acute infections [48–53]. High dietary dosage, as much as improved hygiene and less cross-infection, will lead to an "absence of TB", and other "Old Friends". TB and even BCG vaccination have important roles in educating the immune system particularly the T cell population and reducing the over-reaction to otherwise harmless antigens characteristic of auto-immune and allergic disease [54].

7. Covid-19 discovers our Achilles heel

Covid-19 probably interferes with the tryptophan uptake pathway and therefore T cell and Interferon responses via a chaperone mechanism with the Angiotensin-converting enzyme (ACE2) receptor through which it enters cells. This amino-acid uptake mechanism also malfunctions with mutations that lead to Hartnup disease that includes a pellagra-like syndrome [55]. Some clinical manifestations of Covid, such as on gut, skin and cognition, or "long Covid" (whose multi-organ symptoms as happened to pellagrins were often doubted), could be "formes fruste" or new versions of pellagra as is supported by documented abnormal tryptophan and nicotinamide metabolism [56–59]. At risk groups such as the elderly or those in poor countries on poor diets may be at risk as they start off from an NAD depleted state. It remains to be seen if supplementation would help before, during or after this or other acute infections.

8. Acute infections and switch to auto-immunity

"Meat transitions" appear to lead to a reduction in many infections and almost simultaneously (as in the late 19th C UK), trigger a demographic and epidemiological switch toward infertility and auto-immune, allergic and other diseases of modernity. Immune intolerance with changes in T cell subset ratios result from inhibition of Indoleamine 2,3-dioxygenase (IDO) and the tryptophan to kynurenine "immune tolerance" pathway as no longer necessary to supply nicotinamide [60, 61]. This immune tolerance extends to the foetus, where it was originally discovered, so may be partly responsible for declines (and occasional reversals), in fertility with modernity – higher doses also affecting cognition and educational levels contributing to a non-coercive form of population control even if not always welcome [25, 62–67]. Dietary modification of nicotinamide or tryptophan in diet, perhaps in concert with other vitamins such as Vitamin D, could affect the incidence of auto-immune conditions such as Multiple Sclerosis [68].

9. Ageing gracefully

Meat transitions and "modernity" have, as if by magic, reduced the incidence of premature ageing, dementia, and death [69–73]. The extraordinary and fast increases in longevity and the fall of age adjusted incidence of dementia have no convincing explanation, and cannot be genetic or related to modern medicine even if antibiotics and vaccinations are part of the answer. In all species there are well described links between NAD metabolism and ageing, alongside resistance to infection, and premature death as was the rule with pellagra – so no magic is required.

NAD levels fall with age and with many diseases of ageing so could respond to nicotinamide supplementation [74–80]. Much has been written about paleo-diets as if major adaptations have not occurred since such as the co-evolved and convergent evolution of genetic (lactase persistence), and cultural adaptations (fermented milk as yoghurt and cheeses and cereals or beer (supplying potent nicotinamide-riboside [81]), and extra amylases for starches as well as careful cooking of maize with alkali as "nixtamal" that may justify the term "Paleofantasy". Yet, there may be something in the elderly being more reliant on the ancestral partly abandoned high meat diet as these and other genetic adaptations may be attenuated once past the reproductive peak [82].

10. Poverty, inequality and discrimination

Early pellagra-ologists, such as Lombroso, may have been right in sensing that pellagrins were atavistic examples of degeneration in the 19th C sense of the term given that increasing meat intake was an important step in our evolution from more herbivorous primates [83]. However this increase was tempered by a move down the food chain in the Mesolithic with more plant based foods, perhaps to increase our fertility, and this move accelerated with the Neolithic agricultural revolution [84, 85]. This was the start of the mixed blessings of "Cereal-ization" and "Calorie-ization" that continues to this day – except for those getting richer where "Meatification" is the rule as observed by Engel and his law [86]. Furthermore for 95% of our evolution as hunter-gatherers we shared meat or individuals were shunned without mercy (even though successful hunters may have used meat to obtain extra mates), so the non-egalitarian meat variances that developed recently are surprising and extreme with 100 fold variances across the globe between rich and poor [64, 87–90]. The poor particularly in poor countries as a consequence face an adverse metabolic and transgenerational NAD headwind that may come to define poverty [91]. Countries that do well ("rosbifs"), by contrast have a healthier anabolic NAD metabolism whereas collapses of empires have been linked to poor diet and uncontrolled "catabolism" unless a meat "safety net" is built [92–95].

Inequalities of meat intake between classes and countries may need to be fairer for everyone's safety. These extremes are traceable back to 17th C common pastureland "enclosure" movements and 19th C colonialism with the creation of the "third world." All these and other mechanisms channel meat to the wealthy. The New World originally had few natural animal domesticates but this was corrected by the Columbian exchange enabling the rise of the West [96]. The global South was also unlucky in its meat supply particularly in Africa where a lack of animal domesticates and an abundance of human and veterinary infections in the tsetse fly belt such as trypanosomiasis and rinderpest and were prone to pellagra. Darker skin colour reduces the diagnostic help from the sunburn of pellagra but is a mixed blessing if it is acting as a warning (including allowing self-treatment), of the more serious cognitive effects of nicotinamide deficiency [38].

Much discrimination may be against groups previously or currently at risk from nicotinamide deficiency and conversely many who claim supremacy or that they are part of a meritocracy may have always had a better diet with more meat and nicotinamide. Engel first pointed out that all groups will increase meat intake once they can afford it and should be seen as an essential need for personal and national prosperity [97] as we elaborate in our companion chapter. Dominance in primates has been linked to high serotonin levels and may be the basis of "Biopower and Biopolitics" of "Superior" humans on the better diet [98, 99].

11. Meat markets

The meat market and food supply chain has become very unequal and may be driving inequality affecting disease and demographic transitions and all working through differential doses of micronutrients relative to caloric intake (**Figure 3**) [100–104]. This dysfunctional market may be having profound effects on planetary and human health including those related to the commercial determinants of disease and the double burden of both wasting and obesity with epigenetic effects playing themselves out over individual's lifetimes and across generations [105–108]. There is a case for de-commodifying meat (and fruit and vegetables), as was true in our ancestral state, enabling healthy living for all whatever their income, gender, or ethnic status [109–111].

12. Too much of a good thing?

A state of hypervitaminosis-B3 is also possible. Many conditions common with affluence and greed with a high meat intake (let alone nicotinamide supplementation), are linked to induction of the enzyme NNMT that includes many cancers, Parkinson's disease and obesity and other aspects of the metabolic syndrome,

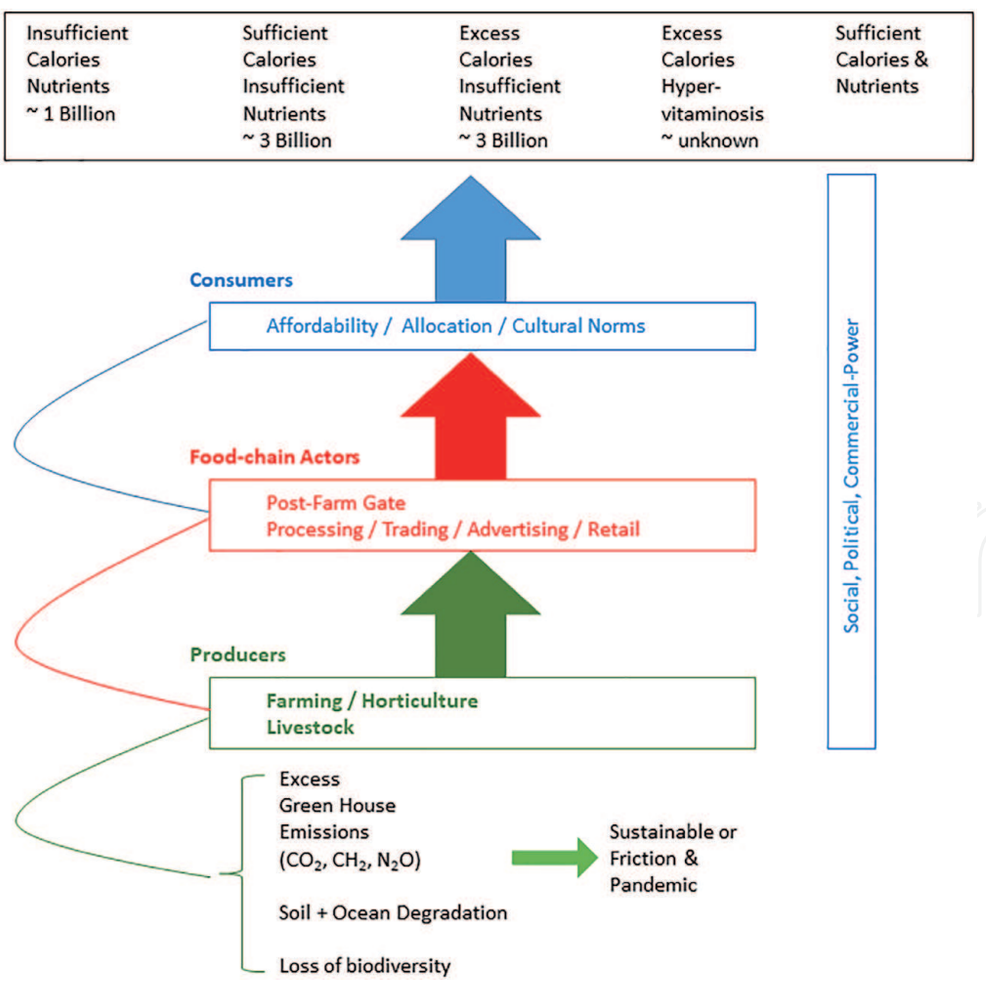

Figure 3.
A solution needs to be found between a more even supply of animal products to the rich and the NAD deficient poor with better farming techniques and supply chains with less waste. Rather than exacerbate climate change this could help through increased human and social capital and reduced risk of zoonoses and political friction.

including diabetes [112–117]. NNMT detoxifies nicotinamide and is induced by high doses (being absent in herbivores), but consumes valuable methyl groups and nicotinamide overload might over-inhibit NAD-consumer enzymes that are metabolic master molecules (14–16) [118]. Nicotinamide's methylated derivative resembles the dopaminergic neurotoxin MPTP and may, like nicotinamide, be a "double-edged sword". When nicotinamide fortification was introduced in the 1940's (in processed breads), this was never universal and never monitored or aimed at eliminating even classical pellagra worldwide. Furthermore any adverse effects in countries where meat and milk were in ample supply was never investigated even as manufacturers of foods and "high energy" drinks (such as Red Bull) added far more than was necessary for supplementation. Short term there are few signs of toxicity but any adverse effects of nicotinamide overload may be long-term side-effects and harder to spot.

13. Poverty prevention: looking upstream

Pellagra's history is well worth remembering given that nobody systematically makes sure that it or "pellagra sine pellagra" was eliminated. In addition several acquired infectious or metabolic or multifactorial genetic diseases may be ameliorated by temporary or permanent adjustments in the dose. Many in poverty are at risk given that variances of meat intake are now extreme and their acute infections will cause further NAD depletion in a vicious cycle. Pellagra should have remained a public health concern, doubtless helped by supplementation, but not helped by never being a universal policy or, as a multi-organ disease not being owned by any single specialty. Nicotinamide's toxicity in high meat economies was never monitored over the long-term and is not short of potential mechanisms through affecting NAD-Consumer controlled metabolism directly or via the methylome.

Recent poverty literature rarely indexes pellagra even though it is a paradigm of how economics and both material absolute and more relational social and cultural needs overlap let alone giving a mechanism for the extraordinarily strong correlations between income and life expectancy across countries and, to some extent, relative measures of income inequality within countries [119, 120]. Pellagra is a proven pathology of poverty that could make disputed behavioural mechanisms, such as high-fat high-calorie "fast food" or addictions or poor (economic) habits, or lack of exercise or even stress and psychosocial processes and other "life style drifts" secondary phenomena. The North–South geographies of poverty and ill-health is both explained and our responsibility to repair it given as reparations for exacerbation in colonial exploitative times. The "Mediterranean paradox" when, despite considerable income inequality, there is less than expected health inequality is also more understandable as a healthier omnivorous diet is more affordable here than elsewhere – and not considered as much of a mark of status or "Bourdieuian" distinction [121, 122].

Pellagra links poverty and poor diet to poor human and social capabilities and, we propose, if this need for meat was corrected in a "Moral economy" – as opposed to the worst of neoliberalism and demonisation of the poor and "Precariats" born of austerity – would allow for more equality of opportunity and education across lives and across generations with less discrimination. It would also create a new dawn for researchers and policy makers [123–128].

Many were surprised at how previous well-meaning policy interventions in the developed and less developed world had failed to reduce health inequalities that included welfare systems, such as the free at the point of need NHS. Since the introduction of the NHS the UK has seen an increase in many measures of health inequality including longevity [129–131]. Low income increases exposure to toxins and pollutants and accidents that may be partly to blame (as may poor

access compared with the middle classes) but diet that is often squeezed by costs of housing and other understandable social and less materials needs for entertainment and respect is contender. Diet is thought to be at least as important a risk factor for modern diseases as smoking and those that defined poverty as "a family is poor if it cannot afford to eat" may not have been so wide of the mark particularly if transgenerational teratogenic "cycles of disadvantage" are taken in to consideration as many reports on child development and maternal health even 50 years ago emphasised [132–137]. Sorting diet was largely beyond the reaches of the NHS as it is a preventive factor that starts in very early life whereas medical interventions, important as they are, happen late and that may explain their lack of impact on inequality.

Preston curves more optimistically suggest that modest increases in income improves health and happiness quickly with a low ceiling effect and diminishing returns and this is compatible with a climb up Engels curve rather than with improvements in hygiene, health, education or technology [138–144]. Such a materialist effect as the poor eating more meat could be part of a new win-win "Enlightenment" [145]. Dietary dosage or nicotinamide supplements may in addition need to be boosted when individuals have certain mutations or are under stress, whether genotoxic or anoxic/metabolic – or restrained if there really is a hypervitaminosis B3 contributing to diseases of affluence. High meat diets and being NAD-Replete may even help solve the dangers of antibiotic resistance and the emergence of superbugs [146]. The environmental cost of optimising meat intake would be mitigated by affluent countries eating and wasting less but sharing more. The meat supply needs to be safe with the poor not having to rely on "bush meat" or risk food poisoning or old and new zoonoses, such as COVID-19, that are a danger to all [88, 147–149]. Supplementation of nicotinamide alone may however not be enough as animal products contain other helpful micronutrients such as iron and sources of methyl-groups such as choline and vitamin B12.

14. Conclusion

We should imagine along with John Lennon (1971) "No need for greed or hunger – A brotherhood of Man" and allow a return to our meat and micronutrient sharing roots. The immediate need is for further study using real world data by measuring Nicotinamide/NAD/NNMT and tryptophan metabolism. Monitoring should happen widely in populations at risk of both deficiency and excess from cradle to grave and in those with a variety of established diseases or trauma or asymptomatic mutations. Interventional studies should provide firm evidence from better nutritional research that does not assume that meat in moderation is toxic to planetary or human health [150].

Acknowledgements

We would like to thank Queen Elizabeth Hospital Birmingham Charity for funding this study.

Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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