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Big brains, meat, tuberculosis and the nicotinamide switches: Co-evolutionary relationships with modern repercussions on longevity and disease?

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ABSTRACT

Meat eating has been an important trigger for human evolution however the responsible component in meat has not been clearly identified. Here we propose that the limiting factors for expanding brains and increasing longevity were the micronutrient nicotinamide (vitamin B3) and the metabolically related essential amino-acid, tryptophan. Meat offers significant sourcing challenges and lack causes a deficiency of nicotinamide and tryptophan and consequently the energy carrier nicotinamide adenine dinucleotide (NAD) that gets consumed in regulatory circuits important for survival, resulting in premature ageing, poor cognition and brain atrophy. If a trophic supply of dietary nicotinamide/tryptophan is so essential for building brains, constraining their size and connectivity, we hypothesise that back-up mechanisms to ensure the supply evolved. One strategy may be increasing the reliance on gut symbionts to break down celluloses that produces NADH and only nicotinamide indirectly, and may cause diarrhoea. We suggest that a direct supplier was the chronic mycobacterial infection tuberculosis (TB) that is a surprise candidate but it co-evolved early, does not inevitably cause disease (90–95% of those infected are healthy), and secretes (and is inhibited by) nicotinamide. We hypothesise that TB evolved first as a symbiont that enabled humans to cope with short-lived shortages of meat and only later behaved as a pathogen when the supply deteriorated chronically, for those in poverty. (TB immunology and epidemiology is riddled with paradoxes for a conventional pathogen). We test this in pilot data showing that sharp declines in TB (and diarrhoea) – 'environmental enteropathy' strongly correlate with increasing meat consumption and therefore nicotinamide exposure, unlike later onset cancers and Parkinson's disease that increased in incidence, perhaps – as we propose a hypothetical hypervitaminosis B3 (to include obesity and the metabolic syndrome) – as the trade-off for increased brain power and longevity, a recently evolved human characteristic.

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Introduction

Among primates as a whole, meat-eating is limited, being at all common only among chimpanzees and baboons [1,2]. By contrast omnivory and considerable meat-eating, or at least a meat hunger, is universal among modern humans, and appears to have a relatively deep history within our lineage. Meat intake is known to have been very high in the Neanderthals (*Homo neanderthalensis*) but they, like our many herbivorous ancestors, went extinct [3] suggesting that meat moderation was important for anatomically and behaviorally modern long-lived humans (*Homo sapiens*) [4,5]; and it may well have been characteristic of archaic humans (*Homo heidelbergensis* and allies), the common ancestor of ourselves and the Neanderthals. Sustaining an optimal supply was likely to have been a problem and, in cases of poverty continues to be – with an added risk of "too much of a good thing" in cases of affluence.

Brains are expensive to run with a constant need to balance energy budgets that are tight given the high NADH costs, spent during mitochondrial oxidative phosphorylation, necessary to propagate action potentials and process information: recently evolved circuits whether in neocortex or striatum are on an "energy edge" as they have exceptionally complex wiring with synaptic connections and long axons that "die back" if the energy supply fails – or if they are not used – given many neuronal "mouths to feed" that, in effect, compete throughout life over the available NAD(H) [6,7]. Meat – especially when cooked – is a high

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energy food but, as a source of calories, is high risk relative to gathering plants [8,9]. The chance of a kill is highly variable and requires considerable immediate expenditure of energy and stored capital in slowly learnt cooperative hunting and communication skills, attended by substantial risk of brain injury or death. The added value from meat, over and above calories, may be because meat supplies a micronutrient – and we propose nicotinamide, the precursor to NAD – largely unavailable from plants alongside animal proteins with a high tryptophan content that had hitherto constrained brain size, internal connectivity and the ability to construct social and domestic networks and a heritable ecological, energetic and informatic niche [10,11].

Meat intake across the globe varies at least 8-fold, being typically 20–40 g or less per day in sub-Saharan Africa and 300 g per day in the US [12], with a recommended dose of 50–100 g per day to satisfy protein, vitamin B_{12}, iron and zinc requirements known to have beneficial effects on brain and body development [13]. Most of the concerns that have been expressed in this respect have focussed on the ills of excessive meat consumption. Among these disadvantages are obesity, heart disease, diabetes and cancers (whose frequencies all correlate positively with meat consumption, although the mechanism is not understood [14,15]). In contrast, the consequences of too little meat/too much grain are rarely mentioned even though the variance across the world now must be higher than earlier in our evolution when meat intake during the paleolithic was high on average and shortages probably short-lived (or fatal) rather than chronic. We shall argue that the evidence suggests that even mild and intermittent shortage of meat had adverse consequences for energy- and micronutrient-sensitive tissues like the brain that require "Food for Thought" and affect an individual's survival. This is compatible with recent evidence that meat eating, and meat's nicotinamide and tryptophan content, improves cognition (including literacy and numeric abilities), social behaviour and motor development (such as bipedalism), and reduces the later incidence of dementia [16–18]. We suggest that these pressures led to the acquisition of a symbiont that provided a back-up source of the same key micronutrient – nicotinamide – and that the symbiont was the tuberculosis bacterium *Mycobacterium tuberculosis*.

To make a case for this hypothesis, we first discuss pellagra as an extreme, but archetypal, example of the consequences of meat shortage and review the biochemical pathways involved; we then make the case for the acquisition of TB as a solution to the problems created by mild meat shortages, and lastly touch upon the possibility that nicotinamide at high dosage becomes a metabolic toxin and carcinogen.

Pellagra and the consequences of meat shortage and cereal-dependence

The epidemic of pellagra in the southern USA during the early 1900s was largely triggered by socioeconomic collapse in the cotton industry. Poverty induced a monophagic diet that relied on maize (corn) and little or no meat [19,20]. Maize is easily grown, with record yields compared to other cereals. Although cultivated varieties require human input in order to reproduce, they require minimal effort – hence its popularity and the temptation to overlook its dangers. Maize is naturally low in nicotinamide and tryptophan (somewhat helped by careful culturally learnt cooking), as to a lesser extent are all other cereals compared with animal sources of protein: ingestion of maize protein (zein) even decreases plasma tryptophan levels and brain serotonin, and wheat protein (gluten) does little better, whereas bovine lactalbumin causes marked physiologically significant increases [21,22]. So, when combined with little meat, maize was (and still is in Africa where it is a favoured crop) a diet with adverse nutritional consequences severe enough to have driven epidemics and emigrations in the past, though at the other extreme most niacin/tryptophan deficiency remains undiagnosed and untreated to this day [23,24].

The clinical phenotype of pellagra includes poor cognition, illiteracy and acalculia from poor brain development, and a later progressive dementia – often with parkinsonism and even motor neurone disease and multiple sclerosis mimics – alongside many other neuropsychiatric and sociopathic features. Pellagrins are also prone to chronic infections, especially gut infections causing diarrhoea, and at post-mortem tuberculosis. Patients also suffer from a range of metabolic disorders and some cancers. The diagnosis relied on a characteristic photosensitive dermatitis (Casal's necklace) though this was not always present. Sufferers cope poorly with stress (whether instigated by an acute infection, a physical trauma, a chemical toxin, or a social challenge). Addictions were common with a particular craving for tobacco that contains both nicotine and the chemically related niacin, and alcohol, that releases NAD. An "honour" culture of violence was present particularly toward cattle thiefs [25]. Familial cases were frequent due to common environment though heritable epigenetic and factors may have played a part in creating a trans-generational vicious cycle. In the US cotton belt, mortality rates were high and there were clinical and pathological signs of multi-organ degeneration, inflammation and premature ageing. Many, if not most, cases were undiagnosed despite "pellagra sine pellagra" being well recognised as manifesting as poor brain development; for instance causing the documented low rates of success in passing the intellectual tests demanded for military entrance when hailing from badly affected states. Chromatolysis and death of the large pyramidal cells in the cortex was characteristic and signs of protein mishandling with amyloidosis, and, of oxidative stress with lipofuscinosis were also present. The cause was found by Elvehjem (in 1937), following epidemiological detective work by Goldberger to be a deficit in vitamin B_3 (nicotinamide) and the essential amino-acid tryptophan that gets converted by a 'de novo' synthetic pathway to NAD/nicotinamide then presumed to be activated to compensate for the dietary supply of nicotinamide, when inadequate [26,27].

Commentators at the time described individuals suffering from pellagra as atavistic "wrecks of humanity" with a systems degeneration that also wrecked their social (and we argue, symbiotic) networks. Although the most spectacular examples of pellagra are from the US south-east around 1910 and, even earlier, from 18th century Europe (where it was officially described by Casal though long known to and named by the polenta eating peasantry), there is historical evidence of pellagra-like conditions and a poor constitution, particularly as far as imported infections were concerned, in earlier maize-based and low meat (few natural animal domesticates compared with the "fertile crescent") cultures in meso-America as clearly noted by the first European arrivals (even Columbus who may have suffered himself) over two centuries earlier – making niacin deficiency an old issue – that may, less clearly, have even been described in ancient Egyptian writings on the "Steles of Famine".

The biochemical pathway and a nicotinamide "switch"

Nicotinamide (vitamin B_3) is essential to the production of NAD, the electron carrier and transfer agent that feeds mitochondria and is oxidised to produce proton-motive forces to form ATP that drives household cellular activities and defences against microbes. NAD is often limiting (whereas the hydrogen (H) can be extracted from any source of calories mainly during glycolysis and Kreb's cycle), and is the key regulator within NAD/NADH redox ratios. NAD^+ forms NAD(P)H, which in turn acts as the co-substrate for various redox reactions and dehydrogenases, such as of alcohol and lactate, as well as playing a pivotal role in the regulation of ion channels

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and oxidant defences [28,29]. A good diet and nicotinamide supply would be expected to improve robustness against acute microbial attack as well as optimising brain function. Importantly for our hypothesis, recently described effects on the survival and programming of stem cells by nicotinamide and tryptophan/serotonin put them in a position to benefit brain development and maintenance, and enable evolution of big brains: only a few extra cycles of cortical neurogenesis affecting proliferation of cells migrating to the pre-frontal and parietal cortex with enhanced differentiation of post-mitotic offspring, such as large cortical pyramidal neurones (including 'von economo' neurones), could lead to the bigger and better connected neocortex that shapes our mind [30–35].

NAD serves as a precursor of ADP-ribose-containing messenger molecules and drives many cell and social processes so this is not only about the energy supply (Fig. 1). NAD consumer-hubs involve SIRT's and PARP's, that are inhibited by nicotinamide and have natural diet-derived agonists such as resveratrol, integrate a number of external interactions such as foraging, exercise, social interactions and learning, as well as internal regulatory roles that affect the immune-system, cell fates and cycles such as differentiation, growth, autophagy, chromatin regulation with epigenetic gene silencing, microtubule organisation and DNA repair. All of these link with pathophysiological stress mechanisms relevant to repairs, regeneration, survival, ageing and disease: there are many examples of these NAD circuits being at the nexus of metabolic homeostasis and an "NAD or Hydrogen world" has been proposed – dating from the geothermal origins of life and the simplest reactions fixing carbon dioxide using the reducing power of hydrogen [36–38]. Indeed NAD homeostasis could be added to, and in large part replace, the five key factors that Cannon originally envisaged as the "Wisdom of the Body" as it incorporates environmental information, initially through NAD-dependant circadian rhythms, as well as physiological needs with NAD(H) powered brains to adapt to prevailing circumstances and niche construct future "NAD worlds" [39].

This metabolic, behavioural and immunological cross-road centres on the tryptophan to NAD 'de novo' pathway whose initiating and rate limiting enzymes Indoleamine 2,3-dioxygenases (IDO-1 & 2) or Tryptophan 2,3-dioxygenase (TDO) are induced by cytokines, classically infection induced interferons predominantly in professional antigen-presenting cells, or directly by infections such as HIV, that via kynurenines in turn affect immune function (by influencing the population of T cells favouring regulatory over cytotoxic T cells). Largely via excitotoxic and pro-oxidant quinolinic acid (picolinic acid is a neuroprotective chelating agent but is not on the final path to NAD), the kynurenine pathway is implicated in many (neuro)degenerative, inflammatory and infectious disorders and cancer [40–43]. This tryptophan path links with protein mTOR paths that sense tryptophan deprivation and also play a pivotal part in immunity and ageing [44].

The nicotinamide and tryptophan to NAD pathway is a "tolerance" link with the immune system allowing selected symbionts to prosper (not, we think, just tolerated because the immune response to eliminate them would be too energetically expensive, or, involve too much collateral damage), and interfaces with the "social" neurotransmitters (notably serotonin), allowing group activities that benefit the food supply [45]. It is unlikely to be a coincidence that this is the 'de novo' pathway for NAD synthesis from tryptophan as all these activities would improve the vital NAD supply, often however at a cost. NAD deficiency from dietary sources activating this pathway has in recent times been underemphasised relative to cytokine induction. Many infections (e.g. Toxoplasma gondii, Leishmania donovanii and Clamydia sp) activate this pathway and may stimulate NAD production to the hosts benefit at times but consumes tryptophan important for their own (and the hosts) growth and produce toxic compounds: so it is hard to see much overall benefit, unless the microbe increases the supply of tryptophan or nicotinamide – as we argue happens with TB.

Nicotinamide switches

A switch away from the 'de novo' pathway, logically when there is adequate nicotinamide from diet, could lead to less chronic infection and less degeneration with increased longevity but if the nicotinamide dose rises too high could switch toward immune intolerance (including infertility and inflammatory/allergic disease), and several cancers with some risk of serotonin toxicity (such as autism) – as has tended to happen with increasing affluence [46].

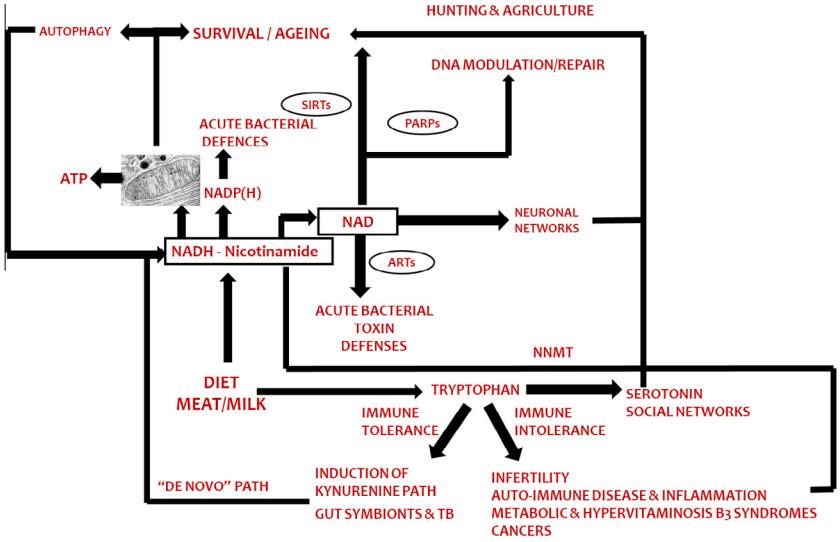

Fig. 1. The de novo pathway for the semi-vitamin nicotinamide is also the immune tolerance pathway and is closely connected to serotonin synthesis and social signalling. This may be a homeostatic circuit that supports energy and nicotinamide/tryptophan acquisition and responsive internal solutions such as autophagy and symbionts that supply nicotinamide and NAD(H), or, pseudo-symbionts such as cancer that sink nicotinamide excesses as do metabolic and inflammatory syndromes, but lead to longer term toxicity. Key: SIRTs – Sirtuins; PARPs – poly ADP ribose polymerase; cADP – cyclic Adenosine di-phosphate; ARTs – T cell ADP ribosyl-transferase; NNMT – Nicotinamide-N-methyl-transferase.

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Our argument is that if the original switch toward high nicotinamide in diet was important in our evolution because it supplied high quality energy, hormone-like signalling properties and the metabolic wherewithal to support big brains, then, given the inherent difficulties in guaranteeing a source of meat, strategies to cope with short-falls should have evolved. Egalitarian meat sharing and innovative hunting and butchery technology, that were all important characteristics of early man, would have helped. Nicotinamide occurs in milk, chiefly as a riboside (that may be particularly important for neuronal function that influenced the general success of mammals), but dairy products are a late 'invention' and the capacity to ingest unprocessed dairy products is limited to those few cultures that developed husbandry where it evolved several times independently under strong selection pressures emphasising its late advantages (the adult lactose-intolerance problem for non-Caucasians): also supported by the co-evolution of cultural practices partly pre-digesting milk products such as cheeses and even gut symbionts that can digest lactose [47,48]. Auto-carnivory, a feature of starvation and many degenerative diseases, is another option that can be mediated by mitochondrial and oxidant stress or excitotoxins on the kynurenine pathway [49], but can only be an emergency solution. Something less threatening to survival would be advantageous. We suggest that this was a symbiont with a 'de novo' pathway able to overproduce niacin for export rather than an increase in the use of our own pathway which would have consumed tryptophan seriously constraining brain evolution by limiting developmentally and socially important serotonin that affects anxiety levels, personality, and responses to adverse circumstances [50,51].

Symbioses

Symbioses (a famous date being the acquisition of mitochondria and NADH nicotinamide ring based energy packs), broadly defined, have been important in human evolution whether as domesticates for food (particularly meat, milk and crops), or (as with other metaorganisms) genetically modifiable microbial engines whose population size can be controlled by the immune system to digest celluloses toward compounds that can supply NADH or produce micronutrients for the host. It is notable that our (gut) symbionts and responses to infections are very different from those of great apes (even those primate zoonoses that colonised us), which may have been important in allowing us to colonise new habitats as has happened with the metagenomic evolution of other invasive species. The apparent paradox is that the species hosting the "parasite" is fit even though the same microbe decimates related populations: recent examples in nature recall some famous invasions and capitulations, such as that of the Americas, in human history [52,53]. Symbiont populations are sensitive to diet and xenobiotics including vitamins (our microbiome varies depending on meat-intake, for instance) explaining these context dependant results especially when coupled with symbionts effects on brain development and behaviour that can be mind altering (communication occurs through neuroendocrine and neurotransmitter means, such as serotonin, and via the vagus nerve) [54,55]. We suggest that *M. tuberculosis* may, rather counter-intuitively from a modern or medical perspective, have been one of these novel symbionts.

A co-evolutionary role for TB?

TB evolved early, well before "out of Africa" 70,000 years ago. It derived, not as originally thought from bovine TB (both evolved from a common ancestor), but from a free-living organism perhaps as much as 2 million years ago [56–60]. Our large brains (three times the absolute volume of those of the largest-brained primates) also evolved early, but did so in three main phases of rapid increase (although there are exceptional significant reverses in size, perhaps *Homo floresiensis*, suggesting considerable flexibility depending on the environment [61]) – the first (a 60% increase in brain volume over great apes and australopithecines) around 1.8 million years ago with the appearance of *Homo ergaster*, and two later phases at ~500,000 years ago (*H. heidelbergensis*, a further 50% increase over *H. ergaster*) and ~200,000 years ago (*H. sapiens*, a 16% increase over *H. heidelbergensis*), with the second of these steps being the larger increase in absolute terms that has been closely linked with primary dietary change and enabling genetic adaptations or pre-adaptations improving digestion and metabolism, such as of starches (and we propose meat/nicotinamide), altered regulation of gene expression (such as enzymes involved with NAD synthesis and nicotinamide catabolism), in part via epigenetic differences in DNA methylation, and all improving mitochondrial metabolism [62–64] As we noted in the Introduction, our meat-based diet probably started with *H. ergaster* in a modest way, but became seriously important with *H. heidelbergensis* and their descendents (Neanderthals and modern humans) from around 500,000 years ago. On the timings available, TB could have been acquired as early as *H. ergaster*, but the dramatic increase in brain volume associated with archaic humans suggests that the most likely point at which it was acquired would have been around 500,000 years ago alongside improvements in hunting and cooking skills (that releases nicotinamide unlike most other micronutrients that get destroyed or diluted).

TB might seem like a surprising choice as a symbiont. After all, it now kills up to 2 million people in Asia and sub-Saharan Africa every year and causes morbidity in as many as 8 million [65]. Overall, one third of the world's population are infected and this can rise to 100% in high risk areas. However, seemingly contradictory but actually context-dependant behaviour (often depending on the hosts diet) of this kind is far from unknown among symbionts [66]: other members of the mycobiome and gut microbiome known to synthesise micronutrients or harvest energy may cause diarrhoeal disease. Welcomed guests can appear to turn hostile. TB still has the advantage that, the large number of deaths notwithstanding, 90–95% of those infected have latent or dormant TB and are healthy.

Bacilli such as *Bifidobacterium* can overproduce vitamins K, B_{12} and other B vitamins, as well as affect choline metabolism in the microbiome of the colon. Importantly to our argument, nicotinamide is unique amongst the water soluble B vitamins in not having any yet known contribution from the normal microflora of the large intestine, which instead typically require their own supply competing with the host – or, if they do synthesise it, retain it intracellularly [67]. However, TB excretes nicotinamide copiously enough to be useful as a diagnostic test that measures high levels in the culture medium, and is enough to elevate blood levels in patients. Evidence that TB causes disease does not seem to come until long after its acquisition, coinciding with the Neolithic agricultural revolution when the meat supply declined as we became more dependent on cereals compounded by a less egalitarian social structure with less meat sharing. This decline in meat consumption would have had an interesting effect on tryptophan metabolism as the replacement with carbohydrates with a high glycaemic index (or biphasically the recently manufactured alcohol) enhances insulin secretion lowering blood levels of all amino acids except tryptophan – that would then cross the blood–brain barrier easily as the amino-acid transporter is competitive and leads to higher brain tryptophan levels available for serotonin and NAD synthesis [68]. However the decline in meat consumption and therefore both dietary sources of nicotinamide and tryptophan may have gone too far, despite this buffer, as there was considerable evidence for a deterioration in height and health, even as populations exploded [69,70].

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Unlike most pathogens, TB neither contains nor exudes any toxins. Curiously, on prevailing paradigms, intravenous injection does not make laboratory animals sick, initial infections are usually completely benign in man and stimulation of natural immunity by vaccination has little effect. Even curiouser, granulomas are recently recognised as sites where the organism reproduces easily contradicting the traditional view that these structures are there to "wall off" the pathogen [71]. Phagocytosis does not kill the microbe – indeed, it can actively multiply in phagocytes [72] in part because it has evolved a mutation (the nuoG gene) that acts as an anti-poptosis agent and allows it to colonise macrophages without these committing cell suicide so as to prevent successful invasion [73]. Importantly for our ideas, *M. tuberculosis* has been shown both to synthesise nicotinamide de novo and to scavenge exogenous NAD and to be able to switch between these two strategies as a function of circumstances through a DosR regulon. This allows it to take niacin from the host when the host is able to supply it (though it inhibits its growth), but also to provide itself and (via excretion of the excess due to a limited ability to scavenge and recycle niacin to NAD), the host with niacin – particularly when in oxygenated sites such as the lung that is its favourite habitat, unlike most symbionts that prefer fermentation reactions in the anoxic gut [74,75].

Importantly for our argument, evidence – largely forgotten – began to accrue during the 1940s demonstating that nicotinamide had beneficial effects on the treatment of TB in the laboratory (as well as on the mycobacterium causing leprosy) [76]. As with subsequent antibiotics the organism resists and, in fact, always survives but goes dormant even with the unusually long courses of treatment relative to most infections. This fact and the fact, already mentioned, that the bacillus itself excretes nicotinamide (which became the basis of a reliable diagnostic test for pathogenic human strains) [77] led directly to the development of isoniazid (a nicotinamide analogue) as a "designer drug." Other drugs such as pyrazinamide impact on the same pathway (indeed resistance to this drug correlates strongly with resistance to nicotinamide), and are still among the standard treatments – although killing most of the microbes can precipitate pellagra, despite untreated patients having high blood levels of nicotinamide presumably because it is supplied by the live organism [78]. It is also a peculiarity of the biochemistry and immunology of TB that exogenous nicotinamide profoundly suppresses the hypersensitivity responses that are important drivers of the pathology as measured by the skin response to injected tuberculin protein (providing the basis for the Mantoux response) [79]. Steroids that often have to be used during treatment to suppress the immune response will suppress the activated kynurenine pathway providing another link with nicotinamide metabolism [80,81]. Thus, surprisingly for a pathogen but perhaps not for a symbiont, TB contains within it the seeds of its own control. Table 1 lists some of the key characteristics of the TB bacillus and asks whether they are of the kind that one might expect in a symbiont but not in a pathogen.

Table 1
Comparison of traits exhibited by the TB bacillus in terms of the behaviour expected of a symbiont versus a pathogen.

Trait	Symbiont	Pathogen
Low virulence rate with		
High dormancy/persistence	√	X
Nicotinamide secretion	√	X
Nicotinamide role in brain growth	√	X
Self-regulation to prevent host death	√	X
Origin should coincide with major brain expansion	√	X
Capacity to switch from NAD production to extraction	√	X
Trade-off with meat consumption	√	X

Testing the hypothesis: some pilot data

Our hypothesis is that the tuberculosis bacillus acts as a live, amplifiable, and genetically modifiable factory-farm for nicotinamide when meat is scarce. Support for the hypothesis would be provided if we could show that there is a close relationship between TB mortality rates and meat consumption, and that this relationship is specific to TB and is not observed in other familiar pathogens and diseases. If there was no relationship at all between TB and meat consumption then it would be difficult to defend our proposition.

For this purpose, we focus on Britain 1850–1950 because there is a good epidemiological record with striking declines in TB rates that have never been adequately explained despite exhaustive debate [82,83]; some favouring dietary others public health explanations – there is little support for genetic adaptations being wholly responsible as it happened so fast and was geographically localised occurring, for instance, much later in Japan (where red meat was banned by decree for many years). Meat consumption was changing fast over this century: meat imports thanks to refrigeration and better transport to the UK were 3.3 million kg in 1841 rising to more than 900 million kg in 1900 – a 300-fold rise – outpacing population increases, even discounting increased home production in the aftermath of the recent agricultural revolution. Milk production per cow also rose during the 18th and 19th centuries, as did milk consumption, particularly after the building of the railways. In addition, focussing on this period allows us to avoid some potential confounding factors such as medical interventions, earlier/better diagnosis and HIV co-infection. We sourced data on real incomes, money wages and food price data from [84]. Data on meat consumption are from [85]. Mortality rates for tuberculosis, malaria (including ague), enteric fever, cholera, smallpox, polio, rheumatic fever and other infectious diseases were sourced from [86], the data on cancer from [87] and the Parkinson's data from [88], all based on the Registrar General's registrations for England and Wales.

Mortality from TB decreased over the century between 1850 and 1950, while meat consumption and real incomes rose (Fig. 2). The relationship with meat consumption is highly significant ($r = -0.958$, $N = 14$, $p < 0.001$; data up to 1950 only: $r = -0.968$, $N = 12$, $p < 0.001$). This is particularly evident when analysed by social class: the upper classes ate more meat and drank more milk and had much lower TB rates than wage labourers [86].

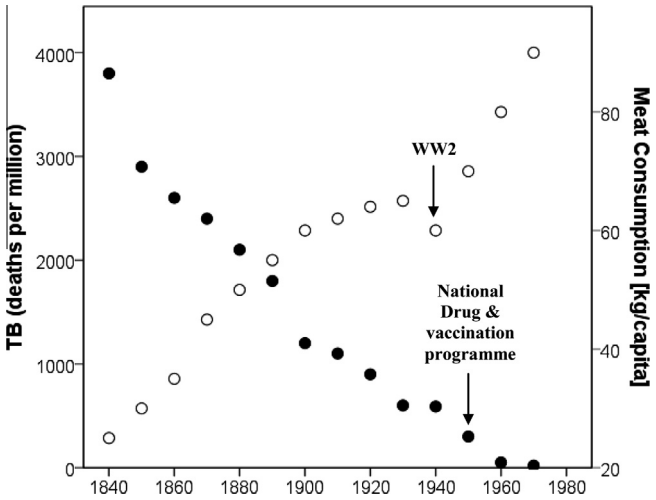

Fig. 2. Shows meat consumption (kg per capita) plotted against the decline of TB between 1840 and 1960 in the UK.

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This relationship is not peculiar to England and Wales, but can still be seen on a country-by-country basis across the contemporary world (Fig. 3: for $\log_{10}$-transformed data, $r = -0.730$, $N = 169$, $p < 0.001$) [data sourced from Refs. 89,90]. The raw data suggest that the relationship is asymptotic, with TB mortality plateauing out close to zero once meat consumption rises above ~60 kg/capita/annum (around 2.5 times the internationally recommended minimum). A linear regression fitted to the normalised (standard deviates) data with meat consumption censored to include only countries where consumption is less than 60 kg/capita/annum yields a slope of $b = -1.079$, which does not differ significantly from a slope of $b = -1$ ($t = -0.418$, NS), suggesting a direct tradeoff between these two variables.

TB death rates were, of course, significantly affected by the rise in real income in England and Wales during the 19th century ($r = -0.664$, $p < 0.001$). The relationship between wealth (or income) and meat consumption (the well known Engel Effect) has been known for some considerable time, but the link to TB morbidity and mortality has not previously been noted.

Turning to other diseases, malaria death rates are one of the few causes of mortality to exhibit a significant negative correlation with meat consumption ($r = -0.730$, $N = 14$, $p = 0.003$). However, the onset of the decline in malaria deaths precedes the rise in meat consumption by several decades (others have wondered if the explanation was that more cattle around provide an alternate blood meal for the vector consistant with malaria's emergence as a disease during the neolithic agricultural revolution and the rise of cereal-dependancy [91]). Diarrhoeal illnesses correlate negatively with meat consumption ($r = -0.923$, $p < 0.001$). Rheumatic fever, cholera, smallpox and poliomyelitis declined during this period, but were uncorrelated with meat consumption (and have better alternate explanations such as cleaner water or vaccination programmes not relevant to TB) ($r = -0.361$, $r = -0.472$, $r = -0.500$ and $r = -0.133$ respectively; all $p > 0.05$), while the incidence of cancer ($r = 0.981$, $p < 0.001$) and Parkinson's disease ($r = 0.846$, $p < 0.001$) correlated positively with meat consumption as does longevity ($r = 0.832$, $p < 0.001$).

Circumstantial evidence offers support for our hypothesis. The North American Indian populations were decimated by TB during the 19th century, but only after they had been driven out of their natural habitats and moved to reservations where the food supply and the ability to hunt were severely restricted [92]. In 1925, the Norwegian government built new spacious barracks in Trondheim as the incidence of TB was so high in naval recruits, but there was no improvement in their health until there was a radical improvement in their meat intake [93]. Recruits to the US navy in 1949–51 had four times the incidence of TB if they showed signs of being under-fed [94]. In the 1930s, the pastoralist Masai (who traditionally ate mainly milk, blood and meat) had lower TB rates than the neighbouring agricultural Kikuyu (who ate cereals and fruit) [95]. In an experiment, TB re-infection rates in families given supplementary vitamins were lower than in a control group [96]. In a major WHO review, Scrimshaw et al. [97] reported that TB rates increased dramatically in several European countries during the two World Wars on several discrete occasions when populations became malnourished due to food shortages or sieges (or in the case of Dennmark over-exporting meat to Britain), and rapidly declined again once conditions improved. Early investigators showed that poor diets could increase susceptibility in laboratory animals and suggested that animal protein provided protection, while Dubos [98] was impressed with the value of skim milk.

These pilot data establishes a close relationship between meat consumption and TB – and only TB (and diarrhoeal illnesses) among a range of familiar pathogens. We suggest that TB can be tolerated by the host so long as the host is not excessively challenged nutritionally (or by iatrogenic or HIV-related immunosuppression, mimicking and in the case of HIV compounding (HIV-Dementia complex closely resembles pellagra at many levels) the immune deficiency of malnutrition – though inyet another paradox overactivity of the immune system can also be a risk factor for TB and is a feature of HIV) [99]. This initial toleration or rather, we say, an immunological welcome mat for a small population of TB is supported by the general good health of the vast majority of those infected and indeed in Victorian times it was well recognised that such individuals could be unusually creative (many writers and poets were affected), before they became sick. Under extreme conditions, we think, a tipping point is reached and the host is unable to control the bacillus' population size resulting in host deaths, as a fragile cross-species homeostatic system is ruptured.

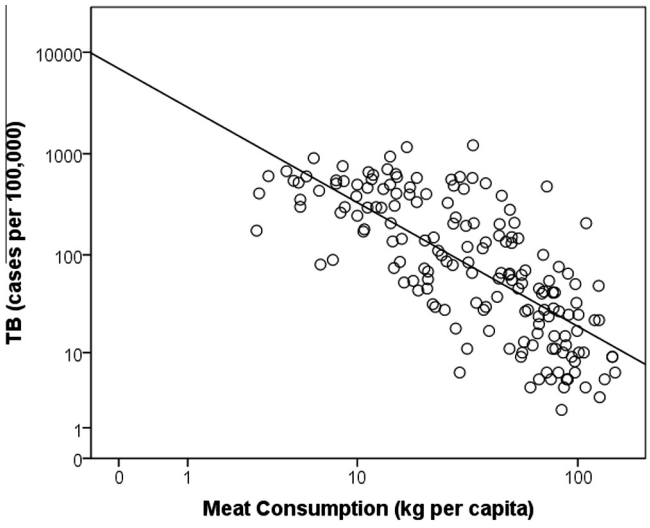

Fig. 3. Frequency of current TB cases plotted against meat consumption for individual countries.

Conclusion

Our claim, based on clues from diverse disciplines many historical, is that the tuberculosis bacillus co-evolved early in the human lineage as a symbiont that buffered us against periodic shortages of meat once meat became an essential component of the diet to fuel the growth and maintenance of especially large brains. We have argued that the paradoxical biochemistry and immunology of TB points to the fact that it is supporting nicotinamide metabolism and not a conventional pathogen that happens to be particularly adept at evading our immune system by manipulating the kynurenine tolerance pathway. The critical point detected is that the tuberculosis bacillus secretes a key micronutrient found in meat (nicotinamide, vitamin B_3), deficits of which result in adverse consequences for brain development and function. An alternative explanation for our findings might be that nicotinamide is simply an antibiotic and although this is true (it has some effect against other micro-organisms), we believe that the relationship with TB is more complex and more interesting if only because organisms normally excrete antibiotics to deter others (that interestingly may include leprosy a rival mycobacterial infection sensitive to nicotinamide that can spontaneously disappear when TB appears or diet improves [100]), not themselves. Another possibility is that nicotinamide simply boosts host immunity through the NAD(P)H pathways; again, there is support for this (many acute organisms and some chronic infections, such as HIV, and their toxins compete

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with us over the NAD supply with hormetic tests of our resilience with benefit for the survivors (akin to the hormetic effects of caloric restiction), but with survival only of the fittest), but we argue that TB only uses our NAD/nicotinamide when we are replete, and that inhibits its growth. Whatever the explanation public health measures to increase nicotinamide dosage in diet should reduce the incidence of clinical tuberculosis and increase longevity as it appears to have done during the UK's natural experiment 1850–1950 and anecdotally repeated elsewhere, even today.

We should emphasise that we are *not* suggesting that pellagra was the actual selection factor for TB symbiosis; rather, we offer pellagra as a tip-of-the-iceberg example of what happens when there is extreme dietary shortage of vitamin B_3. Our claim is that even mild shortages of dietary nicotinamide, as seen with "pellagra sine pellagra" result in deficits in neural development that have significant cognitive and social consequences, and hence that any alternative pathways that buffer against dietary shortages would be advantageous. Nor are we claiming that vitamin B_3 is the only factor of importance in brain development: it is one of a number of nutrient demands that must be satisfied that include a better supply of methyl donors from folate, vitamin B12 and choline – the latter is closely interlinked with nicotinamide metabolism and similarly affects brain development and long term maintenance as precursor to acetylcholine and key brain phospholipids [101]. But, and this is perhaps crucial, it is one of the few that can *only* be satisfied from meat or animal products (at least up until the Neolithic agricultural revolution when cultivars like wheat, rice, potatoes and peanuts that have higher niacin contents than most plants were brought on-stream, some 500,000 years after the B_3 mechanism became crucial). Of course, much later widespread nicotinamide supplementation, at least in rich countries, means even strict vegetarians will obtain the 10–15 mg a day recommended and omnivores could easily exceed ten times that dose, that may reach toxic levels. We suggested that, taken together, the biology of the TB bacillus is more consistent with its being first a mutualistic symbiont and second a pathogen when dietary circumstances later changed (and changed again with antibiotics driving drug resistance in transferable "persister" cells that may be protected by the host [102]).

The fact that the TB bacillus can, and does, kill its host is not in itself a counter-argument to the hypothesis, particularly given that this may only have become a widespread problem later when much more serious and chronic meat shortages became common and the relationship went rogue. Most biological processes, including symbionts, have a U-shaped performance function and one can point to many examples where a perfectly sound natural mechanism has adverse consequences when it runs to excess particularly when cross-species interdependent networks are involved as they can be fragile. Gut microflora offer examples that are directly relevant as we have discussed to the TB case. Symbiotic gut bacteria break down celluloses to short chain fatty acids that act as a source of NADH for the host or produce micronutrients for export, but pushed too far can cause diarrhoea and death as probably happens in the globally common environmental enteropathies, that include kwashiorkor, that kill or maim physically, emotionally and cognitively one third of the world's children – and surely relate more closely to "formes fruste" of pellagra than has been recently thought [103]. Even the dose of nicotinamide itself could have a U-shaped toxicity curve and when intake is excessive switches from a "vitamin" to become a metabolic or neuronal toxin or carcinogen (niacin like nicotine is present in tobacco whose actual carcinogen has never been identified) and explain the positive correlations with cancer, Parkinson's disease and other diseases of affluence. Cancers, like infection and degeneration, have been linked with both low nicotinamide states perhaps impairing DNA repair caused by genotoxins but several others with inflammation and clearing nicotinamide by induction NAD synthetic pathways and even obesity and the metabolic syndrome – NADH is then not oxidised back to NAD normally in the presence of oxygen (the unexplained Warburg paradox) encouraging a runaway process: in a complementary fashion the well described induction of nicotinamide catabolism by NNMT in many cancers including lung and colon (linked with red meat excesses or tobacco or both) sinks nicotinamide whilst consuming methyl groups demethylating the epigenome and promoting pro-cancerous (epi)mutations, or producing, when smoking is less involved, dopaminergic neurotoxins [104–109]. Nicotinamide as the precursor to NAD needed by consumers such as PARP's and SIRT's also inhibits their actions providing a mechanism for how underdosage, or NAD consumption from genotoxic stress, and overdosage could produce a partly similar biochemical endo-phenotype – as might induction of NNMT (by nicotinamide or stress) as if induced early but the supply later lessens cells could become nicotinamide deficient despite an apparently adequate dietary intake (confusing epidemiological dietary surveys).

We have shown that TB mortality correlates negatively with meat consumption, both through time within the UK and across countries today, providing some evidence for a tradeoff between alternative sources of nicotinamide. This is not, of course, a definitive test of the hypothesis although we have identified a mechanism and considerable biological plausability through nicotinamide's undoubted "antibiotic" actions, so this is not simply a correlation. Further tests of the hypothesis would require a more detailed biochemical study of nicotinamide metabolism in both partners under different dietary conditions and, ideally, randomized controlled trials with meat or nicotinamide as the intervention and the incidence and severity of TB and other infections (notably those causing diarrhoea) and measures of brain development and function and a wide range of neurodegenerative and neuroinflammatory disorders (as seen with pellagra) as endpoints. If results are positive, returning to our egalitarian past and redistributing meat or its components that supply NAD, avoiding both the highs and the lows both between individuals and over individual lifetimes, may be more effective (and the increased prosperity from unlocking human potential should easily pay for the intervention) than subsidising corn grain that predominantly supplies calories and is not a good source of either nicotinamide or tryptophan.

Our claim is simply that there is sufficient *prima facie* evidence on the profound effects of meat transitions to make such ecologically and evolutionary-inspired studies worthwhile, particularly given serious concerns over poor nutrition and poor cognition and the limitations of the widespread use of antibiotics where iatrogenic evolutionary pressures have driven multidrug resistance in many organisms, including TB. The situation in North Korea is a current case in point where a 7-fold rise in TB, including drug resistant forms, is unanimously agreed to have it's origin in a recent epic famine, known locally as the "Arduous March" – meat is still only being distributed on public holidays yet it is TB not diet that is being described, as in previous centuries, as "Public Enemy Number One" [110].

Finally, this train of thought may shed light on the mechanisms of both the historical and the current epidemiological patterns of disease and demographic transitions (and avoid any toxicity from future "meat transitions") that may be rooted in how we evolved and sustained our large brains and information processing capabilities in an "NAD world" now of our own making, in the first place.

Conflict of interest

Neither author has any conflicts of interest to declare.

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