



Nicotinamide homeostasis: A xenobiotic pathway that is key to development and degenerative diseases

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Summary Monkeys and man are very closely related genetically. Yet intellectually there are big differences and they suffer from a broad range of different diseases. For example, monkeys do not get Parkinson's or Alzheimer's disease. The former is surprising given that both get parkinsonism from MPTP poisoning and the latter initially less surprising as the cortex predominantly affected in Alzheimer's never developed as fully in the monkey. Man is an omnivore whilst other primates are predominantly herbivores. The one primate who was almost wholly carnivorous was Neanderthal man who became extinct. Red meat has a high content of Nicotinamide, Choline, and methyl donors. The enzyme NNMT converts nicotinamide to *N*-methyl-nicotinamide using SAM as the methyl donor. It is not present to any degree in herbivores. It has recently been shown to be present in human brain and up regulated in Parkinson's disease. Omnivores presumably need it for nicotinamide homeostasis but the production of *N*-methyl-nicotinamide will also be beneficial as it will reduce the export of Choline from neurones. Both will aid brain growth and development. However, as *N*-methyl-nicotinamide resembles MPTP it could cause parkinsonism later in life for man but not monkeys as they would be predicted not to have as much NNMT. Humans with a diet low in Nicotinamide, Choline or methyl donors early in life and low enzyme activity may be prone to Alzheimer's as their brain and therefore its reserves may never have developed as fully. The possession of NNMT plus a diet rich in Nicotinamide, Choline and methyl providers may explain many of the advantages but also the disadvantages of the human condition. One prediction is that a diet rich in these micronutrients whilst young will improve brain development and reduce the risk of Alzheimer's but that a lower dose later in life will reduce the risk of Parkinsonism. A second prediction is that it will become clear that dietary factors including vitamins are signalers and at the head of vital biochemical pathways. A time point will be reached when errors emerge that could not be deleted by evolutionary pressures. Finding and rectifying them will be the key to preventing many common diseases.

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Background

Man is the only primate to suffer naturally from Parkinson's disease despite sharing 95% plus [1,2]

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of their genome with monkeys. Man has also developed his cortical function onto a higher plane compared to other primates. The chemical *N*-methyl-phenyl-tetrahydropyridine (MPTP) causes a parkinsonian syndrome in man that closely mimics Parkinson's disease [3,4]. MPTP does exactly the same sort of damage to other primates [5] demonstrating that their dopaminergic neurones and systems are just as prone to toxins as well as being organized similarly and yet they do not get the disease in the wild. Apes are not as intellectually gifted as man, (even though their basal ganglia are much the same), as their cortex particularly the frontal, temporal, parietal and associative areas are smaller; on the other hand neither do they degenerate and get Alzheimer's and vascular disease with age. These are curious facts given the great genetic similarity and suggests that one should scrutinise the chemical environment, chiefly diet, of man and other primates for stimuli that may have led to a chain of gene expression—environmental interactions for an explanation.

Most of the great apes are herbivores but a few are omnivores as they eat small quantities of meat predominantly from insects and invertebrates. Rarely chimpanzees hunt and can be cannibals. Man alone took up hunting seriously to such an extent that it caused extinction of some species and later raised animals for his own consumption. Man eats significant amounts of red meat regularly manifestly having more carnivorous tendencies. Since Darwin the idea has been around that hunting and meat eating were important to man's evolution from apes without a convincing mechanism. However, the one hominid who is thought to have been almost wholly carnivorous Neanderthal man became extinct despite developing a larger cranial capacity than homo sapiens; a failure that needs an explanation.

Man's physical and intellectual improvements seemed to have happened on such a short time-scale that it has taken many by surprise. Brain size increased 3-fold over 3 million years. Big jumps such as the development of language, inventiveness, risk taking, violence, culture, and height have happened at different times in different parts of the world over the last 10,000 years leading to a profound competitive advantage for a while for that society and altering the course of history. These cultural events have appeared to coincide with domestication of animals and plants and developing methods of food storage and preparation and hence a more consistent omnivorous diet with a major and often daily meat containing meal [6]. Better cereals and other crops will have played their part but an over-reliance on them may not

have been sufficient. Original examples of this can be postulated in ancient Mesopotamia and China who were blessed at times with an in house supply of domesticatable animals and a climate that already supported plants suitable for development as crops. In contrast famine and pestilence have been linked since biblical times (Ezekial 5.12). Discovering the precise dietary triggers to such advances and reversals of fortune would not just be academic as they may be key to maximizing brain development, and reducing disease, more evenly world-wide in the future.

Vitamins might be worth considering as they are by definition universal and important. They are peculiar in evolutionary terms in that they were progressively lost from animals synthetic metabolism yet are essential components of many coenzymes. This seeming ambivalence over the most reliable or safe source might mean that their evolutionary role and actions, whether beneficial or perhaps toxic depending on dose and timing, are more complex than usually portrayed. In a sense they have been outsourced presumably for a good reason relating to better control. The deficiency diseases that brought them to light only occur under extreme and unusual circumstances, such as scurvy on long ocean voyages without fresh fruit and pellagra on a poor corn diet with no meat, and they do not appear to have been important at first glance as ancient issues or diseases (see Figs. 1–3).

A second port of call may be enzymes that deal with xenobiotics (foreign chemicals). These include vitamins but are usually associated with other compounds derived from the environment particularly drugs (pharmacogenetics). Traditionally these have been assumed via a series of safe syntheses to detoxify chemicals but on occasion can mistakenly perform a lethal synthesis and form a toxin. However, their prime function may have been to positively collaborate with compounds in diet and act as one of the engines of evolution-ecogenetic evolution in a palpable sense and the following should be taken as an illustrated speculation. There is a precedent for this type of co-evolution as seen between insects detoxification pathways and poisonous plants where progress is fast due to an apparent arms race. Man may also have co-evolved with key nutrients during development and natural remedies during decline.

Nicotinamide and NNMT

Nicotinamide is a simple pyridine that is likely to be primeval in origin and NADH could have been one of

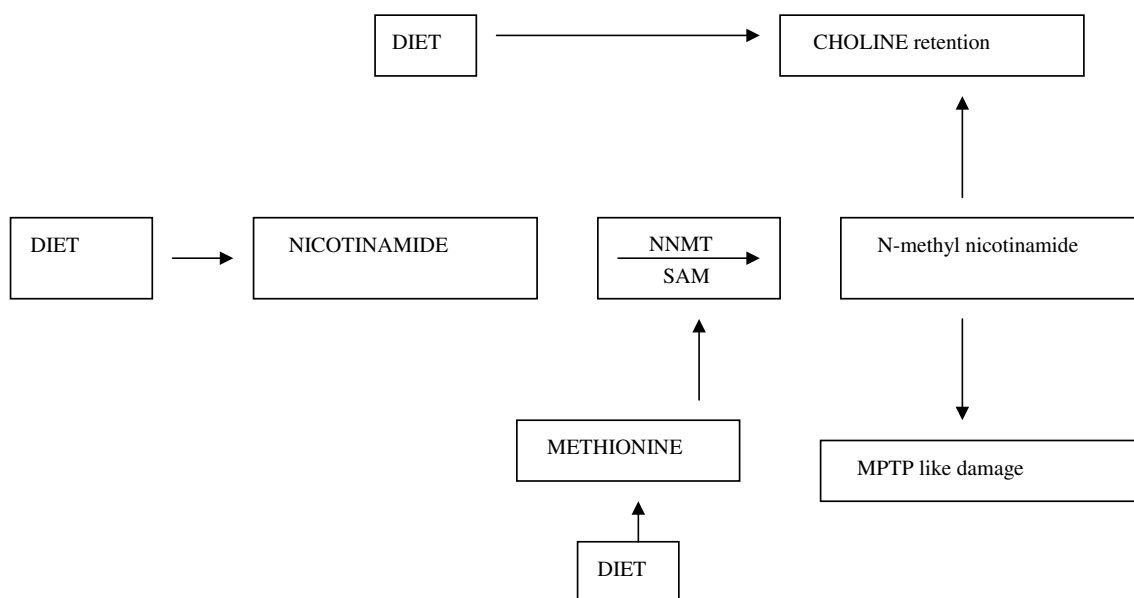


Figure 1 Dietary intake will vary with availability and programmed preferences. NNMT helps nicotinamide and *N*-methylnicotinamide homeostasis and thus acetylcholine which will help develop the brain. However, it cannot protect against long range consequences of early phenotype, or, against long latency toxicity. Nicotine and probably caffeine and other recreational drugs interfere with NNMT giving a link with addiction and carcinogenesis. Consumption of SAM will affect neurotransmitters, hormones, and DNA methylation and thus development, proliferation and behaviour. NADH levels influence oxidative capability and control of toxicants and biological agents.



Figure 2 A changing dietary factor may start off by inducing the receiving protein/enzyme in the individual but eventually if advantageous getting incorporated into the mitochondrial and autosomal genome without any early requirement for mutations. Biological agents like viruses and gamma irradiation will achieve the same result but usually work the other way round as of course will spontaneous mutation. However, the environmental trigger may be the better and more sensitive way of producing the choice variation needed for natural selection to be successful.

the first catalysts. It is vital even in the simplest and oldest bacteria as the important part of the NADH dehydrogenase complex (Complex 1 of the mitochondrial chain) which forms ATP from an absorbed proton and proceeds to the synthesis of proteins from amino acids, RNA/DNA and carbohydrates from CO₂ via the Calvin cycle. Symbiosis then produced the chloroplast and mitochondrion. Nicotinamide (vitamin B3) in plants can be synthesized from aspartic acid and glyceraldehyde phosphate but in man is a degradation product of Tryptophan. This pathway is less efficient in women though is upregulated in pregnancy limiting any effect of the increased demand but only if dietary sources are adequate. Nicotinamide is a vitamin by convention, though it can be produced in

part from this essential amino acid, a reaction enhanced by the other B vitamins, pyridoxine and riboflavin as well as iron and zinc. All therefore need to be present in diet and have as their chief natural source meat, fish and to a lesser extent fresh vegetables. Beef is a particularly rich source. Nicotinamide is the precursor to the coenzymes NADH and NADPH and where deficient its supply may well be rate limiting. Their structure is remarkably similar to RNA/DNA having a pyridine rather than a purine or pyrimidine base. They remain close physical neighbours on the mitochondrial genome so perhaps functions overlap although they have all specialised. These nucleoside pyridines may be as important as RNA or oxygen as they are crucial to around 200 enzymic

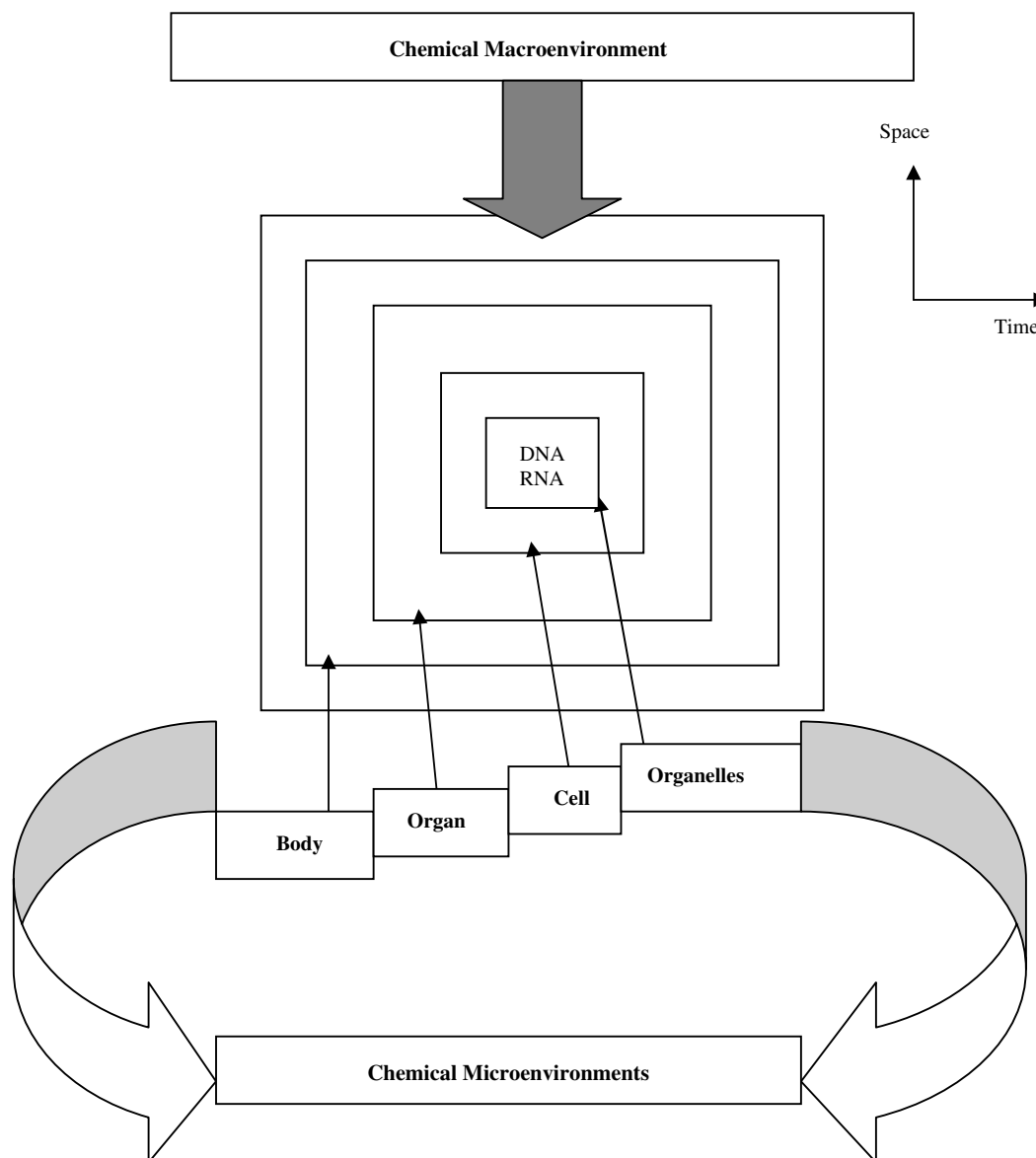


Figure 3 Necessary compartments in our 'chemical machine' need good communication from signallers and receptors, and, regulation by feed back mechanisms within a system with an afferent and efferent arm. Trying to make sense of the efferent actions and reactions without knowing the afferent motivation is a recipe for confusion. The xenobiotic enzyme system is on the furthest and up to now least appreciated frontier. Co-evolution will have eliminated most mistakes/mutations and have inbuilt adaptability within reason to an ever changing environment so time may pose the greatest risk of error. Individuals may have been programmed by trial and error to listen and act on signals from current experience as a youngster whilst the system is most plastic as it is best for survival and maximal reproduction when combined with largely historical information and executive actions stored from previous generations experience and encoded in the genes. Feed-back mechanisms that may attempt to keep the dietary environment safe could be in place from an individual's preference of smell/taste and appetites hence the link of these circuits to early memories and early degeneration. (We accept the concept of such signals and responses for the xenobiotic, oxygen, and biological agents that are in a sense packaged and self-replicating xenobiotics that can also produce toxins or that can force the host genome to make former xenobiotics.) Being on the edge may make this xenobiotic/xenobiotic protein/DNA interface the most influential when young in phylogenic or ontogenic terms, but dangerous for some when old triggering complex secondary internal homeostatic failures (degenerative and proliferative). Molecules that have crossed internal boundaries to perform a communicative function are commonplace, putting the apparent outsourcing of vitamins into perspective. Diseases and other malfunctions are the messenger not the message so dealing with them will rarely be totally satisfactory. Clues to the message like MPTP, viruses, radiation or smoking and immediate dietary triggers or other chemical exposure (such as seen in migraine) should lead to the xenobiotic pathway involved and if not an induced xenobiotic protein or relevant gene may be a reliable signpost.

reactions that are vital for cellular function such as the production of ATP and oxidant defensive and offensive functions. In addition it has an increasingly recognised role as a cytoprotectant at a series of distinct levels [7]. Many of these are concentration specific suggesting a method of controlling events during development and a need for homeostasis that initially takes place in the liver where it is stored and released as required. Links with growth factors, hormones and immunity will become evident. Nicotinamide has clinical toxicity when too low as seen in pellagra when people are forced onto a poor vegetarian diet. Pellagra causes depression and dementia emphasizing a major role for nicotinamide in cortical function. Outbreaks were seasonal in affected areas and were worse in women so could imprint the foetus and the individual. Indeed it may be the explanation for the very high incidence of foetal death on nicotinamide deficient diets as most deaths under similar circumstances are due to gross neural maldevelopment [8]. Amenorrhoea was common which would also have made individuals less fit in a biological sense.

The enzyme Nicotinamide-*N*-methyl-transferase (NNMT) is a xenobiotic metabolising enzyme that is barely present in herbivores [9]. However, it is abundant in carnivores though with significant variation between species and individuals. This could be a key observation. The full molecular basis of this variation is uncertain and there are as yet no known mutations or polymorphisms but it is inducible by its substrates and by stress. Presumably a genetic mechanism is present but yet to be discovered and may reside in regulatory elements or possibly the switch inducing the gene can be made permanent. NNMT is abundant in human tissue, such as liver [10] and has recently been shown to be present in human neurones which may be the second key finding particularly as there is a striking regional distribution being high in temporal lobe and frontal cortex, the parts of the brain expanded in man, and low in substantia nigra, the part of the brain destroyed in Parkinson's disease and MPTP poisoning [11]. Levels are high in the spinal cord. Furthermore levels of the enzyme were found to be high in Parkinson's Disease but also Cancer. NNMT irreversibly converts nicotinamide to *N*-methyl nicotinamide as well as other pyridines to their *N*-methyl-pyridinium ion using *S*-adenosyl-methionine (SAM) as its methyl donor [12]. This may first have been a homeostatic mechanism to control surges of nicotinamide from diet or perhaps was developed because *N*-methyl nicotinamide was useful. It is possible that the latter was initially opportunistic and later got modified to great

effect. However, it came about both greater control over neuronal nicotinamide and *N*-methylnicotinamide levels have apparent benefits with different amounts of NNMT in cortical vs. nigral neurones for instance reflecting different preferences for the best ratio, e.g., cortical neurones requiring more *N*-methyl-nicotinamide.

There are close links between nicotinamide and its methylation and serotonin, noradrenaline and dopamine circuitry and catabolism (all for instance sharing the same methyl donor) and therefore reward, libido, mood and consciousness suggesting a route whereby humans may seek novelty, or instigate suitable environments/diets; for instance high in nicotinamide completing a feed-back loop. Demethylated SAM induces sleep which may be the biochemical rest necessary for re-methylating the system. The rapid changes in nicotinamide metabolism necessary in pregnancy to supply the foetus may be behind some dopaminergic sounding side effects like vomiting and blood pressure control. Exercise could release nicotinamide from muscle and excitement/stress/anger influence the enzyme. Two compounds nicotine and caffeine protect against Parkinson's disease [13]. They interact at several levels with these pathways and like many other drugs of addiction and some sedatives and anaesthetics are *N*-methylated compounds that may interfere with the action of NNMT as does alcohol which uses NADH during catabolism and by a feedback mechanism would shut down nicotinamide methylation. The effect on the enzyme needs further study and some apparent paradoxes may be because a compound can be a substrate and competitively inhibit an enzyme but still induce it (and vice versa). These drugs do not have a reputation for improving cognition long-term even if their short term effect are found helpful by some people. Many are teratogenic causing low birth and brain weight and some methyl compounds like 2-methoxyethanol, exencephaly. Human carnivores who would be predicted to have high NNMT are very prone to addictions and infections as the history of contact with indigenous hunters will attest. Thus, there are complex relationships worthy of further study relating to this enzyme and addiction, behaviour and development.

Choline

Choline like Nicotinamide is also often classified as a semi-vitamin as there is much evidence that dietary intake is important even though it can be

synthesized in small amounts from phosphatidyl-ethanolamine after a series of methylations. Chief sources for choline and the precursor methionine for the methyl donor *S*-adenosyl-methionine (SAM), as well as vitamin B12 and folate who donate methyl groups to homocysteine to form methionine, are animal organs such as liver or animal products like eggs with some from vegetables. There will be times when availability is rate limiting. Choline is the precursor of the important neurotransmitter acetylcholine particularly necessary for memory and general intellectual ability. Its role in spinal cord function may also be important and may have been necessary to achieve an upright posture and greater dexterity. As phosphatidylcholine (lecithin) and sphingomyelin it has other important functions in membranes and as precursors to cell signalers in the brain. It also after oxidation to betaine can act as a methyl donor and separately forms platelet-activating factor giving a link to vascular disease. Low choline in the maternal diet impairs brain development especially memory, attention and learning in the offspring of rats. High choline helps memory and extraordinarily the effect is lifelong with no sign of deterioration with age [14]. These critical findings have been studied and confirmed at the behavioural, anatomical, physiological and neurochemical level. *N*-methyl nicotinamide like choline is a charged *N*-methyl compound and once formed in the neurone by NNMT blocks the export of choline there but also in the kidney thereby stabilising and increasing levels of this vital compound [15]. Because of its charge *N*-methyl-nicotinamide would not cross the blood-brain barrier hence the recent finding of NNMT in human brain and not just organs such as liver was crucial to this hypothesis.

Development

Primates like man who became more carnivorous may have steadily developed their NNMT-Nicotinamide axis to improve nicotinamide homeostasis and by forming *N*-methyl-nicotinamide found that they could simultaneously preserve choline. In concert the supply of enough relevant nutrients including that of methyl donors progressively increased for those in the right place at the right time enabling brain function and spinal cord to rapidly develop perhaps over surprisingly few generations. Differences in availability may explain differences in development between individuals, sexes and societies. Indeed extrinsic influences are suggested by the lack of any evidence that genes heavily in-

involved with development have changed much with speciation (and even allows for some redundancy) and that may explain why ontogeny appears to recapitulate phylogeny as the environmental drivers at work may be similar but acting in a different time and place. Interruptions to growth are behind teratogenicity and specific defects can be linked to several vitamins and many drugs may well interrupt the same pathways and their manifestations giving clues to the key compounds, e.g., vitamin A and the eye, B1 and heart, D3 and bone, etc. These are unlikely to be passive 'building blocks' and their supply must be controlled for quantity, quality and timing by diet – maternal/placental and foetal xenobiotic systems; two extra layers of checks and balances (and still one extra during lactation not counting the chemical microcosm that is family life thereafter). Exquisite responses to environmental agents and dietary hormones are routinely accepted in the plant world. In the animal kingdom there are also many telling examples, e.g., higher pro-vitamin A in the diet can in time produce a new species of bird with a redder beak who may, given the known effects of vitamin A on retinal and brain function, have other less visible benefits.

Once these chemical interactions were solved and increasing brain capacity was the result then learning, social and cultural forces could play their undoubted major role in a self-reinforcing cycle.

Parkinson's disease

Less fortunately for ageing humans, whose life-expectancy has unpredictably increased so markedly, *N*-methyl nicotinamide resembles *N*-methyl-phenyl-pyridinium ion (MPP⁺) in its structure and actions [16–20]. (MPTP is a protoxin converted to MPP⁺ by MAO-B in brain and then poisons Complex 1 of the mitochondrial chain). Despite low levels of NNMT in basal ganglia and some safety margin in the number of dopaminergic neurones *N*-methyl compounds may slowly poison the substantia nigra and cause Parkinson's disease. High production of *N*-methyl nicotinamide may be aided and abetted by the very high and largely artificial (as much is now inserted by cereal and other manufacturers) levels of nicotinamide in diet at least in the western world where Parkinson's disease is much commoner both directly and indirectly by inducing the enzyme. The highest incidences recorded are in Argentina famous for its high consumption of beef and the lowest in poor rural and largely vegetarian Nigeria and China [21]. There is no evidence for a

fundamental racial predisposition as black Americans get Parkinson's at the same rate as whites within a few generations as their economic circumstances and therefore meat consumption improves. NNMT is partly under genetic control allowing an idiosyncratic response to high exposure. Exposure to high levels of its substrates will induce NNMT as happens in Parkinson's disease brain and some cancers as will stress compounding the amount of methylation taking place and this may indirectly affect other methylation pathways including those involved in reward, mood, appetite and DNA repair. Monkeys as herbivores would be predicted to have lower levels of both the enzyme and of nicotinamide in diet and therefore on this hypothesis would not get Parkinson's disease despite being just as sensitive to MPTP. On the other hand they did not get the evolutionary advantage of higher brain choline and its likely effect on the development of cortical function as well as other major benefits from higher but more stable amounts of intraneuronal nicotinamide and therefore NADH and NADPH. Parkinsons patients do dement but usually from Lewy-body dementia not pure Alzheimers as this hypothesis would predict.

Alzheimer's disease

A pathway that served us well during evolution and currently in early development and with defence systems against both toxins and biological agents may pose dangers later in life at least for those on an inappropriate amount of say nicotinamide and is an example of pleiotropy and a link with theories on senescence. Other theories such as those involving free radicals, DNA methylation, somatic and mitochondrial mutation can be effortlessly incorporated. Pleiotropy was a scenario envisaged by Haldane and Medawar and later elaborated by Williams [22–24]. The reverse side of the coin is that the dose of an environmental trigger may need to be adjusted markedly for age to compensate and thereby avoid the downside. This is little different conceptually to the treatment of conditions like phenylketonuria. In the case of nicotinamide it would be relatively easy as much is inserted into diet artificially and if that was not enough the amount of red meat ingested could be altered. Even in western societies some will not access enough of these micronutrients for optimal benefit and might be expected to have problems with tasks that man has more recently acquired such as reading or cultural or social skills. The hypothesis is pro-cholinergic and if in individuals, or their mothers,

these pathways were never fully operational but the situation then deteriorated further in later life through an unfortunate diet plus declining NNMT or SAM activity with age from yet to be identified natural enzyme inhibitors or known ones such as nicotine, one might have a mechanism for late onset initially selective degeneration of cholinergic neurones and other neurones sensitive to nicotinamide levels, i.e., risk factors for Alzheimer's disease. There have been reports of nicotinamide helping symptomatically.

Other diseases

A recent fashion for reductionist genetic arguments is on the wane as single mutations may precipitate and mendelise diseases such as Parkinson's and Alzheimer's but so far have not led to a cause even in the affected families and are rare. The majority of cases of all the modern human common diseases in advantaged economies appear to be mysterious and multifactorial yet their downstream mechanisms often overlap. It is an environmental-gene reductionist argument to wonder if that could be explained by interference by a range of environmental triggers with a pathway that distinguishes us from other primates but that could simultaneously be an Achilles heel. Tissue and cellular target specificity could depend more on access, timing and dose of toxin or biological agent than on the process. That could put several human diseases that do not occur in other primates into a more understandable framework and lead to their prevention. Dietary manipulation of the methyl donors, folate, and the precursor to SAM, methionine, affects conditions as different as congenital neurodevelopmental disorders, epilepsy (viz. B6), vascular disease (viz. homocysteine), autoimmune disease (viz. zinc), cancer and schizophrenia [25–27]. Disparate evidence suggests abnormalities of methylation or NADH–dehydrogenase and other component complexes of the mitochondria in a very wide range of other modern maladies including, AIDS, metabolic syndromes, and depression, as well as being control mechanisms during development but until now there has been no unifying hypothesis [28,29]. AIDS is prevalent in areas where diet is poor/vegetarian or perhaps in affluent societies groups who are relatively vegetarian/low in nicotinamide when the enzyme would have already been induced in the whole population. The result for the cell is the same – low nicotinamide; Pellagra depending on whether it comes about from pure nutritional deficiency or co-existing with an

infection may have several phenotypes. Clinically and pathologically neuropellagra and HIV – Dementia/Myelopathy/Neuropathy sound so similar that they could be identical. There is considerable evidence that vitamins specifically nicotinamide and others that relate to this pathway influence progression; the retrovirus is not generally pathogenic in monkeys who are the original hosts. Early theories on Creutzfeld-Jacob drew clinical and pathological parallels with pellagra and prion proteins are neuroprotective (when low in methionine), and their diseases often linked with eating meat and jumping species (i.e., cannibalism in man, herbivorous cattle forced to eat animal products, sheep eating placenta, humans eating beef) that could induce NNMT.

Pestilences may be the casualties of co-evolution with other proteins and nucleotides supplying NADH but packaged as biological agents with their dosage related to replication rather than appetite and different modes of access and type of cellular target. Survivors are stronger biologically as the smaller party mutates until there is a mutually satisfactory result. Youth here is a disadvantage as it is with nutritional deficiencies and for much the same reasons but detail of the mechanisms involved could lead to a reduction in pathogenicity by bolstering nicotinamide levels.

Links of all types of xenobiotics with mitochondrial and autosomal DNA may be the clue as to why transgenerational and early developmental influences on late onset multifactorial disease are being increasingly noticed and need to be taken very seriously. There are too many correlations to dispute the observations and though the explanations so far given have caused controversy the implications are major and not yet fully appreciated.

Comparative biology

Nicotinamide–NNMT–*N*-methyl-nicotinamide homeostasis may be a major factor relating to the acquisition of many of mans unique qualities, addictions and diseases. The pathway will not be unique to man even if the detail proves different as it must have evolved in many other carnivores independently; comparative zoologists will have to judge if carnivores are more intelligent compared with a herbivore peer group. This question may already be partly answered as although brain size has escalated over time in both ungulates and carnivores at any one time carnivores had the bigger brain [30]. Almost without exception during the origin of

mammals a small carnivorous taxa gave rise to the next major radiation suggesting a degree of cunning relative to herbivores [31]. Contemporaneous examples are rare but one question is whether the omnivorous bear is brighter than the bamboo eating giant panda or the carnivorous grasshopper mouse more intelligent than the average field mouse and if so is the difference of the same magnitude as that between man and monkey? If the answer is yes, then the growth of the human brain may have had a rather mundane initiating mechanism. However, it is conceivable that on our sort of genetic background being too carnivorous throughout life has dangers. Perhaps this explains the demise of Neanderthal man who despite a larger brain became extinct with the only clues being an early death and broken bones perhaps from falls due to neurological disease and relatively small social groups compared with early homo sapiens. Large brains have been linked with extremes of intelligence, creativity and sociability and such a society might be less cohesive or fecund than one with a more conservative range particularly if the average ability is lower. Only a small disadvantage in birth rate or mortality would over several thousand years lead to extinction [32,33]; that assumes that the phenomenon of the extinction of Neanderthal man is correct and that we are not simply observing the slow and incomplete phasing out of near-carnivorous man often after contact with affluence. Relying on data from mitochondrial DNA may be prone to an artefact if it can be affected by diet and the right control might need to be more modern carnivores such as Inuits and a comparison with patients with degenerative disease could be interesting. The idea that a hypervitaminosis syndromes could have been a problem is not outlandish as homo erectus suffered from the bone changes characteristic of hypervitaminosis A and fertility would have been reduced by its serious teratogenicity. Neither is the idea that diet can lead to extinction as this is generally accepted as what could have happened to an earlier hominid, the herbivorous *Australopithecus afarensis*.

Other vital compounds

Nicotinamide methylation status will not be the only environment-gene interaction up regulated and where a regulatory gene may now be polymorphic for which there is precedent [34]. Other methyl pathways may well be critical and affected indirectly by SAM consumption or directly by the increase in methyl donor concentration from the

changed diet. Folate and neurodevelopmental problems and vascular disease is a clear parallel. Trace metals take part in these pathways as well as many other critical enzymic reactions. Essential fats like linoleic and linolenic acid or other essential amino acids available mainly from animals and necessary for brain development have been suggested and may well be necessary factors; cholesterol is also important and again a pleiotropic argument could be forwarded and dietary induction of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase and its inhibition by statins a precedent particularly as there is interest in their effect on Alzheimers disease and the overlap with vascular dementia. Intriguingly the pro-vitamin, D3, has just been shown to be important for brain development giving a link with non-dietary environment [35,36]. Man developed first in a sunny climate especially after deforestation forcing him into the savannah and to change diet then losing body hair and varying skin colour and clothing as homeostatic mechanisms to control UV-B exposure and thereby vitamin D3 levels, though some will be derived from diet once again mainly animal but now more from fish. There is an immediate price to pay when the homeostasis goes wrong in the form of rickets and maybe poorer brain development but also perhaps later with a risk of schizophrenia or multiple sclerosis [37]. Vitamin D3 directly increases the expression of nerve growth factor amongst others and alters dopamine, serotonin and acetylcholine, the latter by elevating choline acetyl-transferase. It has neuroprotective actions increasing glutathione and attenuating MPTP poisoning, anti-proliferative roles and its receptor is reduced in Alzheimers. Thus, a square can be constructed with nicotinamide except that its deficiency state, rickets, has no obvious neurological consequences which may suggest a more ancillary role.

Conclusion

Nucleoside pyridines may yet be promoted to a prime position along with purine and pyrimidine nucleotides as central molecules of evolution and literally, via ATP, the power supply. Starting with chemistry, physical principles of energy will then propel the process forward. Chemical environment, xenobiotic proteins, evolution, extinction, development and disease seem intricately connected by a long and ancient string. Huxley in the 1930s in his dystopian novels [38,39] partly predicted such a pathway. Brave new world was an essay on the potential as well as the dangers of

dietary manipulation to alter adult phenotype and was not far off suggesting that it could alter genotype. Euphenics was a term used by Lederburg for improvements of the environment leading to genetic improvement (a familiar example is the story of haemoglobinopathy and malaria) and may need resuscitating. McKeown made salient points on environmental improvements being underestimated in the past as powers for good in controlling disease. Any concerns should be seen in the light of current socioeconomic/nutritional status already having a major effect on brain size and intelligence and being felt to be the major cause of cancer and perhaps degenerative disease [40–44]. However, that has to be seen in the context of increases in overall longevity in many countries on affluent and more varied diets perhaps lowering cumulative doses of selected xenobiotics that are unnecessary and poisonous; but increasing the dose of necessary indeed vital xenobiotics some of which like nicotinamide and *N*-methyl-nicotinamide are double edged swords but only at certain doses at certain ages in certain people can they be toxic. Taking a world not a parochial view, age, and future generations that have been imprinted into consideration, will be required to sort the best way of optimising nutrition to encourage future and fairer brain and body development and avoid the accidents of cancer, new and old pathogens and degenerative disease.

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