Hydrogen symbioses in evolution and disease

A.C. WILLIAMS and D.B. RAMSDEN

From the Divisions of Neurosciences and Medical Sciences, University of Birmingham and Queen Elizabeth Hospital, Birmingham, UK

Summary

Hydrogen is the source of energy that unites the metabolisms and fuels the innovative potentials of all living organisms. Autotrophs use hydrogen emitted into hydrothermal vents, where symbiotic communities that share hydrogen thrive. On the surface, life developed using photons to cleave water, releasing hydrogen carried into a reverse Krebs cycle to produce carbohydrates, from which hydrogen and its constituent electron and proton are extracted. Fluctuant electrogenic power is harnessed by extensive exchanges and symbiotic sharing schemes of hydrogen sources and carriers. These communicate with electrostatic nuclear centres, forming a positive feedback loop. If the proton-motive circuitry fails from loss of Redox potential, premature ageing and all-category disease can result.

Introduction

‘Children of steam and scalded rock, what is the story you have to tell?’
Davis (at Yellowstone Springs in 1897)

Paracelsus discovered hydrogen, and believed it to be the quintessence of life. Or to put it in modern terms, hydrogen may provide the free energy that allows variety to emerge, thus allowing selection and evolution. Prout proposed that hydrogen, the lightest and commonest element, was the primordial material from which all matter was formed. This turned out to be prescient: we now think that hydrogen was formed 3 min after the ‘big bang’ and by its own process of speciation, produced helium, emitting electromagnetic radiation and forming other elements important to life, that all had to evolve chemically.

The early earth had a high hydrogen content, but much of it escaped into space from volcanic outgassing. Darwin realized the importance of biogeochemical cycles that are now known to halt such losses, forming mantles that sustain biological complexity and can change land- and sea-scapes. Redfield first demonstrated that biomass determines the chemical composition of the environment, including life acting as a hydrogen sink that affects the redox state and temperature of the earth. William Harvey discovered internal circulations and formed an energy hypercycle with the sun and the water cycle. Boyle, Lavoisier, and Pasteur through to Pauling and Mitchell, postulated on the importance of hydrogen (the ‘water generator’) to combustion, respiration, fermentation, the stoichiometry of matter and proton-motive forces.

Taking an energy perspective, starting from principles set in an early hydrogen-rich atmosphere, may help us begin to understand both our ecological succession and then variation in health and disease.
Early origins

Life is currently thought to have begun in or under hot (85–200°C) hydrothermal vents,\textsuperscript{10–22} if so, DNA was probably formed in the same ecological niche.\textsuperscript{23} Such environments, first described in the Galapagos rift, are rich in elemental hydrogen and carbon oxides, creating redox gradients with the help of metal catalysts: circumstances conducive to the formation of organic molecules.\textsuperscript{24–26} An early reaction may have been $\text{Fe}^{+}\text{H}_{2}\text{S} \rightarrow \text{FeS} + \text{H}_{2}$, producing hydrogen used by Archaea, our likely ancestor that already contained relevant enzymes such as NADH dehydrogenase and carbonic anhydrase.\textsuperscript{27–29}

Hydrogen is the universal fuel, and is carried by NAD, derived from nicotinamide and tryptophan in eukaryocytes and \textit{de novo} from aspartate in prokaryocytes. NADH in turn produces energy by reacting with electron acceptors. In eukaryotes, the electron acceptor chain culminates in oxygen, transported by flavinoid dinucleotide-iron-sulphur cytochromes. Bacteria use a wider variety of electron acceptors, including arsenic, so they can exist almost anywhere, and can run on hydrogenases or exocellular compounds, creating a purely electrical connection with the physical world or non-atmospheric oxygen.\textsuperscript{30–35}

Early Krebs cycles work in reverse when the partial pressure of carbon oxides is high. Indeed, in evolutionary terms, many metabolic cycles start off ‘backwards’. At first, a useful substrate is derived from dietary products. If the substrate then becomes available for direct consumption by the population, the metabolic cycle can be reversed to obtain the products. Thus the original Krebs cycle is synthetic, taking hydrogen and carbon oxides and building a carbohydrate backbone, then incorporating nitrogen (azote) and phosphorus to form nucleotides.\textsuperscript{36–40}

Heterotrophs such as ourselves, on the other hand, use glucose and its derivatives in a catabolic cycle, where we rip hydrogen out using dehydrogenases that are highly variable both at a population, individual and tissue level, being both isozymic and polymorphic. Synthetic cycles can then be supported, balancing NAD(H) and NADP(H) through transhydrogenases and including defence pathways such as those for oxygen radicals. Protonmotive forces build ion gradients from sodium, potassium and calcium, and enable cellular functions from volume to cytoskeletal contraction, movement/chemotaxis (toward nutrients away from toxins), neurotransmission, development and memory.

Response systems

In the hydrothermal vents, symbiotic relationships developed quickly, with an array of interacting bacteria, gutless worms, clams and crabs; even unicellular organisms were farming endosymbionts in specialized apartments that were then inherited.

![Figure 1. Energy-fired evolution. NAD is the main transporter for hydrogen. Protons are transported in membranes and electrons in flavinoid-iron-sulphur cytochromes. Protonation is used to determine rate or type of reaction. (Pro)drugs and (pro)toxins have different protonation states. Mutations affect protonation sites, as do hyperventilation, radiation, trauma and electromagnetic therapies.](image-url)
Immune systems evolved to collaborate with symbionts, sampling and reporting back on macromolecules of promise. The need of the organism acting as host thus would be to welcome and control, rather than destroy, symbiont populations. Unwelcome invaders will have a non-complementary metabolism; this may explain why the vast majority of the microbial world ‘ignores’ us. Similarly the function of the xenobiotic genes/protein biocomplex is to respond to the harvest of lower-molecular-weight compounds: not just to detoxify poisons, but to act as a xeno-sensor system that reports via nuclear receptors, cross-regulating with inner messengers such as steroids. Cytochromes P450 use their mono-oxygenase activity to degrade diverse organic matter to yield metabolizable sources of energy. A further function is to receive and control xenobiotic vitamins, including later across the placenta.

Gene sharing, and an impetus from starvation and sex

Horizontal transfer between archaea and bacteria of families of genes involved in hydrogen metabolism has been observed, and can incorporate the use of viruses (and in the case of retroviruses, can be then transmitted vertically). Essentially this is eating another’s DNA and splicing useful operons/regulons into one’s own chromosomes, in a process known as ‘natural competence’. The ‘lac’ operon is a good example: an inducible system can cope with varying substrates, depending on the best hydrogen source.

Tellingly, both transposable elements and autophasy are easiest to induce in starvation conditions, as is differentiation, including fruiting bodies, in organisms such as amoeba/slime moulds. Such a metazoal transformation suggests that fluctuations in the energy supply can have remarkable developmental and life-history effects. Seasonal and other harmonics abound in nature, and the observation that molecules integral to the energy and information chain can switch vitamin-like from metabolism to the environment, in this case cAMP, suggest important keys to chemical evolution.

Another aspect of starvation is that in species that have a choice, sexual reproduction is always chosen over the asexual at these times, despite meiosis being energetically more expensive than mitosis. Mixing two partners ecotypes may be as important as mixing their genotypes in producing adaptable offspring, especially as they will not be random. Selective breeding conditions that combine information from all sources, including the current cytoplasmic energy supply to the gametes and foetus (which may set the range of diet-inducible proteins for life) is a potent inducer of variation. Mates pick their partners depending on feeding grounds. They use clues as to their developmental, nutritional and immune status such as physical and mental prowess, song, the use of volatile compounds or their appearance. These are all energy-sensitive marriages, to get the next generation of dependants/symbionts off to a good start, supported by the NAD(H)-dependant respiratory burst at the onset of fertilization. From this perspective, pH, electrical charge and nicotinamide were the first diet morphogens, and nicotinamide anti-metabolites are the classic teratogens: the dosage of nicotinamide makes the difference between uncommitted cells becoming muscle or cartilage, and extracellular NAD⁺ controls the calcium waves observed during development.

Hydrogen sharing

Many bacteria contain hydrogenosomes that convert hydrogen into protons and electrons (and the reverse). Inter-species hydrogen transfer systems are well accepted in these microbial societies. These vertical microbial mats are in turn thought to have been bulldozed by primitive clay-eating (no conventional nutritional value) lug-worms bioturbing the oceanic floor. The lug worms gave rise to vertebrates by taking their inverted

![Diagram](image-url)
(purely electrostatic) systems involving a controlled water circulation around them in their burrows, and converting them to inner circulations, partly by using shells and bio-mineralization, and partly by a more conventional metabolism extracting hydrogen from nutrients. This may have produced a step-change in the energy supply that fuelled the Cambrian explosion and thus the animal kingdom.56,57

Photosynthesis and oxidative phosphorylation

Photosynthesis developed after a symbiotic acquisition of chloroplasts and mitochondria from rickettsia, capturing energy from photons by generating hydrogen. This happened first in purple-sulphur bacteria, which split H₂S for their hydrogen needs. Later, cyanobacteria cleaved H₂O, as do plants (which pump water). Some algae photosynthesize in the day and convert to using hydrogen at night, rather like facultative anaerobes, or team up symbiotically with fungi that produce hydrogen from putrefaction, as lichens.58,59 The development of oxidative phosphorylation was a big step in both the animal and plant kingdoms, as it is more efficient at producing ATP than anaerobic fermentation reactions where carbon is both the electron donor and acceptor, although such reactions produce molecules such as nicotinamide that are of use to others, making them popular symbionts.

Improvements in hydrogen capture and control

The existence of vitamins and essential amino acids is something of an evolutionary paradox,60 given that bacteria such as E. coli, who coevolved with mammalian colons and now number 10²⁰ at any one time, can manufacture them all, including nicotinamide, from aspartate. This is impressive, given that microbial symbionts typically have a massive loss of genes, compared with their free-living ancestors.61 However, in the context of a symbiotic relationship with micro-organisms that ferment mostly in our anaerobic gut (which outnumber cells in our body by 10 : 1), it becomes more understandable. The latter can mutate faster to adapt, because of their shorter intergenerational time, and can capitalize on an ever-changing nutritional environment that they share with their host. The host provides substrate and removes excretion products and is in a position to drive mutation, and can potentially move or even be driven by the ‘parasite’ to better pastures.62,63

The story of vitamin C (a vitamin for primates) is apposite. As the fruit content of our diet rose, its dietary availability increased, as did that of glucose, also from fruits and a major source of hydrogen as are saturated animal fats. This outsourcing of other molecules such as nicotinamide would improve the energy supply, if it was linked to developing a taste for fruit meat and animal husbandry. Inducible enzyme/gene systems to receive these compounds are recent and map to hydrogen sources, as has been shown for yeasts and the metabolism of alcohol, where the genes for fructose metabolism date to its availability from flowering plants.64

Hydrogen usage

Hydrogen gets its remarkable qualities from the fact that it exists in three forms: cations, anions or covalent hydrogen. The position of a single hydrogen can alter the function of a molecule, as seen with isomers (whether dextro/laevo or cis/trans) and loss of hydrogen bonds denatures proteins. Protonation of biomolecules, from ligands to enzymes and DNA, affects their function, so that they exist as multiple species depending on whether certain residues are protonated, and typically they are weak acids/bases at pH 7.4, such as histidine, arginine or adenine that can switch with tiny changes in local pH or by mutation. Living organisms have picked one or the other isomer as their food or their produce, which may relate to the need to have some anchors for electrostatic patterns. Hydrogen bonding holds together complex molecules such as proteins, RNA and DNA that can act as a transporter of charge, and as an adaptive receiver, thus affecting molecular structure and function from isolated molecules to aggregated clusters and superclusters, but with enough insulation to perform as a symbiotic community that forms functional clusters rather than a wire.65–67

Hydrogen homeostasis

pH is highly controlled homeostatically, including by taste sensors. Marked gradients of hydrogen ions exist across the body and within organelles affected transiently by their activity.68 This does not guarantee hydrogen entering oxidative phosphorylation, which depends on NAD to become ‘active’ hydrogen. The source of NAD is largely milk and meat. The importance of NAD is exemplified by multiple salvage pathways, which were restructured in
mammals along with the invention of milk and an increase in nicotinamide riboside, and which include roles for multidrug transporters. Catabolism involves the enzyme nicotinamide N–methyl transferase; this substrate-dependent inducible system appears only in omnivores as the supply of nicotinamide further improves but puts an extra onus on maintaining a good dietary supply to avoid pellagra. More nicotinamide boosts serotonin and dopamine synthesis, N-methyl nicotinamide aids choline retention, and all are growth factors necessary to build bigger, better-connected and longer-lived brains.

Another interesting homeostatic mechanism is the relationship with gut flora. Many species are completely reliant on gut flora as the source for their NAD(H) supplies. In contrast, NAD is a growth factor for many acute infectious agents such as haemophilus (Factor V), cholera and diptheria, whose toxins compound the problem as they all bind NAD (as does tetanus and botulinum) and whose vaccines/anti-toxins boost NAD. (Many synthetic toxins such as organophosphates also bind NAD, and could cause a double hit). Here there is direct conflict and a fight to the death or for containment, but as commensals/parasites they pose the danger of activation as scavengers if host NAD levels fall. The strength of the initial phagocytic respiratory burst, and therefore the innate immune response, relies on NAD (H) status, as does CD38 signalling. The tryptophan/kynureneine pathway is an important crossroads, as a shortage of NAD would feed back to gamma interferon, down-regulating the adaptive immune response, and allowing populations of symbiotic organisms to expand.

Localized energy failure could also be compensated for by autophagy, releasing NADH for use by neighbours, or by changing to carbon-based metabolism in fermentation, which is a feature of inflammatory tissues and cancer. Correcting these disturbed metabolic fields may render such degenerative or proliferative reactions observable on functional imaging, unnecessary.

**Hydrogen deficiency states**

Scurvy is one example of a condition that causes hydrogen failure, and a reduction of covalent hydrogen bonding in collagen. The most telling is pellagra, caused by loss of NAD. The dementia, skin rash and gut disturbances are best-remembered, but the extent of the phenotypic variation was extraordinary, and ranged from depression and dementia to pure parkinsonism, a motor neuron disease, a multiple sclerosis-like and a myasthenia-like syndrome, as well as myoclonic encephalopathy. Patients also got epilepsy and migraine. Development was poor, and patients aged quickly and died young. A metabolic syndrome included diabetes and sudden death, and there was an increased risk of cancer. Organs, joints and muscles were atrophic. All patients had at least one chronic infection, such as tuberculosis and malaria, as well as gut and yeast infections. Epidemics are triggered by economic causes, attempts to remove symbionts such as hookworm, and a reliance on maize (where transposons were originally described reflecting its ability to cope with environmental stress, but with little spare for secondary metabolites such as nicotinamide or tryptophan, making it a popular but poor crop for Africa).

The neurology and biochemistry of HIV and pellagra are strikingly similar and the presence of a rapidly mutating virus does not exclude dietary factors being causal, as the experience of Keshan disease, coxsackie and selenium deficiency proves. The ancient practice of eating and splicing DNA for nutritional gain could include adenine-rich HIV. Indeed, additional observations suggest that a revisionist view on how our hydrogen fuel cell has evolved, and how it reacts to supply failure, is necessary:

1. Hydrogen and tryptophan excretion are measures of gut flora overgrowth, and biological hydrogen production is so profuse that it may be a major source of future commercial energy.
2. The bilateral effects of diet on intestinal microflora were originally appreciated by Pasteur, as gnotobiotic life outside a laboratory on a normal diet is impossible. There is a recent view that the beneficial role of parasites in food webs has been underestimated. Closely related primates, who are however herbivorous and have a very different nicotinamide metabolism, respond with less pathology than man to parasitic infections such as HIV, malaria and tuberculosis.
3. Pathogenicity in mycobacteria is assessed by their nicotinamide excretion. Other pathogens can be differentiated by their hydrogen metabolism, and yeasts excrete many vitamins.
4. All the first anti-tuberculous agents, such as isoniazid, were nicotinamide analogues by design.
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form of life, reliant on energetic shifts between
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and hydrogen is understood, most of the functions of
the animal economy will be known’.91 Hydrogen
allows self-organization far from thermal equili-
rium, allowing information processing and error
correction, by forming attractors that defy the
second law of thermodynamics. Hypotheses about
hydrogen in evolution contain an element of truth,
relaying as evolution does on trial and error.38,39,52,53
The most imaginative hydrogen hypotheses suggest
that on a cold planet, solid hydrogen alone could be
a form of life, reliant on energetic shifts between
ortho- and para-hydrogen and, on the primitive
earth, that radiation could split hydrogen that played
on clay.92,93 The need for hydrogen gradients runs
through the energy supply to all cellular functions,
although now that there are a myriad of inner
spheres, all with their own arrangements
(weaknesses), the vital harmonics with diet
and symbionts are less obvious than they were in
pre- or unicellular life forms. Many ecospheres exist:
one that is familiar is the mycorrhizosphere, where
mycelia colonize the roots of 80% of land
plants, vital to carbon fluxes and nitrogen azote
fixation (producing NADP for photosynthesis), and
contract in size with artificial feeding. Both inner
and outer spheres are best seen as a metabolic
whole, united by transfers and swaps between
the two compartments, such as by vitamins that are not
mistakes or to save on synthetic energy, but the
evolutionary glue that forms units of variation and
selection.

We do not monitor NAD (H) or H+/e− ratios in
man (yeast researchers use Redox as an indicator
of metabolic health) and cannot be sure that pellagra
entirely went away; the overt disease may have
been masked by dangerous microbiological provid-
ers. An optimal dose for NADH precursors is likely
to act as a brake on the size of the symbiont
population, but if these precursors are raised to very
high levels, by an artificial diet high in meat
and supplements, NAD may paradoxically fall
and exhaust the single methyl donor (S-adenosyl-
methionine) from increasing catabolism, which
could cause a range of mal-differentiated pheno-
types linked to affluence.94,95 (Mal)differentiated
cells that all contain the same genome surely
cannot be defined (in health or disease) without
such electrochemical coded patterns emanating
from their chosen habitat. These are received by
the (epi)genome, which is sensitive to protonation
and methylation, protected and carefully timed
especially for the young, with secondary internal
relay stations, as Turing first suggested for morp-
genesis.96,97 Thus these adverse scenarios (which
may break down with age) should be seen in the
context of a system that allows for situation-sensitive
adaptability. The beak shapes of Darwin’s finches
revealed that a change in diet (similar to our own
dietary history from herbivores to frugivores to
omnivores) had triggered speciation, compounded
by geographic isolation and selective breeding
on the islands. Recently separate species observed in
the same ecotype, rare by definition, were noted to
become phenotypically identical, implying that the
power of diet to cause polymorphic variation may
have been underestimated.98,99

Conclusion
Percelsus and Prout, both physicians, were right
about hydrogen, as was Foucroy 200 years ago:
‘...when the mechanism of the addition of azote
and hydrogen is understood, most of the functions of
the animal economy will be known’.91

We call the communities that inhabit volcanic
vents extremophiles, although their rapid growth
suggestions an easily shared hydrogen energy supply.\textsuperscript{100} Horizontal gene transfer teamed up with selective mating and vertical transmission straddled by retroviruses as a major symbiotic strategy between visible and microscopic life (Darwin’s tangled bank). The environment on the surface was taxing, so animals developed a neural network to move, feel, learn, remember and finally allow written and oral vertical and horizontal communication. A self-referential system that plans communal supplies constructs niches and builds an abstraction of the outside world’s energy resources, with plus and minus connections influencing the pattern of neural connections, using defining culls by autophagy determined by diet, and sensory inputs including learning and motor outputs all flowing through protons, would have adaptive significance. Strategies at all hierarchical levels then are aimed at making optimal use of energy through a common currency.

An overriding emphasis here is on inter- and intra-agency co-operation. However, the same species can decompensate under resource stress and cause social strife and cheating even in microbes using their nutrientome, let alone in social beings with other weapons.\textsuperscript{101} In a largely collaborative world, some conflict will be of value to choose hardy survivors to corner an energetic niche and to scale new phenotypic heights. The nanomolar concentration of hydrogen in most tissue indicates that hydrogen formation is frequently rate-limiting, and that capturing it has been a challenge for most life forms, with all solutions coming with risks and trade-offs.\textsuperscript{102}

Medicine is pragmatic, liking answerable questions, so we end by throwing down a gauntlet: would infectious diseases or diseases of affluence, however categorized, exist as major problems if we organized good NAD(H) husbandry with optimal Redox poise worldwide?

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**References**


