IRON THE METAL OF LIFE AND DEATH

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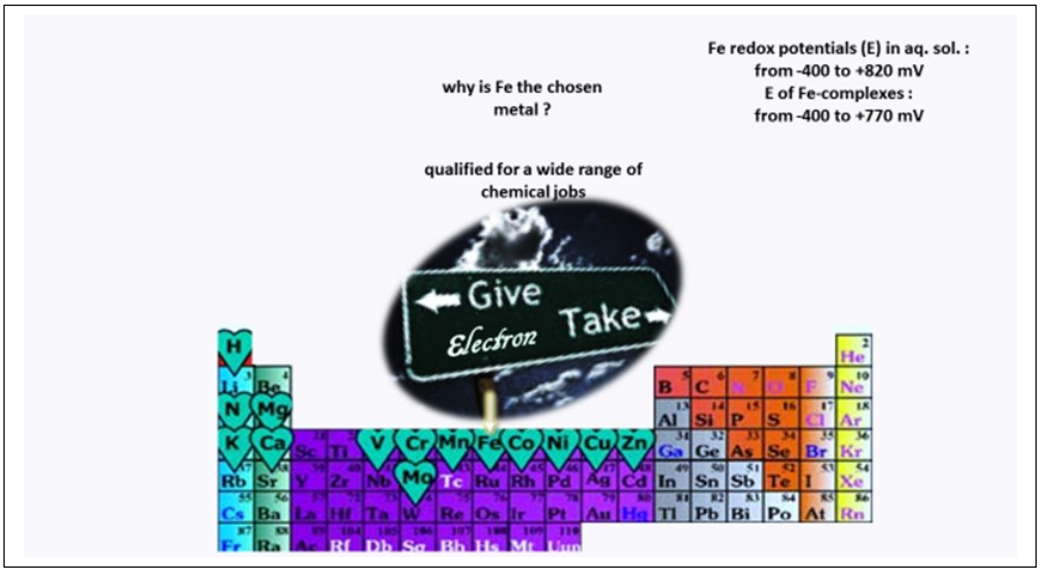
Iron, like Janus, the Greco-Roman God of all beginnings, was "chosen" (among all available elements) to be an essential part of life. From the onset and over the four billion years of evolution, iron continues to play key roles in living systems (energy production, synthesis of DNA and neurotransmitters, oxygen sensing and transport, to mention a few), fulfilling Aristoteles entelechy principle of "realizing what is otherwise merely potential" for life as for death. Maintaining life is a constant investment in mobilizing (among other things) iron so as to meet metabolic demands and concomitantly in preventing-correcting collateral damage promoted by the metal. That brings us to ask a generic question- why was iron "chosen" (i.e. selected) to lead so many life-essential reactions while, in the same time, posing major risks? (which are reflected in numerous iron-associated diseases) and even serve as signal of programmed death (referred as ferroptosis). Was iron selected because it is endowed with an ability to engage in a wide range of chemical reactions but also amenable to narrow that ability to specific activity ranges? Was it because iron was readily available at the site of chemical abiogenesis and millions of years later also in biogenesis? Indeed, most geochemical models indicate that, prior to the appearance of molecular oxygen, the primordial seas were rich in redox-active iron and served for millions of years as a habitat for anaerobic organisms. But then, with the advent of oxygen, that rendered the metal water insoluble and thus progressively less bio-accessible, the dependence on iron became a liability. Moreover, the encounter of iron with oxygen posed further risks due to metal- catalyzed formation of biologically noxious reactive-O-species (ROS). We can phrase the "evolutionary rationale" for the selection of iron also in dialectic terms as: why weren't other metals or metal-independent mechanisms chosen to replace the risky-iron-dependent ones. In fact, modern protein design has already shown that by rational modification of amino acids in the secondary sphere of the copper-protein azurin it is feasible to fine-tune the redox potential so as to cover the entire bio-redox spectrum. However, had such strategy succeeded what would have been the cost in product quality (chemical stability, reactivity, specificity). Judging by what has evolved and is continuously evolving in nature, life's and reliance on iron (in its various chemical forms) has sustained evolutionary challenges posed by the dearth of a metal that is vital but also potentially toxic, reflecting the two inseparable faces of Janus.

In an attempt to address the above generic question (why iron?) we shall refer to three classical maxims as paradigmatic (or guiding) principles that apply to iron and life:

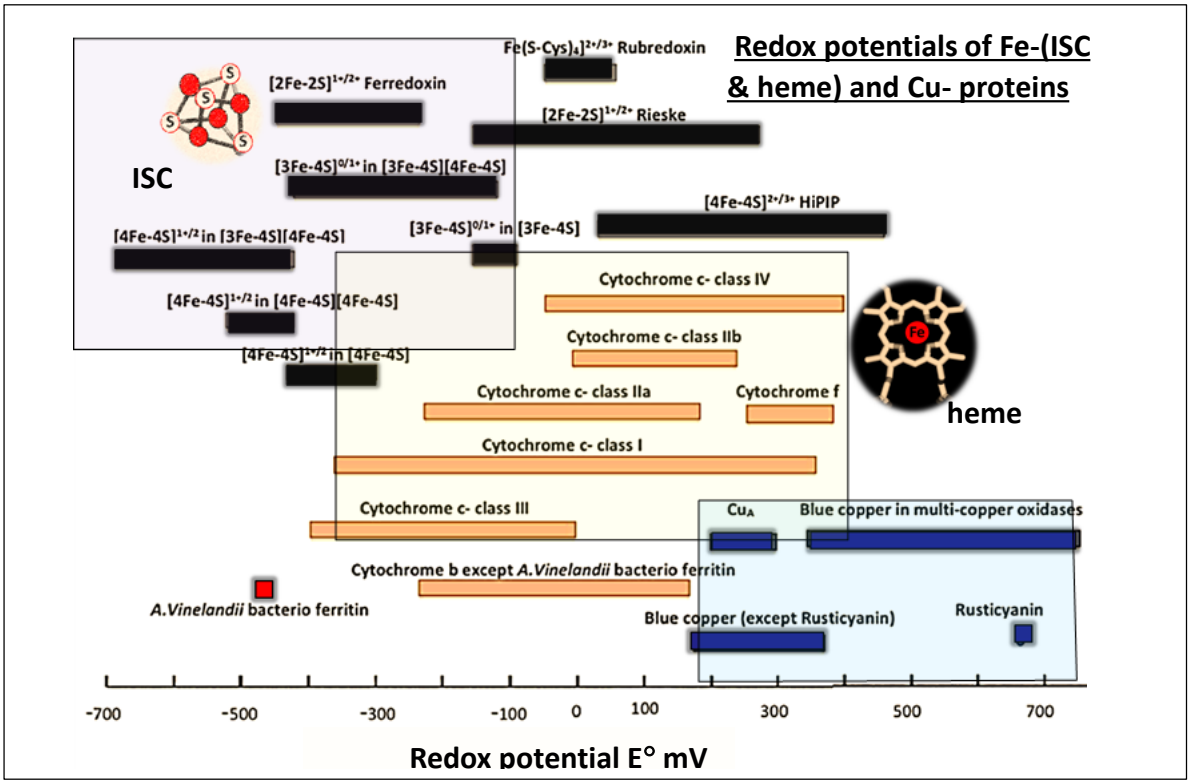
- ***Life is nothing but an electron looking for a place to rest*. Albert Szent Györgyi (1937 Nobel laureate). Can we deduce that "*Disease is when electrons park badly, i.e. in wrong places"…?***
- ***Life is merely avoiding decay into equilibrium* Erwin Schrödinger (1933 Nobel laureate).**
- ***Nothing in Biology makes sense except in the light of evolution*. Theodosius Dobzhansky 1973**

***Life is nothing but an electron looking for a place to rest*.**

As chemical reactions are governed by an interchange of electrons, the element iron, residing in the middle of the row of transition elements, is most suited for the of job transferring e^-'s, covering (as Fe^{2+}-Fe^{3+} couple) a wide redox potential range in aqueous environment.



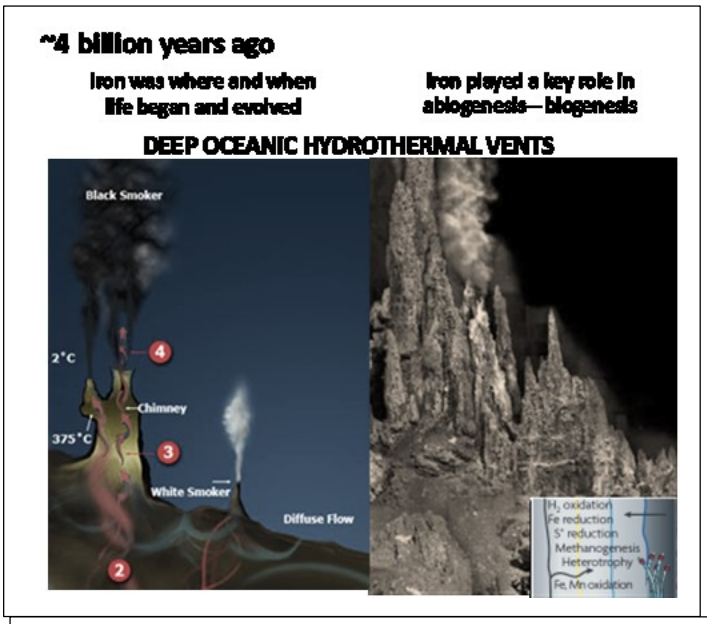
However, to serve biological needs, an element of such "flexible" charge transfer ability (or chemical "promiscuity") needs to be constrained to a selective/specific chemical reactivity window. For that purpose Nature has designed over the billion years of evolution-an enormous repertoire of iron-ligands in protein niches, organic complexes or cofactors bound to proteins, each tailored to a particular target and a given activity window. Some of those molecules work as soloists (enzymes such as ribonucleotide reductase- RNRase or radical S-adenosyl-l-methionine-(SAM) superfamily,



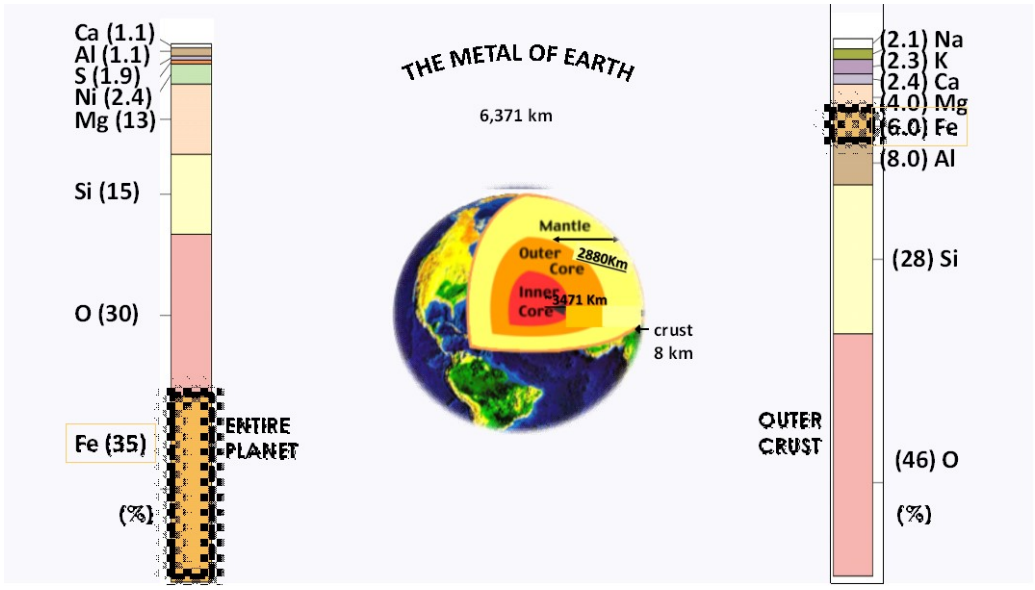
the O_2-carrier hemoglobin –Hb) and others that are part of functional ensembles such as the respiratory chain, which is comprised of an array of iron-sulfur-cluster (ISC) proteins (or ISPs) and of heme-containing cytochromes. It is of interest to note that ISPs, which are among the oldest functional proteins involved in e^--transfer reactions, preceded evolutionary the cytochromes, which in turn widened the biological spectrum of biochemical activities, primarily with the advent of O_2 and its role as ultimate electron acceptor. The transition to aerobism might have led, on the one hand, to the elimination of some ISP-dependent agencies due to the chemical susceptibility of ISCs to oxidizing conditions, and on the other hand, to the integration of ISPs in functional ensembles such as the respiratory chain by serving as e^-donors to heme-cytochromes and those in turn to the Cu-center in cytochrome oxidase-for a full proof-delivery of e^-s to the final acceptor O_2.

THE METAL OF LIFE

Hypothesized scenario of early life on earth

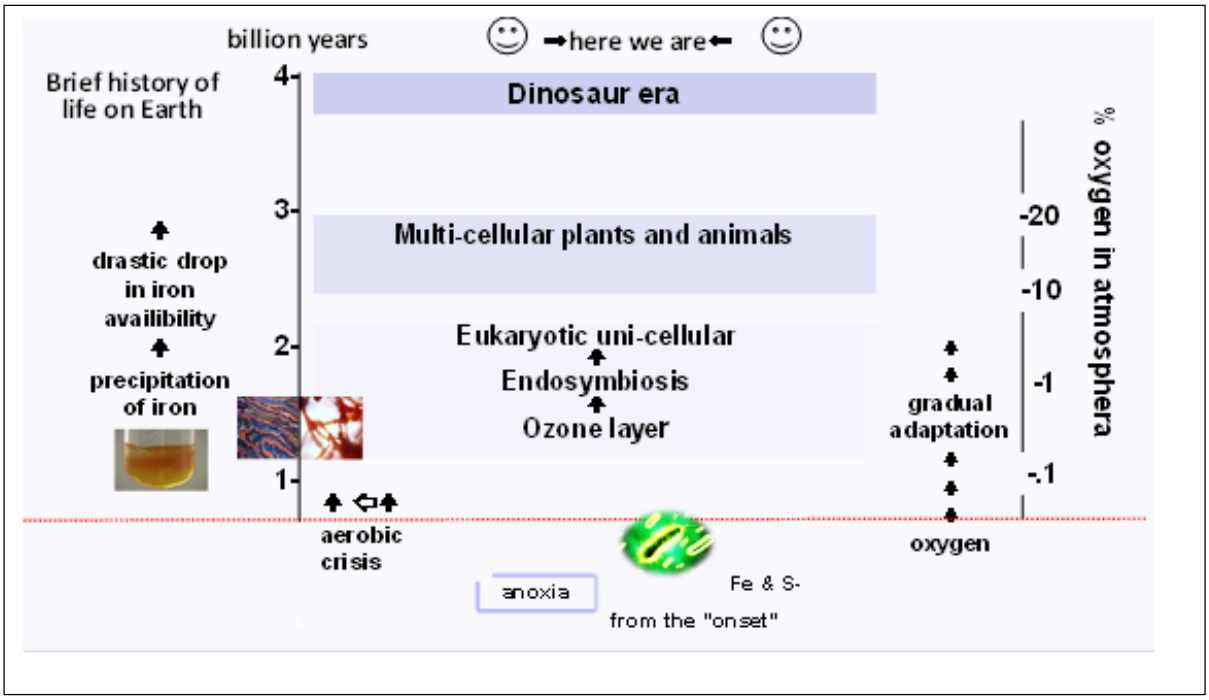


The earliest signs of life Earth are thought to have appeared about 4 billion years ago, although most likely, reactions that led to primordial molecules of biochemical significance have long preceded them. That hypothesis is largely based on chemical reactions known to take place in deep oceanic hydrothermal vents often referred as abiogenic niches. Various hypothetical scenarios that could lead to a primordial living entity have been proposed on the basis of schemes in which iron, which prevailed in primordial seas, played a pivotal



Elemental composition (%) of our entire planet *(left)* or the outer crust-(*right*) that represents only 8 km of the 6371 km.

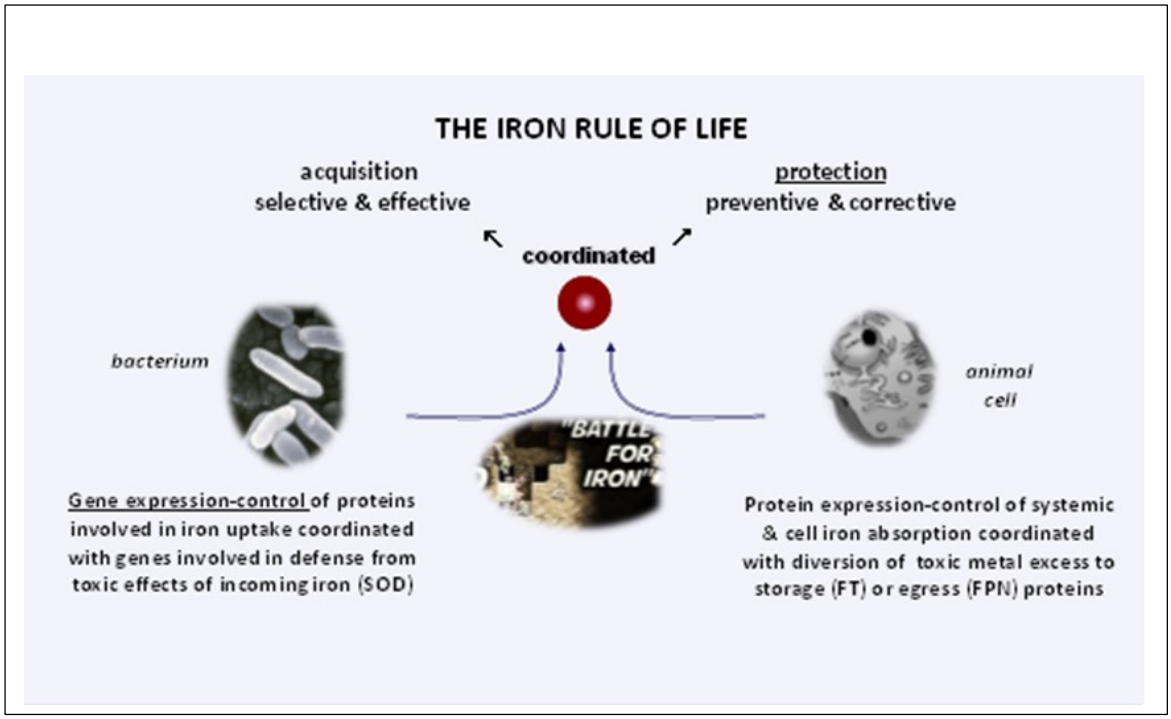
chemical role. That concept fits first and foremost with the fact that iron is the most abundant element on Earth, as it comprises ~30% of all elements in the planet as a whole and 6% in the crust layer, second to aluminum among all metals. Second, when dissolved in aqueous solutions (as in the primordial O_2-free sea water), iron can engage in a wide range of redox activities (as ionic metal per se or in complexes) that can lead to the formation of a variety of bioorganic



molecules.

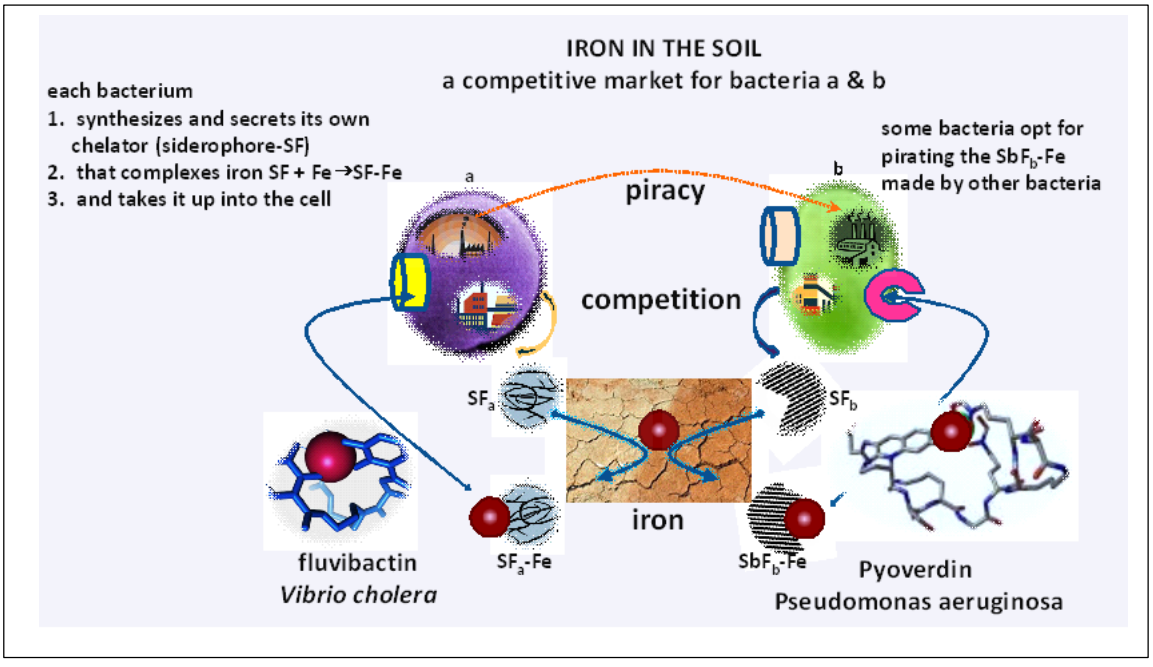
Bona fide records that attest to the richness of life in our planet in ancient times are found in the bounded iron forms (BIF) that resulted from iron precipitation due to oxidation by UV irradiation and by the appearance of O_2 generated by photosynthetic bacteria. That transition led over time to a major crisis by: a. depriving the anaerobic organisms from access to a vital element, demanding the generation of appropriate acquisition machineries and b. creating a scenario whereby exposure of iron to molecular oxygen leads to the formation of noxious ROS, demanding shielding of the metal in protected structures and/or counteracting the metal provoked ROS formation.

Thus, a new rule of life emerged in the aerobic world, whereby survival depended on operating mechanisms of iron acquisition that are both selective and effective but also safe, so that a potential metal-provoked damage is minimized (either by preventive or corrective measures). Mechanisms that operate along the above lines in a coordinated manner evolved in all living species, following a basic rule of life that appears in two modalities, depicted here for prokaryotes and Animalia. Such mechanisms have played a major role in evolutionary biology as survival filters between and across living species competing for the metal in given environments such as the soil, the human skin or gut or in internal animal fluids (e.g. sepsis). They comprised what is often referred as the biological "battle for iron".



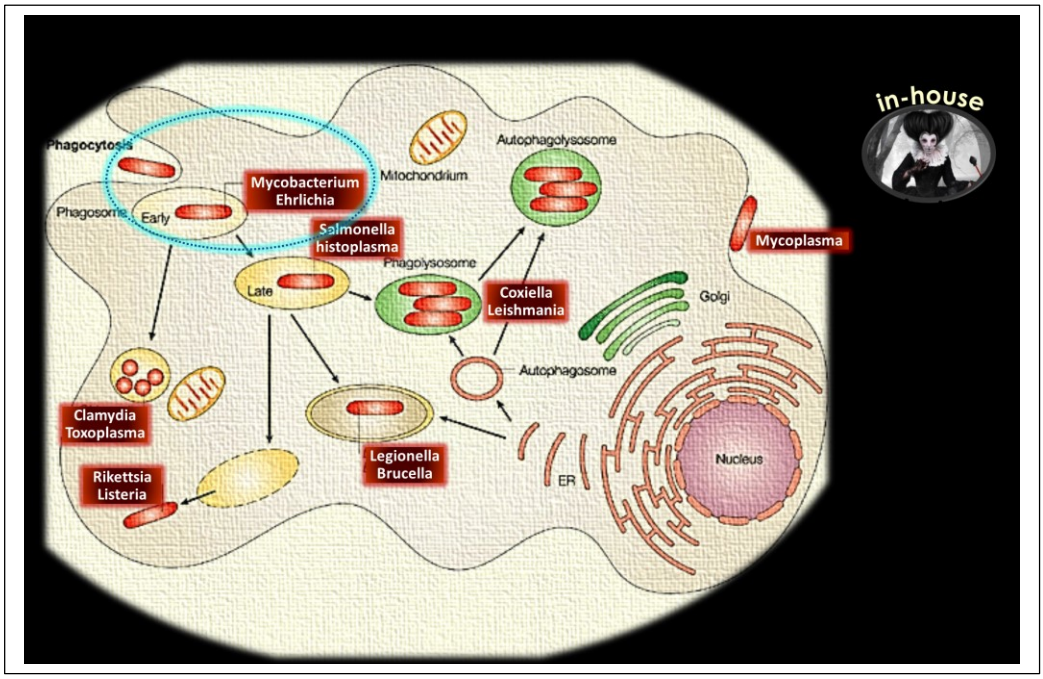
" *Nothing in Biology makes sense except in the light of evolution"* T. Dobzhansky 1973

The soil can be viewed as a competitive market for iron acquisition by different bacteria, each: 1. generating its own machineries for manufacturing unique sets of siderophores that once secreted can capture the metal by forming high affinity complexes (or chelates); 2. expressing specific cell surface receptors that seize the chelates and 3. translocate them into the bacterium by a series of transfer agencies. However, some bacteria manage to back-up iron acquisition by diversifying just the import agencies (2&3) while giving up altogether the production-secretion of siderophores (1).

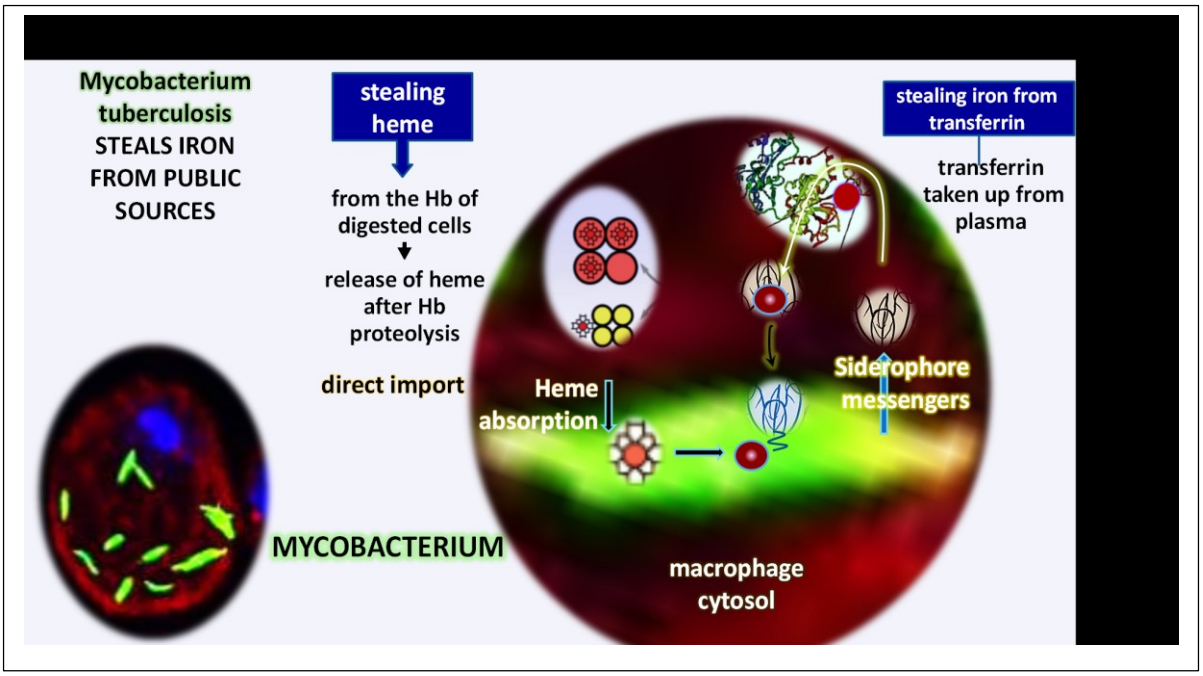


The adoption of a strategy based on molecular piracy of foreign siderophores is accomplished by horizontal gene transfer from one bacterium to another, a mechanism that often confers upon the "adopter" a survival leading edge. This so called "black queen strategy" results in an optional loss of redundant or "wasteful" genetic information with obvious economic advantages. In some cases, such advantage can be gained by switching to a less competitive metal species, as is the case for Borrelia burgdorferi, which gave up iron for manganese.

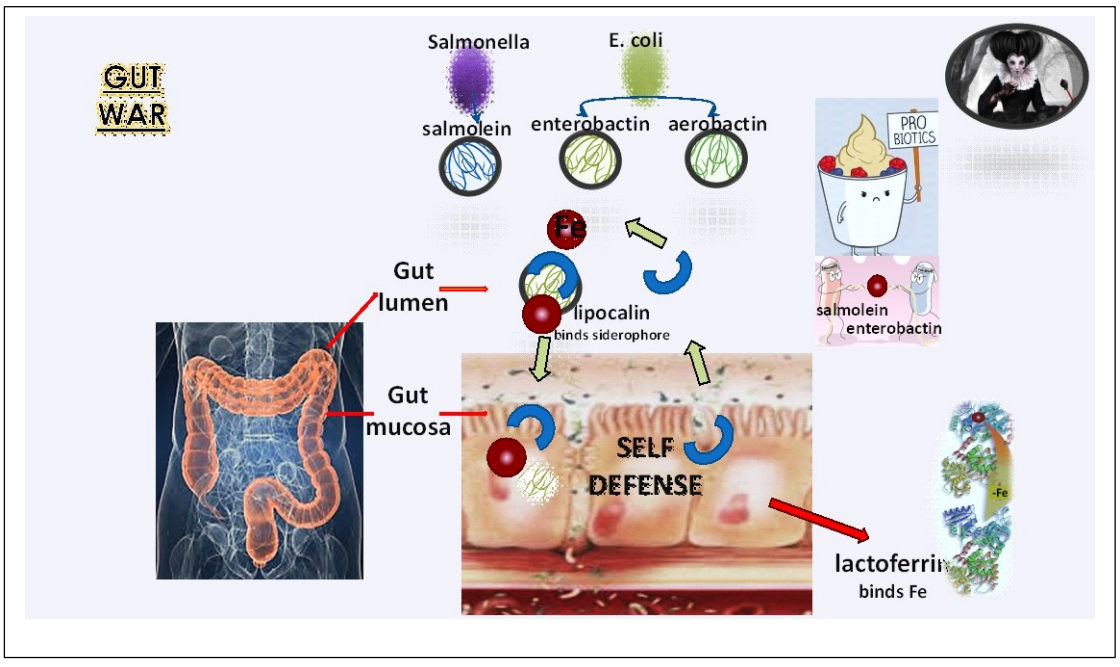
Iron piracy by bacteria is a widespread strategy among intracellular pathogenic bacteria, some of which adapted to specific "protected" niches within particular cell types, such as macrophages. That adaptation required also the development of strategies for mobilizing iron



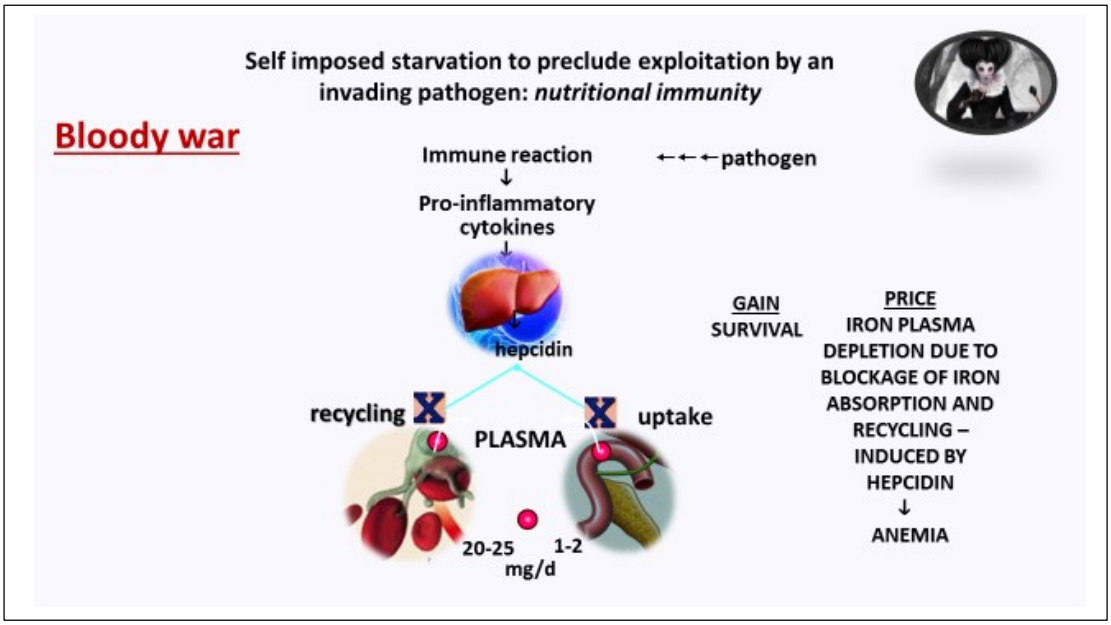
from diverse chemical sources available in macrophages, including those specialized in erythrophagocytosis. The following exemplifies the multiple strategies that Mycobaterium tuberculosis have generated for iron acquisition from within the macrophage lysosome.



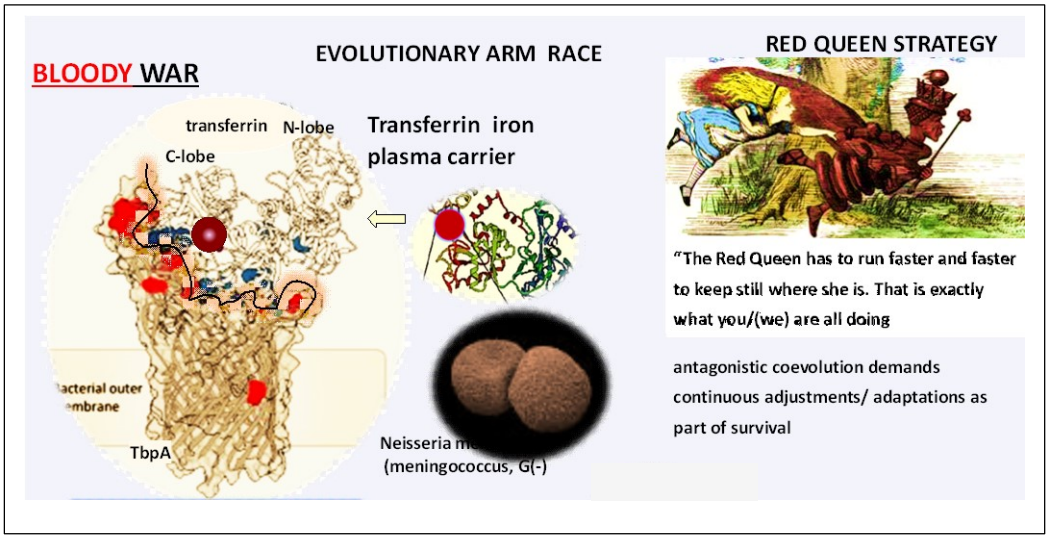
Battling for iron is a widespread phenomenon among bacteria that dwell in the animal gut, each species producing its own set of siderophores, included those provided by the host as foreign probiotics. The host itself takes also part in such battles despite its limited ability to curb bacterial growth by competing with high affinity bacterial siderophores for iron (e.g. by secreting lactoferrin). Instead, as found in the gut and particular in the urinary tract, the host relies on the production-secretion of siderocalins or lipocalins (e.g. N-GAL) that can sequester the iron-chelates (e.g. Fe-enterobactin) and thereby deprive the bacteria from iron.



A natural defense mechanism against pathogens is also found in chronic anemia induced in higher animals by invading pathogens or by inflammatory insults. That has often been referred as nutritional immunity purportedly designed to protect the host by self-imposed iron deprivation, which can be viewed as a form of (high cost) "black-queen strategy".



A different strategy in the battle for iron between host and pathogenic bacteria is exemplified by the evolutionary changes observed in the host iron carrier transferrin versus transferrin binding protein A (TbpA), a bacterial protein that literally snatches iron following a tight docking on the C-lobe of primate transferrin. The C-lobe has apparently been a hotbed of mutations that result in conformational changes, mostly (16 out of 18) found in primates. In strains of *Neisseria gonorrhoeae* and *Haemophilius influenzae*, the mutations in TbpA (occur on domains involved in attachment to the C-lobe of human and gorilla transferrin but not in that of other primates like chimps, orangutans, gibbons and baboons. In humans, C is expressed as C1-isoform in 3/4th of the population whereas the remaining carry the C2 version, that differs in just one AA. However, while the pathogenic N. *meningitidis* and N. *gonorrhoeae* recognize both the C1 and C2 forms, H.

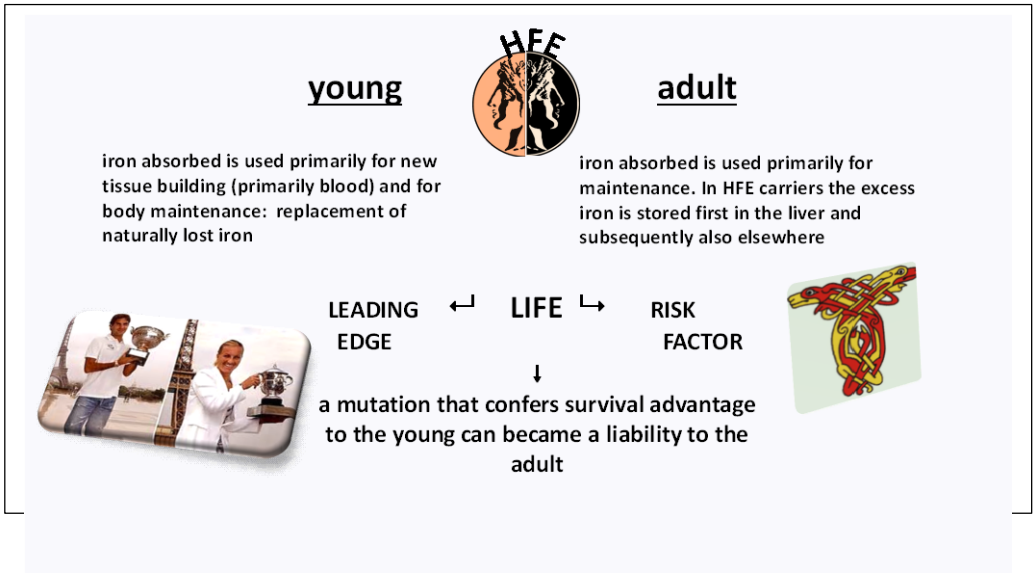


influenzae **opts for C2. Thus, depending on how common and deadly those bacteria are, they might affect (or even determine) the number of "surviving" people carrying the C1 or C2 versions.**

This exemplifies the role of iron in antagonistic coevolution of host versus pathogen that demands continuous adjustments/adaptation as survival measures (the re queen strategy of "running twice as fast to stay in the same place"-i.e. alive). In the words of Erwin Schrödinger *Life is merely avoiding decay into equilibrium*.

THE METAL of LIFE and of DEATH

An interesting observation made among French gold medalist in competitive sport is the high percentage of HFE heterozygous, suggesting a possible contribution of HFE to physical fitness.



The HFE gene product has been known to participate in signal transduction that controls hepcidin expression. In hereditary hemochromatosis (HH), the homozygous C282Y HFE mutants display an under-production of the hormone that leads to increased iron absorption/iron delivery to plasma and ensuing systemic iron overload (HH type I). Since HFE C282Y heterozygotes are generally asymptomatic despite of developing a mild hyperferremia (in adult age of some carriers), it has been speculated that a higher iron availability, that at early age might confer physical advantage, explains the prevalence of HH heterozygous among French sport medalists (HH is highest in populations of Celtic origins, a possible reason why the late-onset disease hemochromatosis is referred as the Celtic curse).

However recent studies indicated that the HFE mutations that characterize HH-type 1 were probably introduced into the British Islands during the Neolithic and Bronze migrations from the Middle East, where they might have conferred a survival advantage (and tribal dominance) to hunters-gatherers that switched from iron-rich to relatively iron-poor nutrition as they adapted to sedentary farm-life.

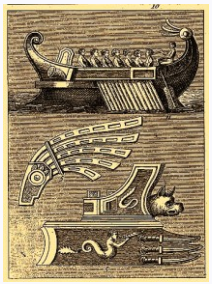
Thus, what apparently confers young HFE heterozygous a physical advantage (which is not just an asset for survival of the fit, but also of dominance stricto senso), might change post-adolescence, as slight elevations in systemic iron might render the organism more susceptible to opportunistic infections (in conditions that don't affect non-HFE carriers). Records of fatal cases in HH heterozygotes resulting from infection by otherwise non-virulent pathogens, support the concept

that iron has played a Janus-like role in human populations by favoring life while young and disfavoring subsequently.

THE HFE MUTATION THAT CAUSES HH prevails in populations of Celtic origin and colonies "visited" by vikings et al

NEW STUDIES INDICATE that the insular Atlantic genome was brought to Ireland following Neolithic and Bronze Age migration from the the ME Cassidy et al PNAS 113:368 (2016)

Was the HFE mutation evolutionary-driven by a change in nutrition from protein and iron-rich to carbohydrate-rich but protein and iron poor diet?



The HH-causing mutation in HFE originated among those hunters-gatherers that settled and moved to agriculture

All the above is not saying that cells/organisms are deprived of homeostatic mechanisms for preventing random fluctuations or transient derangements in cell iron levels but that in pathological scenarios of chronic character such mechanisms might come short of avoiding cell damage and death. Such scenarios appear in various acquired and genetic disorders that affect (directly or indirectly) local (or regional) iron utilization, causing the metal to accumulate excessively (i.e. to toxic levels) in organelles like mitochondria, at the expense of the cytosol. That in turn might lead to a vicious cycle whereby the accumulation (and often precipitation) of iron in mitochondria drags iron from the cytosol, triggering further iron uptake into cells and subsequently into mitochondria, with ensuing damage. Such phenomenon of iron misdistribution prevails in various neurodegenerative disorders, both in those of late onset (Alzheimer, Parkinson and Huntington diseases) as in those inherited disorders of early onset (Friedreich's ataxia, X-linked sideroblatic anemia with ataxia).

All the above further epitomizes iron's dual role in death as in life. Thus as life leans on iron-dependent pathways, death can be specifically driven by iron along a death path referred as ferroptosis. The unique feature that identifies a cell death-path as causatively associated with iron is its reversibility to cell permeating iron chelators that can scavenge labile cell iron but not to anti-oxidants.

"What is called a reason for living is also an excellent reason for dying ".

— Albert Camus, The Myth of Sisyphus

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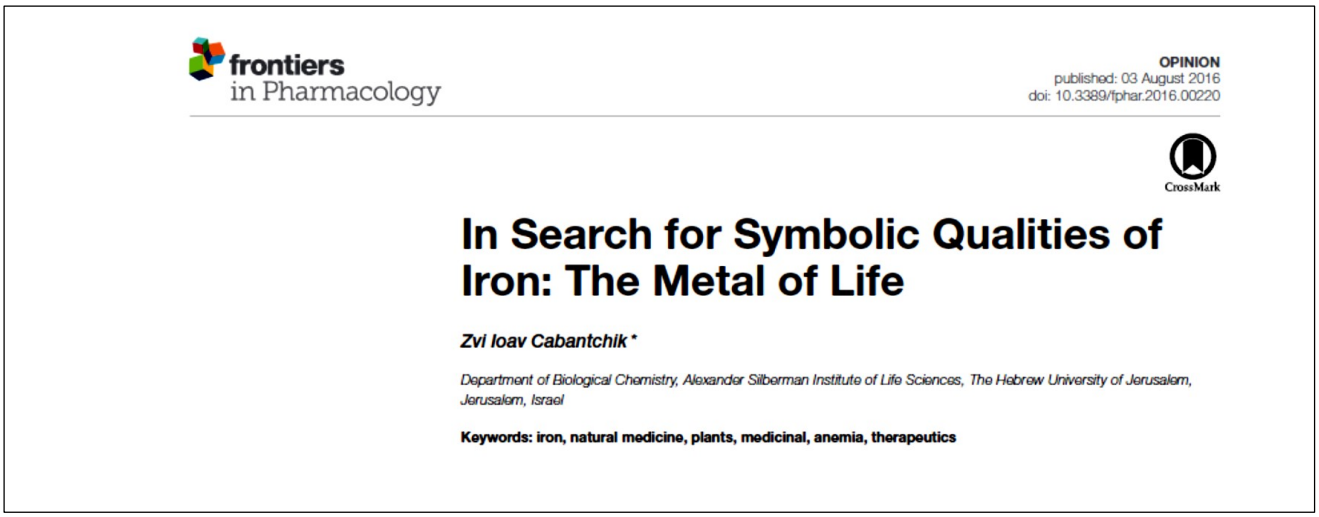

frontiers in Pharmacology

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In Search for Symbolic Qualities of Iron: The Metal of Life

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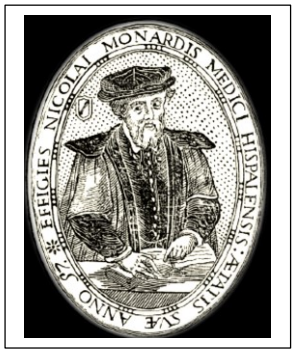
Keywords: iron, natural medicine, plants, medicinal, anemia, therapeutics

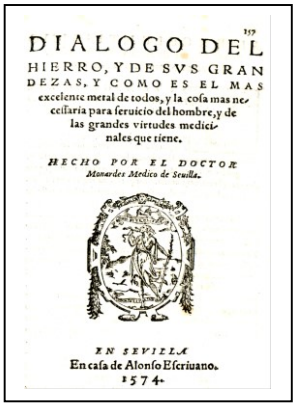
"The *past is never dead. It's not even past" (William Faulkner),*

* Based on an invited lecture "The sounds of Iron" given as Masterclass Lecture at the European Iron Club meeting held in Innsbruck in April 2016

Iron, classically known as the Metal of Mars (Paracelsus, born Philippus Aureolus Theophrastus Bombastus von Hohenheim 1493-1574) has universally been perceived as the symbol of human strength, obstinacy, fortitude, honor, courage, sharpness (of body and mind), tenacity and confidence in power. Legendary personalities like the knight Götz von Berlichingen (the one with prosthetic iron hands) or Margaret Thatcher (the iron lady) epitomized the metal properties in human character. However, it was in Rudyard Kipling's poem "Cold Iron" (see poem at end of article) that a pugnacious Baron elevates iron to a supreme level by proclaiming "cold iron as master of them all" (leaving gold for the mistress and silver for the maid). Ironically, the Baron's strong belief in the supremacy of iron leads him to wage war against the King, but ends up in defeat and humiliation. Although the Baron is pardoned, despite of betraying the king, he rather adheres to his original "iron master" creed to be sentenced with "iron out of Calvary is master of them all". Whether the poem conveys a theological message or is merely a metaphor for a feigned feeling of supremacy, one wonders of its recurrent use by "siderophiles" as symbol for the preponderant roles of iron in living organisms. Shouldn't a more benevolent "master iron" icon be adopted as representative of **iron as the metal of life**?



We learn from History that a symbolism based on genuine iron master qualities in life already existed more than a quarter of a millennium ago. It was in 1574, in the town of Seville, the gateway to the recently discovered and conquered New World, where El Señor Doctor Nicolas Bautista Monardes (1493/1508?-1588) made public an essay entitled "Dialogue about the grandeur of iron" ("which excels over other metals, and is in highest demand to human service and of great medicinal qualities"). The essay was basically an addition to two (previously published) updated sections and a new one, that together comprise The Medical History of goods brought from the West Indies of Medical Usage" (Licensed & Endorsed by His Majesty). [1]The author, generally known as Nicolás Monardes, is a graduate in Arts and Philosophy (and later in Medicine) from the famous Universidad de Alcalá de Henares (near Madrid), who excelled in the practice and writing of Medicine, Botany and Alchemistry. His contributions to those areas earned him honorary titles such as father of pharmacology and the discoverer of fluorescence (for the description of the diuretic and fluorescent properties of an extract of the tropical hardwood or kidney wood *Lignum nephriticum*). His associations with colonial traders of imported goods (primarily of


DIALOGO DEL
HIERRO, Y DE SVS GRAN DEZAS, Y COMO ES EL MAS excelente metal de todos, y la cosa mas necessaria para seruicio del hombre, y de las grandes virtudes medicinales que tiene.
HECHO POR EL DOCTOR Monardes Médico de Seuilla.
EN SEVILLA
En casa de Alonso Escriuano.
1574

[1] In Spanish:" "Historia medicinal de las cosas que se traen de nuestras Indias Occidentales que sierven en Medicina". English traveler John Framton printed in London "T*he Three Bookes written in the Spanishe tongue by the Famous Phisition D. Monardes"* and in the same year (1574) reprinted them under the title "*Joyfull Newes out of the newe founde worlde"*.

medicinal plants and minerals) were instrumental in his scientific career as botanist and in his medical practice as source of miraculous new natural cures. However, commercial misfortunes brought him initially to declare bankruptcy and hide for a decade in a monastery, before managing to repay his creditors and "openly" resume his medical practice and scientific endeavors. Monardes collected, studied, catalogued and grew many rare plants in his own garden and with some he also experimented on patients using as guidelines both classical and novel information gathered from reports brought from the New World (collected from the natives). Based on his Galenic medical training (enriched with books from both Arabic and Jewish scholars) and his own field experience with new plants, he comes out with a singular treatise of Medicine that comprises botanical descriptions, pharmaceutical samples, miraculous cures and wonders and guidelines how to promote the commercial exploitation of overseas resources.

In the "Dialogue about the grandeur of iron" as in the previous "Dialogue named Pharmacodilosis", the Renaissance scholar Monardes follows the tradition of the classics, using as model Plato's Dialogues based on questions asked by the pharmacist Burgos (representing the "praxis") and answers provided by El Señor Doctor Monardes (representing the "episteme-scientia") or the blacksmith Ortuño (representing the "techne"). Monardes misses no opportunity to expose the superior qualities of iron versus those of gold and silver, the much adored metals "brought" from the Spanish colonies. He insists that the quality of precious metals lies on their ability to provide the essence of good health (preventively and curatively) as well as of commodities made from iron-works, such as ornaments, utensils and instruments. For the latter, he takes Burgos to the workshop of the blacksmith Ortuño, who provides a thorough explanation about the qualities of different iron sources and their uses in a variety of iron works (from the sewing needle-mostly venerated by the Indians, to the compass used for navigation, to sophisticated instruments or ornaments as well as weapons for conquering new lands or punishing sinners).

Using alchemistry "logic", El Doctor explains to the inquisitive pharmacist the source and composition of iron and the many combinations that can be used to achieve unique therapeutic miracles or serve as material for making instruments (including those used in surgery and barbershops-often by the same "professionals"). Monardes gives credit to the old masters (Plato, Hippocrates, Galeus, Theophrastus - Paracelsus), Discoirides, Pliny-The Elder, Al-Razi, Avicena , D'acosta and others for their wisdom and guidance, but when appropriate-according to his own experience, he dares to dispute them[2]. In some cases he also refers to old miracles as credible events (e.g. the sheperd Melampus that uses his magical powers to cure infertility in Iphuclus, King of Phylacea, by giving acid wine with rust scrapings from a knife). But then he also emphasizes the importance of using pure/washed iron (oxide) sources for preparing iron-based medications that need to be devoid of traces of other lethal elements (lead, copper or vitrious-

[2] *quid nobis certius ipsis sensibus esse potest, qui vera ac falsa notemus*". Lucretius "De rerum natura" ("What can be more certain than our own senses to distinguish between truth and falsehood". Lucretius "The Nature of things".

silicate) and should be prepared by extraction with white vinegar for up to one month followed by evaporation down to powder. The medical virtues of iron-based medications are represented by their ability to treat: acne● gout● consumption (tuberculosis) ● bloody diarrhea● vesicular bolus● perianal fistulas● encrusting eruptions● erysipelas, paronychia● vaginal discharges● wounds● excessive lacrimation● vomiting● fevers● weakness● edema● hemorrhoids● cystitis● stem bleeding (styptis) ● hemorrhage.

Monardes was well acquainted with the classical literature about iron as medicinal material but also with contributions of his contemporaries, thus satisfying Burgos repeated inquiries about how well updated is El Doctor. Always inquisitive, Burgos further "wishes the sunset to be delayed, as there is so much to be said about iron that Medicine has forgotten, being no human disease from toe to head-hair that iron is not involved and he (Burgos) is privileged to be next to an erudite man that is so knowledgeable of most important things".

Monardes books were printed in several editions and translated to most of the European languages (initially English, Latin and French) and, well known in medical practice until the advent of Chemistry (end of 18th century). A journey through times shows that many of those practices are been used even at present days, both as home remedies and prescribed medicines. His classification of old and newly defined plants (imported from the colonies) has been ample recognized in the taxonomy field and frequently quoted in reference to tobacco, sassafras and other botanicals. Some plants have found their way into the pharmacopoeia, such as *Monarda punctata*, the source of thymol, used as an intestinal antiseptic but mainly because it gives a greenish color to the urine. [3]A renewed interest in the Doctor followed the publication of his Dialogues by the Compañía de Fundición de Fierro y Acero de Monterrey (that adopted Monardes for praising metallurgy) and an article in the Le Socialiste (1962) about "El hierro y sus Excelencias" (praising Monardes, the moralist and naturalist and criticizing the industrialists for commercializing the natural ferruginous sources of iron).

The doctor-scientist Nicolas Bautista Monardes is the "*nueva persona"* that the Spanish Renaissance produced": an educated professional in Medicine that excelled thanks to his inquisitive and highly entrepreneurial spirit but also to his humanistic views. He is undoubtedly a unique historical personality who was fascinated by the properties of iron long before it was scientifically recognized as the metal of life and preceding the industrial revolution. His passion for iron was transmitted through his book

[3] F.A. Oski opens his 1979 Am. J. Dis. Child (133: 315) paper on "Non hematological manifestations of Iron deficiency" with a series of questions about symptoms that are indicative of iron deficiency, and quotes Monardes as been aware of such conditions and of iron-based remedies for apathy, irritability, anorexia, decreased exercise, tolerance, and a craving for ice, glossitis, "spoon nails," the excretion of a pink urine after the ingestion of beet-that results from gastric achlorhydria, occult gastrointestinal bleeding, and failure to thrive.

"Dialogue about the grandeur of iron" (published first in 1574) that became instrumental as vehicle for disseminating medical messages to professionals as to laymen and a paradigm for exploring (and later exploiting) natural sources as remedies for body and soul.

Nicolás Monardes earns a most distinguished place in the Pantheon of IBIS and especially in EIC.

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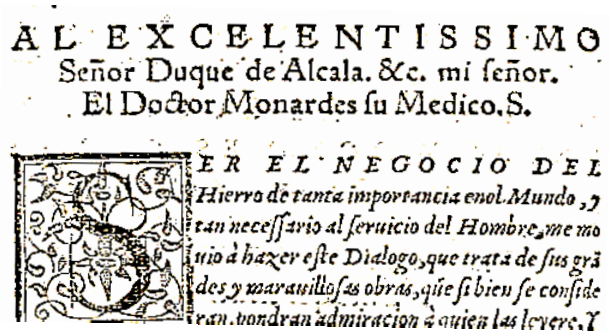
AL EXCELENTISSIMO
Señor Duque de Alcala. &c. mi ſeñor.
El Doctor Monardes ſu Medico. S.

ER EL NEGOCIO DEL
Hierro de tanta importancia en el Mundo, y
tan neceſſario al ſeruicio del Hombre, me mo
uio à hazer eſte Dialogo, que trata de ſus grã
des y marauillo ſas obras, qüe ſi bien ſe conſide
ran, tendran admiracion à quien las leyere. Y

TO HIS HIGHNESS
Sr Duke of Alcalá & c. my senior
your physician Dr. Monardes, S.

BEING THE BUSINESS OF IRON OF
such woldwide importance, and of such a service to Humans, I tried to compose this Dialogue, that deals with its great and wonderful uses, that if faithfully followed, will confer a great admiration to the readers.

The book is dedicated to the Duque de Alcalá, (Fernando Enríquez de Ribera y Portocarrero) and is wife (referred as & c. = compañera) who was no other but the Señora Juana Cortés de Zúñiga, daughter of Hernán Cortés, the conquistador of México.

Rudyard Kipling

Cold Iron

Gold is for the mistress -- silver for the maid --
Copper for the craftsman cunning at his trade."
"Good!" said the Baron, sitting in his hall,
"But Iron -- Cold Iron -- is master of them all."

So he made rebellion 'gainst the King his liege,
Camped before his citadel and summoned it to siege.
"Nay!" said the cannoneer on the castle wall,
"But Iron -- Cold Iron -- shall be master of you all!"

Woe for the Baron and his knights so strong,
When the cruel cannon-balls laid 'em all along;
He was taken prisoner, he was cast in thrall,
And Iron -- Cold Iron -- was master of it all!

Yet his King spoke kindly (ah, how kind a Lord!)
"What if I release thee now and give thee back thy sword?"
"Nay!" said the Baron, "mock not at my fall,
For Iron -- Cold Iron -- is master of men all."

"Tears are for the craven, prayers are for the clown --
Halters for the silly neck that cannot keep a crown."
"As my loss is grievous, so my hope is small,
For Iron -- Cold Iron -- must be master of men all!"

Yet his King made answer (few such Kings there be!)
"Here is Bread and here is Wine -- sit and sup with me.
Eat and drink in Mary's Name, the whiles I do recall
How Iron -- Cold Iron -- can be master of men all!"

He took the Wine and blessed it. He blessed and brake the Bread.
With His own Hands He served Them, and presently He said:
"See! These Hands they pierced with nails, outside My city wall,
Show Iron -- Cold Iron -- to be master of men all."

"Wounds are for the desperate, blows are for the strong.
Balm and oil for weary hearts all cut and bruised with wrong.
I forgive thy treason -- I redeem thy fall --
For Iron -- Cold Iron -- must be master of men all!"

"Crowns are for the valiant -- scepters for the bold!
Thrones and powers for mighty men who dare to take and hold!"
"Nay!" said the Baron, kneeling in his hall,
"But Iron -- Cold Iron -- is master of men all!

Iron out of Calvary is master of men all!"