Vital amines, purple smoke
A select history of vitamins and minerals

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Until 1907, scurvy was thought to be a strictly human disease. In that year, Theodore Frolich and Axel Holst, two Norwegian physicians studying beriberi, a similar appearing but fundamentally unrelated disease, decided for no very compelling reason to use guinea pigs instead of pigeons as their research animals. To their surprise, the guinea pigs on the experimental diet did not develop beriberi, but
scurvy instead. Serendipity often graces science: guinea pigs accidentally made toothless due to weakened connective tissue led to the discovery of vitamin C and, along the way, helped stir up public support for the initiative to iodize salt in the United States.

Much of the developed world has in recent years become over-inundated with news about vitamins, minerals, antioxidants, flavonoids, and the like. Today it is hard to imagine a time when people did not know about the relationship between vitamin C and citrus fruit, or when iodine was just an unnamed element dissolved in the sea. The thoughtlessness with which we can pop a pill filled with thirteen vitamins, thirteen minerals, and six trace elements belies the tortuous path knowledge can take. While we are a far cry from Anaxagoras’ 475 BC proclamation of the existence of “homeomerics” (generative components) in food, it is also true that the primary cause of mental retardation in 2013 is lack of iodine, an easily curable mineral deficiency. The history of vitamins and minerals is a fascinating look—uplifting and discouraging in turn—into how we interact with scientific truth and with each other.

The Limeys, scurbutus, and vitamin C

Hippocrates wrote one of the earliest known descriptions of scurvy. As quoted in A Treatise on the Scurvy, he wrote that patients “had ulcers on the tibia, and black cicatrices.” It is from these cicatrices—which form because of aborted collagen synthesis resulting in impaired tissue repair—that the disease got its Latin name, scurbutus, which then became, via a short detour through Scandinavia, the English scurvy.

In 1747, Scottish naval physician James Lind undertook what was the first almost clinical trial in history. Twelve sailors with scurvy were divided into six groups of two, each of which got the same diet but with one different ingredient. One group got cider, one vitriol, another vinegar, the fourth seawater, the fifth oranges and lemons, and the sixth a spicy paste plus barley water. The results of the trial—one cure and one nearly complete recovery after six days in the oranges and lemons group, as well as partial recovery in the cider group—were published in Lind’s 1753 work, A Treatise on the Scurvy.

Lind was by no means the first to suggest a cure. John Woodall in the early 1600s persuaded the Dutch East India Company to provide lemon juice along with “Limes, Tamarinds, Oranges, and other choice of good helps” for its sailors. And in 1536, the crew of Jacques Cartier, the explorer who claimed Canada for the French, was saved from scurvy by the suggestion of Iroquois prince Domagaya to drink a tea brewed from the annedda (arbor vitae) tree.

These discoveries notwithstanding, scurvy caused the deaths of two million sailors, including the majority of the crews of both Vasco da Gama and Magellan, between 1500 and 1800. Why did it take centuries to institute something as simple as citrus fruit in the diets of navies worldwide?

Part of the answer lies in an astonishing fact: James Lind did not himself believe that citrus fruit alone was a cure for scurvy. This illustrates an important aspect of scientific progress: if a scientist cannot conceive of a reason for a given result, he is far more likely to attribute the result to chance. The term “vitamin” would not be coined for another one hundred and fifty years and hundreds of thousands of sailors would die from scurvy after 1753.

Finally, in 1794, lemon juice was issued on board the HMS Suffolk on a twenty-three week nonstop voyage to India. There was no major outbreak of scurvy on the voyage. This stunning result, coupled with the work of Gilbert Blane, chairman of the British Navy’s Sick and Hurt Board, who knew of Lind’s experiment, resulted in the provision of fresh lemons to the Royal Navy during the Napoleonic Wars. The improved health of British sailors played a critical role in naval battles, including the Battle of Trafalgar. There is nothing like defeat in war to make a country take notice; the French and the Spanish adopted
the British solution in their navies soon after.\textsuperscript{7}

And yet this is only half the story. Three factors combined to deeply confuse matters in the nineteenth century. First, lemons were replaced by West Indian limes—thus the term Limeys for British sailors—because they were more easily obtained from Britain’s Caribbean colonies. But limes intrinsically have one-quarter the vitamin C content of lemons, and they were served as juice that had been exposed to light and pumped through copper tubing, further decreasing their vitamin C content. This was another reason for Lind’s skepticism: after his experiment he had switched from fresh citrus to lime juice, which was not nearly as effective. Second, fresh meat also cured scurvy, and there was no obvious connection between the two foods. Third, the infectious theory of disease was coming into vogue. Under this theory, scurvy was attributed to “ptomaines”—alkaloids—in tainted meat. As late as the early twentieth century, voyagers to Antarctica developed scurvy.\textsuperscript{8}

It was at this crucial time—in 1907—that Frølich and Holst’s guinea pigs came into the picture. The two scientists found they could cure the animals using a variety of fresh food and extracts. Unable to make sense of their results, the scientific community ignored their contribution for decades. By 1928, the anti-scurvy agent, whose structure was still unknown, was referred to as “water-soluble C.” That year, two separate teams, one in Hungary led by Albert Szent-Györgi, the discoverer of the citric acid cycle, and one in the United States led by Charles Glen King, began work to isolate the compound. Szent-Györgi isolated hexuronic acid as a candidate for vitamin C but could not prove it without a biological assay. In 1931, he sent the last of his hexuronic acid to King’s lab, which proved that it was indeed the long-sought vitamin C in 1932.\textsuperscript{9} The compound’s chemical structure was deduced by British chemist Walter Haworth a year later, and it was named ascorbic acid in honor of its anti-scurvy properties. Szent-Györgi was awarded the 1937 Nobel Prize in Medicine and Haworth shared the 1937 Nobel Prize in Chemistry, marking the culmination of the search for the cure for scurvy.

**Polished rice**

At first there is paralysis of the extensors of the legs; the bird sits on a flexed tarso metatarsal joint. Paralysis soon extends to the wings, nape of the neck and the entire musculature. The animal then lies motionless on its side; a deep prostration appears frequently on the second or third day after the onset of paralysis—at the latest, in one week—and is followed by death in all cases; the whole course of the disease is run in a very short time.\textsuperscript{10p93}

So reads Casimir Funk’s chilling description of chicken beriberi. The disease has existed for millennia. The terms for it
paresthesias that were outlined by Jacobus Brontius, the physician all describe the generalized weakness, the bizarre gait, and the paresthesias that were outlined by Jacobus Brontius, the physician for the 1627 Dutch East India Company in Java—whose ship, incidentally, was likely amply stocked with lemon juice.11

How did a disease in the exotic East influence the direction of Western vitamin research when Europeans weren’t the ones getting sick? In the latter half of the nineteenth century, European imperialism had made forays deep into Asia; many Asian countries assimilated European technology. Steam-driven mills sprang up all over the continent, efficiently stripping the hulls (“polishings”) off of rice. White rice quickly replaced brown rice as a staple food, and in the wake of this so-called superior product, the incidence of beriberi skyrocketed.

From 1878 to 1882, one-third of Japanese Navy sailors developed the disease and many died. Kanehiro Takaki, later to be affectionately dubbed the “barley baron” for his work, was a Japanese naval physician who had trained both in traditional Chinese medicine and in London. In 1883 on a training mission from Japan to Hawaii, he noticed two things: the high incidence of beriberi among enlisted men, whose diet was mainly composed of white rice, and the absence of the disease among officers, whose diet consisted of vegetables and meat. Takaki petitioned the emperor to fund an experiment with an improved diet on the same mission the next year. It was a great success—the incidence of beriberi dropped an order of magnitude. The diet, which included meat, barley, and fruit, was implemented throughout the Japanese Navy, virtually eliminating the disease from the fleet.

Takaki attributed the incidence of beriberi to protein deficiency; thus, he was wrong in the particulars. But the disease is indeed caused by dietary deficiency, and in that sense Takaki was years ahead of the prevailing infectious view held both by his fellow Japanese and by Europeans. As late as the Russo-Japanese War of 1904–1905, tens of thousands of deaths from beriberi occurred among soldiers in the Imperial Japanese Army because the doctors in this branch of the armed forces had been trained at Tokyo Imperial University, which subscribed to the theory of an infectious cause of beriberi.12 But Europeans ignored both his results and those of Takaki. In 1886, two years after beriberi rates had begun plummeting in the Japanese navy, the disease was endemic in the Dutch East Indies and the Dutch government sent a commission to discover the cause. One of the investigators was Christiaan Eijkman, whose thesis had been On Polarization of the Nerves, making him an ideal candidate to investigate the peripheral neuropathy of beriberi. Eijkman’s studies with Robert Koch predisposed him to assume an infectious cause, and although none was immediately discerned, an undeterred Eijkman, by now the Director of the Geneeskundig Laboratorium in Indonesia, continued his work injecting chickens with isolates from people who had died of beriberi. In 1889 he got lucky. A disease eerily similar to beriberi broke out among the chickens. Eijkman was nothing if not thorough—when he learned that the chicken feed had recently been switched to white rice, he began feeding experiments and found that both unpolished rice and the discarded rice polishings cured the disease.

Old habits die hard. Influenced by the ubiquitous “ptomaine” theory, Eijkman clung to his infectious framework for years, writing that “cooked rice favored conditions for the development of micro-organisms . . . and hence for the formation of a poison causing nerve degeneration.”13 He thought his results important enough to share, however, and in 1895, before leaving for Europe due to ill health, he told Adolphe Vorderman of his feeding studies.

As the physician responsible for medical inspection of the prisons across the East Indies, Vorderman was intrigued: he remembered having noticed in passing that prisons with different rice had different beriberi incidence. Vorderman was unique in his efforts to avoid scientific bias, both in himself and in others, and the study he designed and implemented, though imperfect, was a tour de force of epidemiology.14 His first step was to write each prison governor with regards to beriberi incidence and the type of rice used, without suggesting a possible connection. When the correlation seemed nearly perfect, Vorderman visited all 101 prisons he had written to, with the purposely vague official mission of “looking in to the health status of prison inmates.” He sampled the rice from each prison, placed it in containers marked only with de-identifying letters, and sent them for analysis. The results were staggering: in prisons with white rice, the proportion of beriberi cases to number of prisoners was 1:39; in prisons with fully unpolished rice, this fell to 1:10,725.

Dutch physician Gerrit Grijns continued Eijkman’s work with Vorderman’s results in the back of his mind. He excluded as a cause every one of the dietary components of a “complete” nineteenth century diet. The nutrient beriberi patients lacked was neither a protein, a carbohydrate, a fat, nor an inorganic salt. Grijns took particular note of the fact that had bedeviled scurvy researchers for years: scurvy could be cured by fresh

 vary widely: Arabic buhr, asthma, and bahr mean “a sailor”; Singhalese Bharyee means “weak movement”; Sudanese beriberi, beribit, berebet refer to “pottering walk”; Hindustan Bhrbari is swelling, edema, while beri refers to “a sheep, in allusion to the peculiar gait in some instances of the disease.”11

All describe the generalized weakness, the bizarre gait, and the paresthesias that were outlined by Jacobus Brontius, the physician for the 1627 Dutch East India Company in Java—whose ship, incidentally, was likely amply stocked with lemon juice.11

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A Dutch physician, F. S. van Leent, had in 1879 proposed that a one-sided rice diet was the cause of beriberi.13 But Europeans ignored both his results and those of Takaki. In 1886, two years after beriberi rates had begun plummeting in the Japanese navy, the disease was endemic in the Dutch East Indies and the Dutch government sent a commission to discover the cause. One of the investigators was Christiaan Eijkman, whose thesis had been On Polarization of the Nerves, making him an ideal candidate to investigate the peripheral neuropathy of beriberi. Eijkman’s studies with Robert Koch predisposed him to assume
meat or by citrus fruits. In 1901, putting two and two together, he postulated that there was some hitherto unknown class of nutrient and that the missing substance in beriberi was either necessary for maintaining metabolic functions in the peripheral nervous system or protecting the nervous system from some other environmental agent.

In 1912, Polish chemist Casimir Funk isolated an amine that he thought was the anti-beriberi compound (in fact it was actually nicotinic acid, vitamin B₃, contaminated with thiamine, vitamin B₁) and coined the term “vital amines,” shortened to “vitamin.” That same year, Frederick Hopkins published his work demonstrating that “complete” nineteenth century diets fail to support animal growth. History is not always just; Grijns, whose work corrected Eijkman’s hypothesis and preceded that of Hopkins, was barely mentioned in either of their Nobel lectures in 1929.13,15

One final peculiar turn of fate: chickens take a long time to develop beriberi and are therefore not ideal research animals for the disease. The isolation of the anti-beriberi factor was therefore tremendously accelerated by the accidental observation that the bonbol, a small tropical bird, develops beriberi with alarming alacrity. In 1926, aneurin (for anti-neuritic vitamin)—subsequently renamed thiamine for a previously overlooked sulfur atom in the chemical structure—was discovered by B. C. P. Jansen and W. F. Donath. And so we come full circle: today we eat white rice without fear of beriberi because it has been fortified since the 1950s with synthetic thiamine, the vital amine stripped off in Asia more than a century ago.

The goiter belt and the globe

Between 1804 and 1814, with the Napoleonic wars raging across Europe, France was in dire need of gunpowder. Gunpowder was manufactured from saltpeter, a collection of nitrogen-containing compounds, made then by mixing manure with wood ash and composting the two with straw. Parisian Bernard Courtois was at that time running his family’s saltpeter business, and in 1811 the wood ash began running low. He began to experiment with seaweed ash. One day, after adding sulfuric acid to the ash, he was startled to find a purple vapor coming out of the glassware. The newly discovered element was later named iodine, after iodes, the Greek word for “violet.”16

Soon after Courtois’ discovery, Swiss physician Jean-Francois Coindet speculated that the mineral might be the ingredient in seaweed that was effective against goiter.17 He began dispensing an iodine tincture to patients with goiter as early as 1820. Jean-Baptiste Boussingault, a French engineer, chemist, and agricultural scientist, in his travels throughout South America, noticed that the prevalence of goiter varied with geography and was highest in areas that did not have access to sea salt. Boussingault advocated the use of iodinated salt—in 1833! In the 1850s, French chemist Adolphe Chatin wrote as explicitly as could be: “the main cause of goiter seems to be a low concentration of iodine in drinking water in certain areas.”18 For a variety of reasons, Chatin’s idea was stifled by the French Academy of Science; iodine would not be widely reevaluated as a treatment for goiter for another fifty years, despite the fact that it was actually used successfully in France around that very time to improve goiter in 4000 of 5000 children.17

People were once again rediscovering—and promptly forgetting—something known for ages. It was fitting that Courtois named the seaweed-borne mineral after a Greek color, for the ancient Greeks had been using seaweed to treat goiter thousands of years earlier. In the first century AD, the Roman poet Juvenal wrote, “who wonders at a swollen throat in the Alps?”19 In 1215 an illustration from the book Reuner Musterbuch depicted an imbecile with an immense goiter, perhaps the first recorded association between goiter and cretinism.20 Swiss physician Felix Platter gave a detailed description in 1602:

Besides, the head is sometimes misshapen: the tongue is huge and swollen; they are dumb; the throat is often goitrous. Thus they present an ugly sight; and sitting in the streets and looking into the sun, and putting little sticks in between their fingers, twisting their bodies in various ways, with their mouths agape they provoke passersby to laughter and astonishment.21

The link between the thyroid gland, goiter, and cretinism was not firmly established until 1885, when neurosurgeon Sir William Horsley, known primarily as the first to perform pituitary surgery, pieced together his own patients’ thyroidecotomy outcomes and wrote in the British Medical Journal: “I am prepared, in my first two lectures, to support the dictum ... that cretinism ... [is] due to ... arrest of the function of the thyroid...
gland.” Ten years later, German chemist Eugen Baumann discovered thyroiodine in thyroid tissue, making it easy to understand how iodine deficiency might lead to cretinism.

Only in 1907 did American physician David Marine begin work using iodized salt to prevent goiter; it took almost a decade to get an eventually successful large-scale trial of iodized salt in Cleveland public schools underway. Even this success, however, was not enough to get iodization of salt onto the list of national priorities. It was only during World War I, when the United States military noticed that the draft had disqualified many men with goiter in the Pacific Northwest, Northern Michigan, and Wisconsin—the latter two being part of the so-called “goiter belt”—that the necessary impetus finally materialized. David Murray Cowie, professor of pediatrics at the University of Michigan, began a push for salt iodization, citing the results of Marine’s trial as well as the Swiss practice of iodizing salt. The timing was perfect: it was the 1920s, and “important discoveries of vitamins and their roles in food nutrition” were occurring. Public opinion was behind him, and on May 1, 1924, iodized salt appeared; later that year the Morton Salt Company began national distribution. Goiter incidence in the United States plummeted, in Detroit from 9.7 percent to 1.4 percent within six years.

Today, it costs five cents per person per year to iodize salt. Yet, according to conservative estimates, twenty million people worldwide are mentally handicapped because of lack of iodine, with nearly two billion having insufficient iodine intake. Even these statistics are a striking improvement from pre-1993 data, the year—almost two centuries after Boussingault’s suggestion—that the World Health Organization (WHO) adopted universal salt iodization.

The WHO, along with organizations such as the International Council for the Control of Iodine Deficiency Disorders (IDDICC), has made major strides in recent years. Ten percent of households consumed iodized salt in the 1990s. In 2003, this number has risen to sixty-six percent. Though much work remains to be done, it is not unreasonable to look forward to a time when an accidental byproduct of French gunpowder manufacturing reborn from ash brings forth the true potential of millions of children the world over.

Reflections on a saga
A few interesting observations on medical progress can be gleaned from the history of medical advances:

1. Science moves forward by the hard work of brilliant and lucky people—Adolphe Vorderman’s trek to 101 prisons in the Dutch East Indies was hard work, Kanehiro Takaki’s insight into the true nature of beriberi was brilliant, and Axel Holst’s and Theodore Frølich’s switch to guinea pigs was lucky.

2. Discovery is rarely the product of one person—while Albert Szent-Györgi received the 1937 Nobel prize in Medicine for his discovery of vitamin C, the prize could well have been divided infinitely among the Iroquois people, James Lind, James Woodall, Frölich and Hølst, Charles King, and on and on. True, Szent-Györgi put it all together, but he built on a multitude of contributions.

3. Truth is not enough—Domagaya’s annedda tea, Kanehiro Takaki’s improved diet, Adolphe Chatin’s calls for iodized drinking water—none of them had a permanent effect on pushing...
Vital amines, purple smoke

Science forward. Sometimes, timing is everything.

4. Disease does not respect international boundaries, and neither does scientific progress. When we ignore this simple fact, people the world over suffer. On the other hand, when we remember this fundamental interconnectedness, medicine serves its true purpose: the prevention and cure of disease, wherever it might be found. A final episode from vitamin history illustrates the point: Wernicke-Korsakoff syndrome, mainly observed in Europe and the United States and long thought to be a result of alcohol toxicity, was hypothesized in the 1930s to be caused by thiamine deficiency. This was conclusively demonstrated in the 1950s. Thus a treatment first discovered to prevent beriberi in Japanese naval soldiers in the late nineteenth century was shown to heal Western alcoholics in the mid-twentieth.

History is laced with serendipitous beauty. There is perhaps no better reminder of this truth than the vital chemicals hiding in our food and the stories of the people who discovered them. Indeed, as the vitamin pill begins to dissolve in our stomachs, spilling its molecular intricacies, a saga bought with the toil and insight of millennia begins to unfold.

References


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